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Anticoagulation in cardiovascular diseases: Evolving role, unmet needs and grey areas

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Published in
Frontiers in Cardiovascular Medicine

ISSN 1664-8714
ISBN 978-2-8325-2073-4
DOI 10.3389/978-2-8325-2073-4

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Anticoagulation in cardiovascular diseases: Evolving role, unmet needs and grey areas

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Citation

Pola, R., Tuttolomondo, A., Pignatelli, P., eds. (2023). *Anticoagulation in cardiovascular diseases: Evolving role, unmet needs and grey areas*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-2073-4

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frontiers | Frontiers in Cardiovascular Medicine

TYPE Editorial
PUBLISHED 10 October 2023
DOI 10.3389/fcvm.2023.1219033

OPEN ACCESS

EDITED AND REVIEWED BY
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RECEIVED 08 May 2023
ACCEPTED 25 September 2023
PUBLISHED 10 October 2023

CITATION
Tuttolomondo A, Pignatelli P and Pola R (2023) Editorial: Anticoagulation in cardiovascular diseases: evolving role, unmet needs, and grey areas.
Front. Cardiovasc. Med. 10:1219033.
doi: 10.3389/fcvm.2023.1219033

Editorial: Anticoagulation in cardiovascular diseases: evolving role, unmet needs, and grey areas

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KEYWORDS

anticoagulation, thrombosis, heparin, direct oral anticoagulant (DOAC), vitamin K antagonist (VKA), atrial fibrillation, venous thromboembolism (VTE), ischemic cardiovascular disease

Editorial on the Research Topic
Anticoagulation in cardiovascular diseases: evolving role, unmet needs and grey areas

Thrombosis is a key pathophysiological mechanism for many serious cardiovascular diseases, including deep vein thrombosis (DVT), pulmonary embolism (PE), acute coronary syndrome (ACS), and ischemic stroke.

Thrombi consist of aggregated platelets, fibrin, and trapped cells, with the distribution of these components differing substantially between arterial and venous thrombi (1). The main component of arterial thrombi is constituted by platelets. These thrombi usually originate in high-shear conditions as a result of atherosclerotic plaque disruption in arteries (2). Fibrin is instead the main component of venous thrombi. These usually arise under low-shear conditions as a result of blood stasis or hypercoagulability. As we will see, such differences may potentially influence the choice of antithrombotic therapy in individual patients. This goes along with the fact that antithrombotic therapy has evolved in a substantial manner over the last decade. Indeed, there is now a wide availability of novel medications—i.e., direct oral anticoagulants (DOACs)—and the promise of even newer anticoagulants entering the field in the very near future. In addition, novel clinical and therapeutic indications to anticoagulation have emerged, as in the case of the prevention of arterial events in subjects with ischemic cardiovascular diseases. Nonetheless, these advancements have increased the appreciation that many unmet needs and grey areas still exist when dealing with patients who need antithrombotic therapies, and this is the reason why we have decided to put together, in a dedicated Research Topic, up-to-date contributions from researchers who have personal and documented experience in the field of anticoagulant therapy.

For several decades, vitamin K antagonists (VKAs) have been the treatment of choice for long-term oral anticoagulation. Unfortunately, VKAs have many disadvantages that limit their use in the real world. Almost all the limitations of VKAs have been overcome by DOACs, which are at least as effective as VKAs in preventing thrombotic events in patients with non-valvular atrial fibrillation (NVAF) and venous thromboembolism (VTE), with the advantage of being safer in terms of bleeding risk (especially intracranial

hemorrhage) and easier to use (2). This has led to a complete change in the therapeutic scenario of anticoagulant regimens. According to all the international guidelines, DOACs are now the treatment of choice for patients with NVAF and VTE. This is also valid in frail and elderly patients and in subjects with kidney insufficiency, at least for glomerular filtration rates above 30 ml per minute (3, 4). The success of DOACs has led scientists to investigate their possible use also in additional clinical settings, such as the prevention of embolic strokes of unknown source (ESUS), which represents about 25% of all ischemic strokes, and the reduction of cardiovascular events in subjects with arterial ischemic diseases. If the studies on ESUS have produced inconsistent results (5–7), those on ischemic cardiovascular diseases have led to important clinical and therapeutic advancements. The landmark example is the fact that nowadays there is a specific DOAC—i.e., rivaroxaban—that has become part of the therapeutic armamentarium of doctors who treat patients with peripheral artery disease (PAD). This is the result of the evidence provided by the COMPASS and VOYAGER trials, which have demonstrated that in patients with PAD, a dual antithrombotic therapy, consisting of the addition of a so-called vascular dose of rivaroxaban (2.5 mg twice daily) to an antiplatelet agent, reduces the risk of cardiovascular death, myocardial infarction, stroke, and limb adverse events (8, 9).

Hard to believe until a while ago, DOACs—which have been called "novel anticoagulants" for many years—might become "older" very soon. This is because strategies that target coagulation factors XI and XII (FXI and FXII) might soon hit the market. These newer medications promise to have the ability to limit thrombosis growth with an impact on hemostasis that is lower than that of DOACs (10). Very recently, a study conducted on patients with NVAF treated with an FXI inhibitor—i.e., abelacimab—was stopped early because of an overwhelming reduction in bleeding compared to a DOAC (11). A grey zone in our knowledge of anticoagulation efficacy is stroke prevention in hemodialysis patients with NVAF, owing to the fact that there is no strong demonstration that DOACs can be used in an efficacious and safe manner in this type of patient. This is one of those settings in which new inhibitors of coagulation factors might provide a great advantage. The clinical potential of FXI- and FXII-directed anticoagulant strategies will be better clarified over the next few years. Current FXI and XII inhibition strategies include antisense oligonucleotides (ASOs) that reduce the hepatic synthesis of clotting proteins, monoclonal antibodies that block the activation or activity of coagulation factors, aptamers, and small molecules that block the active site or induce allosteric modulation.

In the special issue that we have edited, the authors have tried to address some of the unmet needs in the field of anticoagulation in cardiovascular diseases. A contribution that was much appreciated, in terms of both visualizations and citations, was the review by Pastori et al. on the use of DOACs in patients with antiphospholipid syndrome (APS). This is indeed a delicate issue, with controversial recommendations among the different international guidelines. For instance, the European Society of Cardiology (ESC) recommends against the use of DOACs in APS patients. However, the authors correctly argue that these recommendations do not make any distinction between single-, double-, and triple-positive APS patients, between patients who only had venous thrombotic events and those who had arterial events, nor between different DOACs. This is despite the fact that these recommendations are exclusively based on the results of the Trial on Rivaroxaban in AntiPhospholipid Syndrome (TRAPS) (12), which had at least three main limitations: it included only triple-positive APS patients; some of the enrolled patients had not only venous but also arterial previous events; only a specific DOAC, i.e., rivaroxaban, was used. Extending the results of this trial to single/double-positive APS patients who only had venous thrombotic events might not be correct. It might also be questionable to extend to all DOACs the results of a trial that only used rivaroxaban. It is probably for these reasons that other international societies have decided that it is important to make some distinctions between the different clinical phenotypes of APS patients (13–15). According to these societies, there is the possibility of using DOACs in some specific situations. For instance, a patient who is diagnosed with APS when they are already on stable anticoagulation with a DOAC because of a previous VTE might continue DOAC treatment as the benefit of switching to VKAs may not be certain in this case. Likewise, a patient with severe INR instability while on a VKA might benefit more from a stable anticoagulation with a fixed-dose DOAC. There are also patients who are unwilling to take a VKA or unable to undergo regular INR monitoring. In these cases, DOAC treatment might be taken into consideration. Finally, there might be patients with contraindications to VKA therapy, who might therefore be considered for DOAC treatment.

The research paper by Fu et al., which compared the relative risk of embolism and major bleeding between apixaban and warfarin in patients with NVAF and compromised kidney function, was also highly viewed. The use of DOACs in subjects with severe chronic kidney disease (CKD), i.e., hemodialysis patients, was the focus of a meta-analysis by Elfar et al. This contribution is of interest because hemodialysis patients have been excluded from clinical trials on DOACs, and therefore, the evidence of their efficacy and safety is weak in this cohort.

Many contributions to our Research Topic consisted of articles on anticoagulation in frail subjects, including those with cancer, dementia, and increased risk of falling Parsi et al., Liu et al., Zeng et al., Gao et al. These articles are important because they reflect the need for physicians to better understand how to treat frail older adults in real life.

Other contributions that merit mention are the review by Gottsäter, which focused on the rationale for recommendations on dual antiplatelet and anticoagulant treatment in subjects with peripheral artery disease (PAD), the original cross-sectional study by Suo et al. on the evolution of antithrombotic treatments for patients with AF and coronary syndromes in China, and the mini-review by Hardy et al. on the possible importance of DOAC level for an uninterrupted DOAC approach for catheter ablation in AF.

In this Research Topic, there were also contributions on anticoagulation during cardiac surgery. Other contributions were from Wu et al. on the association between the use of anticoagulants and bone fractures, Mirijello et al. on pulmonary artery stump thrombosis, Prouse et al. on the possibility of using the SOFA Score to identify subjects at high risk for VTE among those affected by SARS-CoV-2, Li et al. on a nomogram to predict left atrial thrombus in patients with AF, Liu et al. on the reappraisal of DOACs in AF patients, Lin et al. on the differences in the presentation of arterial thrombotic events between patients with a history of VTE or AF, Liu et al. on intraocular bleeding in patients with AF treated with different anticoagulants, Meihandoest et al. on a heparin-calibrated anti-Xa assay, Liu et al. on the evidence available on DOACs vs. VKA in Latin American patients with AF, Liu et al. on the risk of diabetes in patients with AF treated with DOACs compared to VKA, Cao et al. on anticoagulation in AF patients who have bioprosthetic heart valves, Li ei al. on the clinical characteristics and prognosis of patients with left ventricular thrombus in China, and Gao et al. on the use of sodium alginate hydrogel coatings on extracorporeal membrane oxygenation for anticoagulation.

Author contributions

AT prepared the draft of the Editorial; PP made additions and corrections; RP edited the final draft. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers in Cardiovascular Medicine

SYSTEMATIC REVIEW
published: 22 July 2021
doi: 10.3389/fcvm.2021.713187

Association of Direct Oral Anticoagulants vs. Vitamin K Antagonists With Fractures in Atrial Fibrillation Patients: A Systematic Review and Meta-Analysis

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Background: Current evidence regarding the application of direct oral anticoagulants (DOACs) vs. vitamin K antagonists (VKAs) on the fracture risk is inconsistent. Therefore, we conducted a meta-analysis to evaluate the fracture risk of DOACs vs. VKAs in patients with atrial fibrillation (AF).

Methods: The PubMed and Embase databases were systematically searched until June 2021 for all the studies that reported oral anticoagulants in AF patients. The random-effect model with an inverse variance method was selected to pool the risk ratios (RRs) and 95% confidence intervals (CIs).

Results: A total of 10 studies were included in this meta-analysis. Among AF patients receiving anticoagulants, DOAC users showed a reduced risk of any fracture compared to those with VKAs (RR = 0.80; 95% CI: 0.70–0.91) regardless of gender [males (RR = 0.79; 95% CI: 0.67–0.92) and females (RR = 0.71; 95% CI: 0.57–0.89)]. Apixaban (RR = 0.75; 95% CI: 0.60–0.92) and rivaroxaban (RR = 0.73; 95% CI: 0.61–0.88), but not dabigatran and edoxaban, were associated with a decreased risk of any fracture compared with VKAs. DOAC users had decreased risks of osteoporotic fractures (RR = 0.63; 95% CI: 0.47–0.84) and hip/pelvic fractures (RR = 0.88; 95% CI: 0.79–0.97) compared to those treated with VKAs.

Conclusions: Our meta-analysis suggested that the use of DOACs was associated with a reduced risk of any fracture compared with VKAs. Further studies should confirm our findings.

Keywords: atrial fibrillation, non-vitamin K antagonist oral anticoagulants, warfarin, fracture, meta

OPEN ACCESS

Edited by:
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Reviewed by:
Job Harenberg, Heidelberg University, Germany
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Specialty section:
This article was submitted to Thrombosis, a section of the journal Frontiers in Cardiovascular Medicine

Received: *22 May 2021*
Accepted: *21 June 2021*
Published: *22 July 2021*

Citation:
Wu X, Hu L, Liu J and Gu Q (2021) Association of Direct Oral Anticoagulants vs. Vitamin K Antagonists With Fractures in Atrial Fibrillation Patients: A Systematic Review and Meta-Analysis. Front. Cardiovasc. Med. 8:713187. doi: 10.3389/fcvm.2021.713187

INTRODUCTION

Atrial fibrillation (AF) is becoming an aging-related disease, and osteoporotic fractures are major health threats in the elderly. Oral anticoagulants are widely used for thromboprophylaxis in AF patients for decades. Vitamin K antagonists (VKAs) such as warfarin has been speculated to increase the risk of osteoporotic fracture. Warfarin interrupts the vitamin K-dependent calcium

balance and synergy with vitamin D bone-forming actions. Warfarin inhibits the γ-carboxylation of several osteoblast-specific proteins (1, 2), leading to low bone density and increased fracture risk (3). These observations propose a link between warfarin use and the risk of osteoporotic fractures (4, 5).

Direct oral anticoagulants (DOACs) including thrombin or Xa factor inhibitors (dabigatran, apixaban, rivaroxaban, and edoxaban) are recommended as the first-line drugs for thromboprophylaxis in AF patients. Data from both randomized controlled trials (RCTs) (4–7) and observational studies (8, 9) have shown that DOACs are at least non-inferior to warfarin for stroke prevention in AF patients. Additionally, DOACs might be associated with better outcomes in the elderly (10), as well as AF patients with complications [e.g., stroke (11), cancer, and peripheral artery disease (12)].

Since DOACs have no impact on osteocalcin, their effects on bone fracture have yet been undefined. A prior meta-analysis based on the RCTs (13) showed that DOACs were associated with a relatively lower fracture risk over warfarin in patients with AF or venous thromboembolism. However, there is a lack of consistent evidence regarding this issue in real-world settings. Several real-world studies found that there was no difference in the risk of bone fracture between DOACs and warfarin (14, 15), whereas other studies suggested that DOACs were associated with a lower risk of fracture compared to warfarin (16–18). Therefore, this meta-analysis was performed to compare the risk of fractures between DOACs vs. VKAs in AF patients.

METHODS

The meta-analysis was performed under the recommendations of the Cochrane handbook for systematic reviews (19) and the Preferred Reporting Items for Reporting Systematic Reviews and Meta-analyses (20). The data of the current study are available from the corresponding author on reasonable requests. We did not provide ethical approval because only the published data were included.

Eligibility Criteria

In this study, the following inclusion criteria were applied: (1) population (P)-nonvalvular AF patients; (2) intervention (I) and control (C)-DOACs vs. VKAs; (3) outcome (O)-bone fractures including any fracture, major osteoporotic fractures, vertebral, and humerus/forearm/wrist fractures and hip/pelvic fractures; and (4) study design-RCTs or observational studies. The effect estimates were propensity score-matched or adjusted risk ratios (RRs) and 95% confidence intervals (CIs). Studies with no data, such as reviews, case reports, case series, editorials, guidelines, and conference abstracts, were excluded.

Literature Search

The PubMed and Embase electronic databases were systematically searched from January 2009 (since the first available DOAC-dabigatran was applied to AF patients) to June 2021 for studies that compared the risk of any fracture between DOACs vs. VKAs in AF patients. The search strategy combined three kinds of search terms using the Boolean operator "and": (1) *atrial fibrillation* OR *atrial flutter*, AND (2) *non-vitamin K antagonist oral anticoagulants* OR *NOACs* OR *direct oral anticoagulants* OR *DOACs* OR *dabigatran* OR *rivaroxaban* OR *apixaban* OR *edoxaban*, AND (3) *vitamin K antagonists OR warfarin OR coumadin OR phenprocoumon OR acenocoumarol*, AND (4) *fracture* OR *bone fracture* OR *osteoporosis* OR *osteoporosis fracture*. There were no linguistic restrictions in the literature search. The literature search strategy is shown in **Supplementary Table 1**. To ensure a comprehensive literature search, the reference lists of the retrieved studies were screened to identify the additional reports.

Study Selection and Data Extraction

All the retrieved studies were screened by two reviewers independently. Potential eligible studies were chosen after reviewing the titles and abstracts based on the established inclusion and exclusion criteria. The disputable issues were resolved by consensus, or by a discussion with the third author.

The following information was collected including the first author and publication year, country, data source, study design, baseline data of the participants (sample size, age, and the sex), inclusion period, type of DOACs, the follow-up time of DOAC users, and type of fractures.

Risk of Bias Assessment

For the *post-hoc* analysis of RCTs, the bias risks were evaluated according to the Cochrane risk of bias assessment tool (19). The bias risk of each study was scored as "low," "unclear," or "high" risk in each section. The "low risk" was defined when three out of five biases were "low" (21). The Newcastle-Ottawa Scale (NOS) tool was applied to evaluate the methodological quality of observational studies. A study with a NOS score of <6 was defined as low quality (22).

Statistical Analysis

In this meta-analysis, we performed all the statistical analyses using the Stata software (version 15.0, Stata Corp LP, College Station, TX) and the Review Manager 5.3 software (the Nordic Cochrane Center, Rigshospitalet, Denmark). The Cochrane Q test and I^2 statistic were the most commonly reported statistical methods to assess the heterogeneity, where $P < 0.1$ and $I^2 > 50\%$ suggested substantial heterogeneity, respectively. The natural logarithms of RRs and standard errors of the included studies were calculated and then pooled by a random-effects model using an inverse variance method. The publication bias was assessed using the funnel plots, and further calculated using the Egger's and Begg's tests. The subgroup analyses were performed based on the DOAC types (dabigatran, apixaban, rivaroxaban, and edoxaban), the individual position of fractures (hip/pelvic fracture and osteoporosis fracture), gender (males vs. females), and length of the follow-up period (≥1 vs. <1 year).

RESULTS

Study Selection

The process for electronic retrievals is shown in **Supplementary Figure 1**. A total of 10 studies [one sub-analysis

TABLE 1 | Baseline characteristics of the included studies of this study.

Included studies	Country	Study design	Number of participants	Age (y) /Male (%)	Study period	Data source	DOACs	Follow-up in DOAC users (months)	Controls	Outcomes	Quality assessment*
He-2020	Québec Canada	Observational study	25,663	75.6/50.3	2000–2014	Québec healthcare databases	DA; RIV; API	NA	VKAs	Any fracure,hip fracture, upper extremity fracture, vertebral fracture, Osteoporosis with pathological fracture	8
Lau-2020	Hong Kong China	Observational study	23,515	74.4/52.0	2010–2017	Clinical data analysis and reporting system	DA; RIV; API	14.1	warfarin	Osteoporotic fracture	8
Huang-2020	Taiwan China	Observational study	19,414	71.9/59.0	2012–2017	Taiwan's national health insurance research database	DA; RIV; API	28.8	warfarin	Hip, vertebral, and humerus/forearm/wrist fractures	8
Binding-2019	Danish	Observational study	37,350	NA/57.8	2013–2017	Danish national patient register	DOACs	24.0	warfarin	any fracture, major osteoporotic fractures, initiating osteoporotic medication, hip fractures	8
Lutsey-2019	United States	Observational study	167,275	68.9/62	2010–2015	MarketScan commercial claims and encounters and marketscan Medicare Supplemental and Coordination of Benefitsdatabases	DA; RIV; API	16.9	warfarin	Hip fractures, Inpatient fractures, All fractures	8
Chan YH-2019	Taiwan China	Observational study	24,338	74.6/56.8	2012–2017	National health insurance research database	EDO	>12.0	warfarin	Any fracture	8
Norby-2017	United States	Observational study	77,991	70.3/60.5	2010–2014	The truven health marketscan® commercial claims and encounters database and the medicare supplemental and coordination of benefits database	RIV	12.0	warfarin	Hip/pelvic fracture	8
Lucenteforte-2017	Denmark	Observational study	16,850	NA/51.1	2009–2015	Danish national prescription registry	DA	12.6	warfarin	Any fracture	8
Bengtson-2017	United States	Observational study	61,648	70.1/63.3	2009–2012	The truven health marketscan® commercial claims and encounters database and the medicare supplemental and coordination of benefits database	DA	15.0	warfarin	Hip/pelvic fracture	8
Steffel-2016	United States	*Post-hoc* analysis	20,205	72.0/62.4	NA	ENGAGE AF-TIMI 48 trial	EDO	NA	warfarin	Any fracture	Low risk

ENGAGE AF-TIMI 48, effective anticoagulation with factor xa next generation in atrial fibrillation-thrombolysis in myocardial infarction 48; DOACs, direct oral anticoagulants; DA, dabigatran; RIV, rivaroxaban; API, apixaban; EDO, edoxaban; VKAs, vitamin K antagonists; NOS, newcastle-ottawa scale; NA, not available.

*****The Newcastle-Ottawa Scale (NOS) items were used to evaluate the quality of the observational studies, which involve the selection of cohorts, the comparability of cohorts, and the assessment of the outcome).*

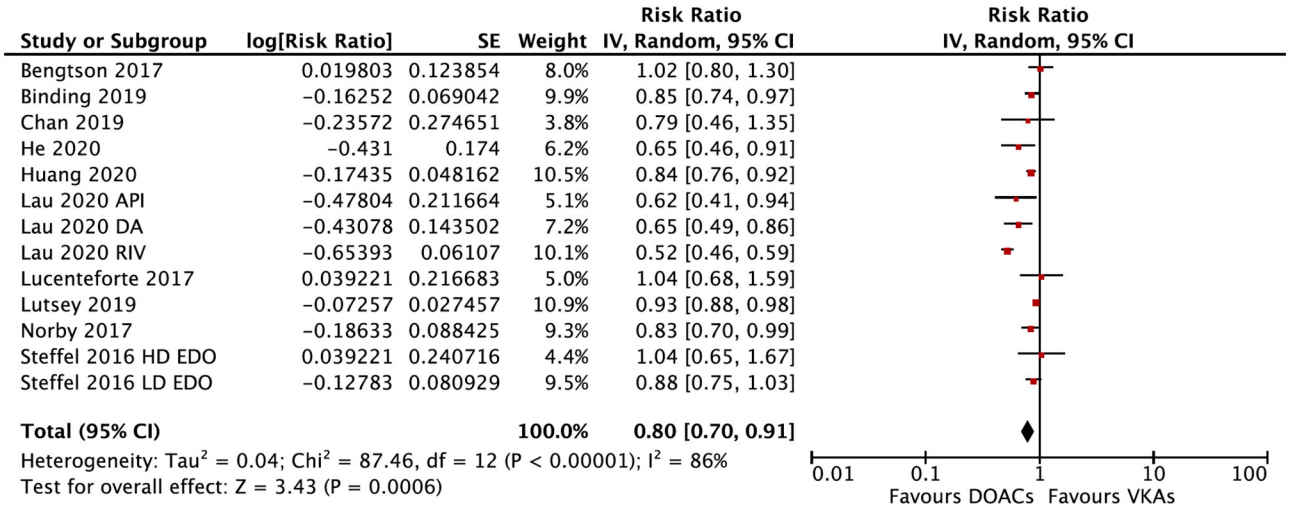

FIGURE 1 | Comparing the risk of any fracture of DOACs vs. VKAs in AF patients. AF, atrial fibrillation; DOACs, direct oral anticoagulants; VKAs, vitamin K antagonists; DA, dabigatran; RIV, rivaroxaban; API, apixaban; EDO, edoxaban; CI, confidence interval; HD, high dose; LD, low dose; SE, standard error; IV, inverse of the variance.

of RCT (23) and nine observational studies (14–17, 24–28)] were included in this meta-analysis. To show the reliability of all the included studies, baseline information of the study participants is shown in **Table 1**. Six studies (15–17, 25–27) had a follow-up time of ≥1 year, 2 studies (14, 24) showed a follow-up time of <1 year, and two studies did not provide the specific follow-up time (23, 28).

We did the quality assessment and found that the sub-analysis of RCT (23) had a low risk of bias, and all of the included observational studies (14–17, 24–28) had an acceptable quality.

DOACs vs. VKAs on the Risk of Fracture

The overall RRs and 95% CIs of fracture risks between DOACs vs. VKAs in AF patients are summarized in **Supplementary Table 2**. In the pooled analysis, compared with VKA use, the use of DOACs was associated with a decreased risk of any fracture (HR = 0.80, 95% CI 0.70–0.91) (**Figure 1**).

In the subgroup analysis based on the DOAC types, compared with VKAs, rivaroxaban (RR = 0.73; 95% CI: 0.61–0.88) and apixaban (RR = 0.75; 95% CI: 0.60–0.92), but not dabigatran (RR = 0.90; 95% CI: 0.80–1.01) and edoxaban (RR = 0.89; 95% CI: 0.77–1.03), were associated with a lower risk of any fracture (**Figure 2**). Compared with VKAs, the usage of DOACs acquired a lower risk of hip/pelvic fracture (RR = 0.88; 95% CI: 0.79–0.97) and osteoporosis fracture (RR = 0.63; 95% CI: 0.47–0.84) (**Figure 3**).

The subgroup analysis based on gender suggested that DOACs were associated with a lower risk of fractures in both males (RR = 0.79; 95% CI: 0.67–0.92) and females (RR: 0.71; 95% CI: 0.57–0.89) compared with VKAs ($P_{interation}$ = 0.48; **Figure 4**). DOACs vs. VKAs were associated with a decreased risk of any fracture in patients with a follow-up of ≥1 year (RR = 0.76, 95% CI 0.63–0.91), but not in the group of <1 year (RR, 0.73, 95% CI 0.48–1.10), although the interaction was not significant between the two subgroups ($P_{interaction}$ = 0.84; **Figure 5**).

Publication Bias

No potential publication biases were found checked by the funnel plots (**Supplementary Figure 2**) combined with the Egger's (P = 0.479, **Supplementary Figure 3**) and Begg's (p = 0.837) tests.

DISCUSSION

In the present meta-analysis, compared with VKAs, the use of DOACs (mainly rivaroxaban and apixaban) was associated with a lower fracture risk among long-term AF patients. There was no significant different interaction between male and female patients. Overall, DOACs might be a safe alternative among AF patients in terms of decreasing the fracture risks compared with VKAs regardless of gender.

The potential increased risk of fracture with warfarin is coherent with the mechanism of anticoagulation. By regulating vitamin K, warfarin inhibits the γ-carboxylation of osteocalcin, which is associated with a low bone mineral density. Two prior meta-analyses assessed the risk of fracture associated with DOACs compared with VKAs (13, 29). One meta-analysis comprising 89,549 patients of 12 RCTs demonstrated that rivaroxaban and apixaban showed a lower fracture risk when compared to warfarin (13), consistent with our current findings. An *in vivo* study indicated that dabigatran has a better bone safety profile than warfarin because warfarin could interrupt bone by reducing the trabecular size and increasing bone turnover (30). Nevertheless, dabigatran has non-inferiority or superiority to warfarin in terms of reducing the fracture risk in the real-world population. Lutsey et al. found that the estimates between dabigatran and warfarin were near the null for hip and all clinical fractures (17). They only found some evidence of a lower risk of fractures requiring hospitalization associated with dabigatran (17). Lucenteforte et al. also presented no significant

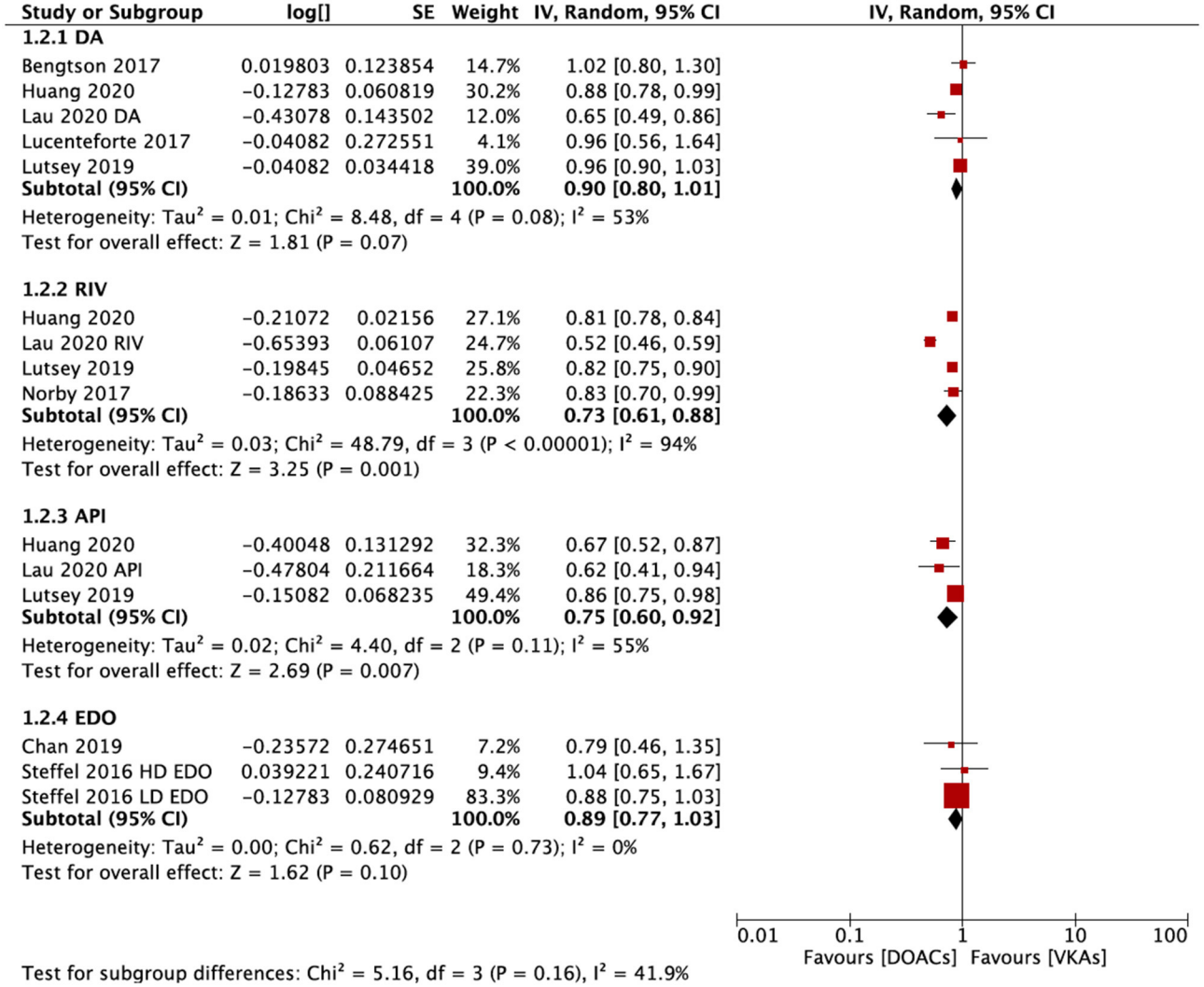

FIGURE 2 | Subgroup analysis based on different types of DOACs regarding the risk of fractures of DOACs vs. VKAs in AF patients. AF, atrial fibrillation; DOACs, direct oral anticoagulants; VKAs, vitamin K antagonists; DA, dabigatran; RIV, rivaroxaban; API, apixaban; EDO, edoxaban; CI, confidence interval; SE, standard error; IV, inverse of the variance.

difference in the fracture risk between dabigatran with warfarin (25). In contrast, a retrospective cohort study published in 2020 reported a significantly lower risk of osteoporotic fractures associated with the use of dabigatran among AF patients (26). One potential explanation for the discrepancies across the studies may be the different definitions of fracture and the duration of oral anticoagulants. The biological effect of warfarin on bone metabolism is cumulative and chronic. Lucenteforte et al. restricted cohort eligibility to patients who had been continuously exposed to oral anticoagulants within 1 year, which might lead to an underestimation of fracture risk in warfarin users (25).

Edoxaban has no effects on the production of Gla-osteocalcin; and thus may have a lower risk of adverse effects on bone health in the rats (31). Although there are still no experiments on humans, evidence of the fracture risk with edoxaban use is limited. A *post-hoc* analysis from the ENGAGE AF-TIMI 48 trial showed that edoxaban has a comparable risk of fracture with warfarin irrespective of the dosage (23). Given the limited number of edoxaban-associated studies included in the meta-analysis, further study should confirm the fracture risk of edoxaban vs. warfarin in AF patients.

In the current meta-analysis, DOACs were showed a decreased risk of overall fracture events comparing with VKAs. Particularly, rivaroxaban and apixaban are showed reduced risks of fracture events. Although Lau et al. (26) did comparisons between dabigatran and rivaroxaban regarding the osteoporotic fractures risk in AF patients, no significant difference was detected. Lutsey et al. (17) yielded no statistically significant differences in the incidence of fracture between DOAC and DOAC among patients with AF. Further studies should confirm

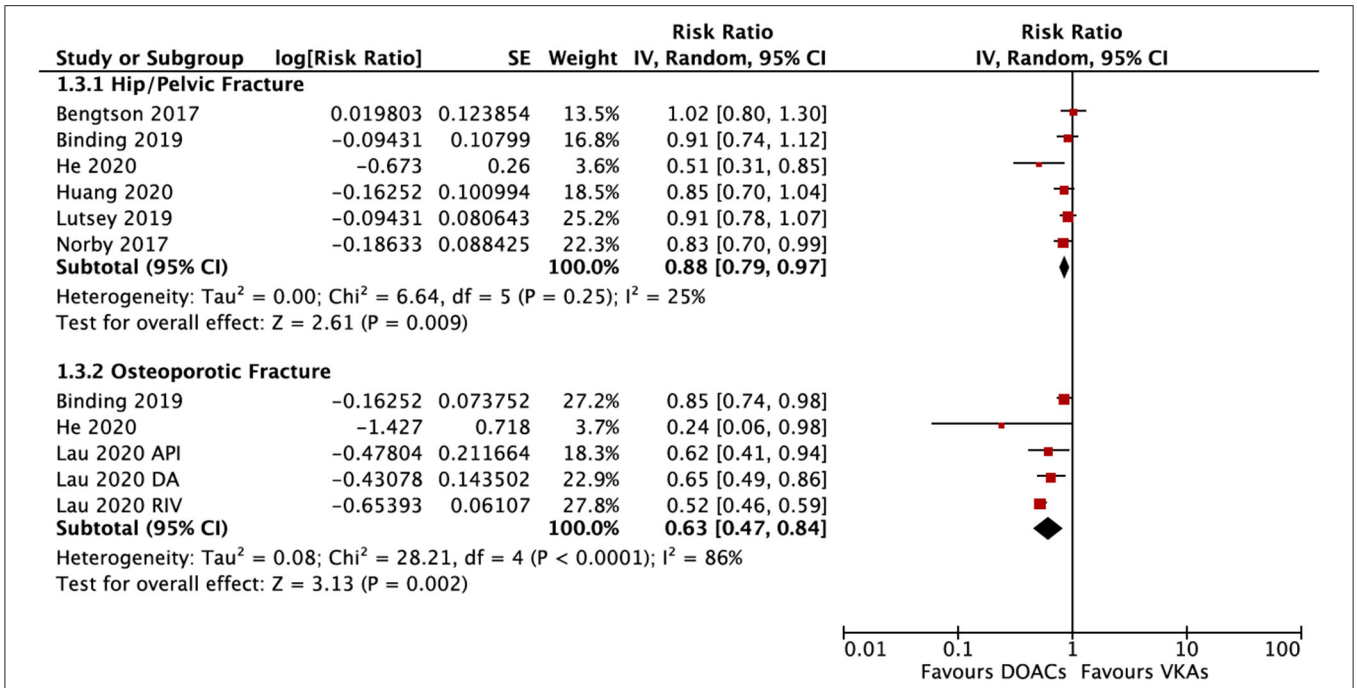

FIGURE 3 | Subgroup analysis based on different positions regarding the risk of fractures of DOACs vs. VKAs in AF patients. AF, atrial fibrillation; DOACs, direct oral anticoagulants; VKAs, vitamin K antagonists; DA, dabigatran; RIV, rivaroxaban; API, apixaban; CI, confidence interval; SE, standard error; IV, inverse of the variance.

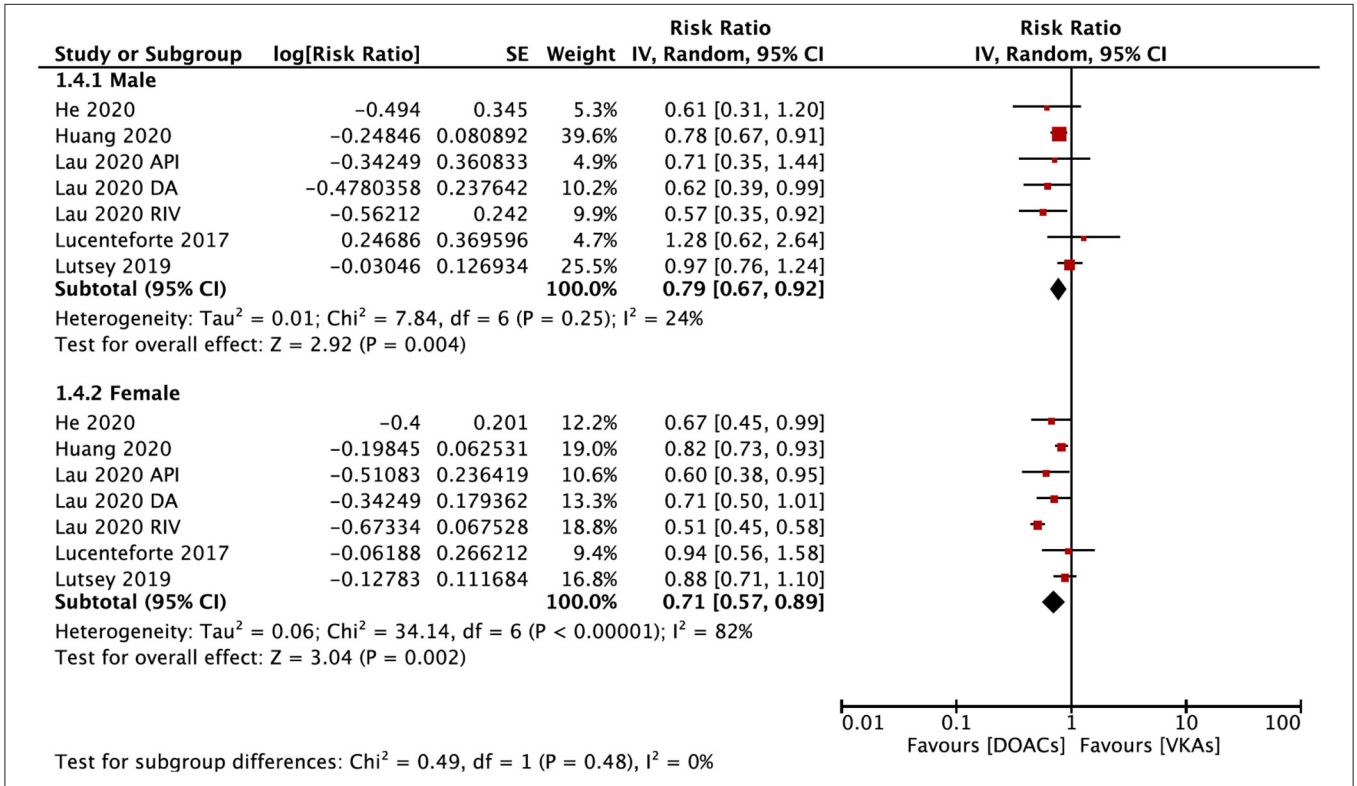

FIGURE 4 | Subgroup analysis based on sex regarding the risk of fractures of DOACs vs. VKAs in AF patients. AF, atrial fibrillation; DOACs, direct oral anticoagulants; VKAs, vitamin K antagonists; DA, dabigatran; RIV, rivaroxaban; API, apixaban; CI, confidence interval; SE, standard error; IV, inverse of the variance.

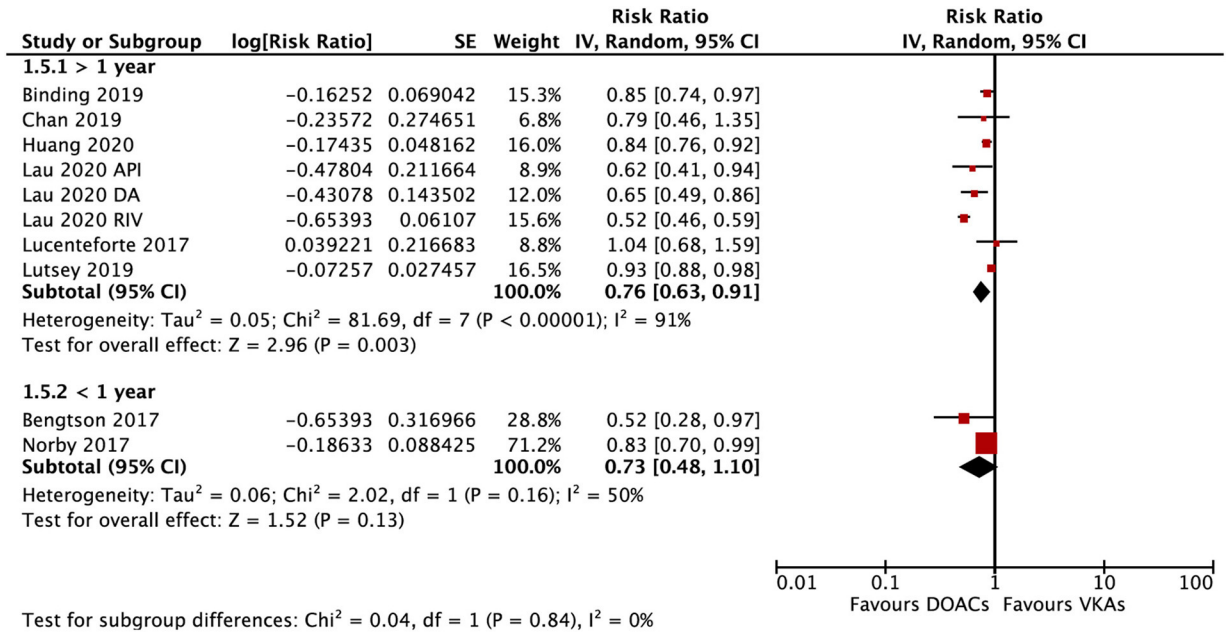

FIGURE 5 | Subgroup analysis based on the follow-up time regarding the risk of fractures of DOACs vs. VKAs in AF patients. AF, atrial fibrillation; DOACs, direct oral anticoagulants; DA, dabigatran; RIV, rivaroxaban; API, apixaban; CI, confidence interval; SE, standard error; IV, inverse of the variance.

the association of DOAC with another DOAC in the risk of fracture.

The incidence of fracture position is an important factor that should be taken into consideration. Loss of bone quality due to aging and high incidence of osteoporotic fractures (especially hip and vertebral fractures) are the major threats to the elderly, causing significant morbidity, mortality, as well as high socioeconomic burdens (32, 33). AF itself is a risk factor for osteoporotic fractures. Overlapped risk factors such as older age, diabetes mellitus, and stroke are often shared by AF and osteoporotic fractures in patients, and they are also the risk factors for stroke (18). Thus, AF patients who take anticoagulants should be considered to be vulnerable to fractures. Our data suggested that DOACs usage is associated with a reduced incidence of overall fracture events. In addition, the benefits were also confirmed after patients were classified by the types of hip/pelvic fracture and the osteoporosis fracture rates, consistent with the results of the previous studies (24, 27).

Limitations

We acknowledged that there are some limitations of this study. First, although we only included studies with the propensity score-matched or adjusted RRs, the quality of our meta-analysis was inherently limited because the potential unmeasured residual confounders would still exist due to the nature of real-world data. The high heterogeneity in this study might affect the reliability of findings, and further prospective studies should confirm our results. Second, only one study (23) provided the time within the therapeutic range value of warfarin users, which would underestimate the efficacy of warfarin. Third, the evaluation was limited to the AF patients treated with anticoagulants due to the limited data regarding patients with deep vein thrombosis or pulmonary vein thrombosis. Fourth, the age-related classifications of participants were also should be analyzed in this item's identification in further studies. Finally, due to the limited data of comparisons between DOAC vs. DOAC, we could not provide a choice of prescribing the most populated DOACs to AF patients especially those who are at a high risk of fractures.

CONCLUSION

Our meta-analysis suggested that the use of DOACs was associated with a reduced risk of any fracture compared with VKAs. Further prospective studies should confirm these findings.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.713187/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cardiovascular Medicine

REVIEW
published: 03 August 2021
doi: 10.3389/fcvm.2021.715878

Use of Direct Oral Anticoagulants in Patients With Antiphospholipid Syndrome: A Systematic Review and Comparison of the International Guidelines

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OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Thrombosis, a section of the journal Frontiers in Cardiovascular Medicine

Received: *27 May 2021*
Accepted: *09 July 2021*
Published: *03 August 2021*

Citation:
Pastori D, Menichelli D, Cammisotto V and Pignatelli P (2021) Use of Direct Oral Anticoagulants in Patients With Antiphospholipid Syndrome: A Systematic Review and Comparison of the International Guidelines. Front. Cardiovasc. Med. 8:715878. doi: 10.3389/fcvm.2021.715878

Antiphospholipid antibody syndrome (APS) requires long-term anticoagulation to prevent recurrent thrombosis. Direct oral anticoagulants (DOACs) have been increasingly used in APS patients, but contradictory guidelines recommendations on their use do exist. We performed a systematic review of literature including studies investigating the role of DOACs in APS patients. At this aim, PubMed and Cochrane databases were searched according to PRISMA guidelines. We identified 14 studies which investigated the use of DOACs in patients with APS, of which 3 randomized clinical trials (RCTs), 1 *post-hoc* analysis of 3 RCTs, 7 case series and 3 cohort studies (2 prospective and 1 retrospective). Among DOACs, rivaroxaban was the most used ($n = 531$), followed by dabigatran ($n = 90$) and apixaban ($n = 46$). Regarding guidelines indications, the 2019 European Society of Cardiology (ESC) and American Society of Hematology (ASH) guidelines recommend against the use of DOACs in all APS patients. The European League Against Rheumatism (EULAR), British Society for Haematology (BSH), and International Society on Thrombosis and Haemostasis (ISTH) guidance provided more detailed indications stating that warfarin should be the first-choice treatment but DOACs may be considered in patients (1) already on a stable anticoagulation with a DOAC, (2) with low-quality anticoagulation by warfarin, (3) unwilling/unable to undergo INR monitoring, (4) with contraindications or serious adverse events under warfarin. Patients with arterial APS or triple positivity should be treated with warfarin while venous APS with single or double positivity may be candidate to DOACs, but high-quality studies are needed.

Keywords: vitamin K antagonists, direct oral anticoagulants, antiphospholipid antibody syndrome, guideline, anticoagulants

INTRODUCTION

The incidence and prevalence of antiphospholipid antibody syndrome (APS) are difficult to estimate given that the definition of APS has evolved over the years making epidemiological studies published before 2000 not adhering to the new classification criteria (1). However, a large recent study estimated an incidence of APS of 2.1 per 100,000 per year and a prevalence of 50 per 100,000 inhabitants (2).

APS is an autoimmune disease characterized by the production of auto-antibodies directed against various phospholipids. APS is diagnosed in case of persistent positivity of anticardiolipin (aCL), anti-β2 glycoprotein I (β2GPI), and lupus anticoagulant (LAC) assays, which also play a pathogenic role in determining the risk of thrombotic events (3). However, the persistent positivity to antiphospholipid antibodies (aPL) is not sufficient alone to define APS, which should be accompanied by clinical thrombotic event in the venous and arterial circulation or by obstetrical complications (4). Other non-criteria clinical manifestations in patients with APS include thrombocytopenia, which seems to have a negative prognostic role (5), neurological manifestations (6), and livedo reticularis (7), suggesting that clinical presentation may be heterogeneous and signs/symptoms are not limited to thrombosis.

Thrombotic manifestations are mainly related to the fact that aPL may directly contribute to thrombus formation and platelet activation (**Figure 1**). Indeed, an increased risk of myocardial infarction (8), ischemic stroke, and peripheral artery disease (9) and neurological disorders in this patient population has been described. After a first thrombotic event, the risk of recurrences sharply increases by 10–67% (10). The thrombotic risk seems to be influenced by the clinical and immunological characteristics of patients with triple positive aPL patients having the highest thrombotic risk, estimated at 5.3% per year (11, 12). However, the thrombotic potential of non-criteria aPL and the value of isolated IgM/LAC is still under investigation (13–15). Furthermore, a significant proportion of patients present a negativization of aPL during follow-up, but it is unclear if it parallels a reduction of thrombotic risk (16).

To reduce the risk of first and recurrent thrombotic events patients with APS require anti-thrombotic treatment. A meta-analysis showed that aspirin administration reduced the risk of first arterial (HR: 0.43, 95%CI 0.20–0.93) but not venous thrombotic event in APS carriers (17). However, after a first thrombotic event, APS patients require long-term treatment with oral anticoagulants. For decades, vitamin K antagonists (VKAs) have represented the only available oral anticoagulant drug. However, some issues regarding the use of VKAs in patients with APS have become evident over time, including the so-called warfarin resistance [i.e., patients needing high weekly amount of VKAs to obtain and maintain therapeutic INR; (18)] and an unstable anticoagulation quality (19). In addition, a significant proportion of patients experience recurrent thrombotic events despite adequate anticoagulation (20), with high-intensity VKA therapy not being superior of standard care in reducing these recurrences (21). Moreover, the addition of aspirin to oral anticoagulation in recurrent arterial APS is still under debate given the lack of clear benefit (22). Finally, adherence to VKA treatment was shown to be progressively reduced over time in different clinical settings (23), with cessation of oral anticoagulation being associated with an increased risk of recurrent thrombotic events in APS (24, 25). For these reasons, adequate anticoagulation therapy still represents a clinical challenge in APS patients.

In the last decade, the direct oral anticoagulants (DOACs) have been increasingly used for the treatment of venous thromboembolism (VTE) and for the thromboprophylaxis of patients with atrial fibrillation. The main advantages of DOACs are the predictable anticoagulant effect, the fixed dose and the rapid onset and offset of action. More recently, the use of DOACs has been tested also in patients with APS with divergent results (26). Aim of this review is to summarize current evidence on the safety and efficacy of DOACs in APS and to compare recommendations provided by international scientific societies.

STUDIES INVESTIGATING SAFETY AND EFFICACY OF DOACS IN APS PATIENTS

Information Sources and Search Strategy

We performed a systematic review of literature including studies investigating the role of DOACs in APS patients. At this aim, PubMed and Cochrane databases were searched according to PRISMA guidelines. We included only clinical studies (both observational and randomized clinical trials) involving humans and in English language. Articles with no full text available were also excluded as well as review, commentary, and letters. We used a combination of "antiphospholipid syndrome" and "direct oral anticoagulants" or "apixaban," "dabigatran," "edoxaban," "rivaroxaban." No time restrictions were applied (last search performed on 27 Jun 2021). The use of "non-vitamin K oral anticoagulants" provided no additional results. Only one study from the same cohort was considered. Case series including <5 patients were excluded.

Data Collection Process and Data Items

Two physicians (DP and PM) independently screened the titles and abstracts of the manuscripts identified through the database searches to identify studies potentially eligible for further assessment. For each study, we collected the following information: Author (year), study design, follow up (months), triple positivity (%), study sample, type of anticoagulant studied, women (%), age (mean), index event for APS diagnosis, any safety endpoint, any efficacy endpoint.

Quality Assessment

Quality of included studies was assessed using the National Institutes of Health (NIH) Tools (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) according to each study type (**Table 1**): (1) Quality Assessment of Controlled Intervention Studies; (2) Quality Assessment of Controlled Intervention Studies; (3) Quality Assessment Tool for Case Series Studies; (4) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

Study Characteristics and Quality Evaluation

Strategy search and reasons for exclusion are reported in **Figure 2**. **Table 2** reports clinical studies on the safety and efficacy of DOACs in APS patients. We identified 14 studies which investigated the use of DOACs in patients with APS, of which 3 randomized clinical trials (RCTs), 1 *post-hoc* analysis of 3 RCTs, 7 case series and 3 cohort studies (2 prospective and 1 retrospective) (**Table 2**). Quality evaluation

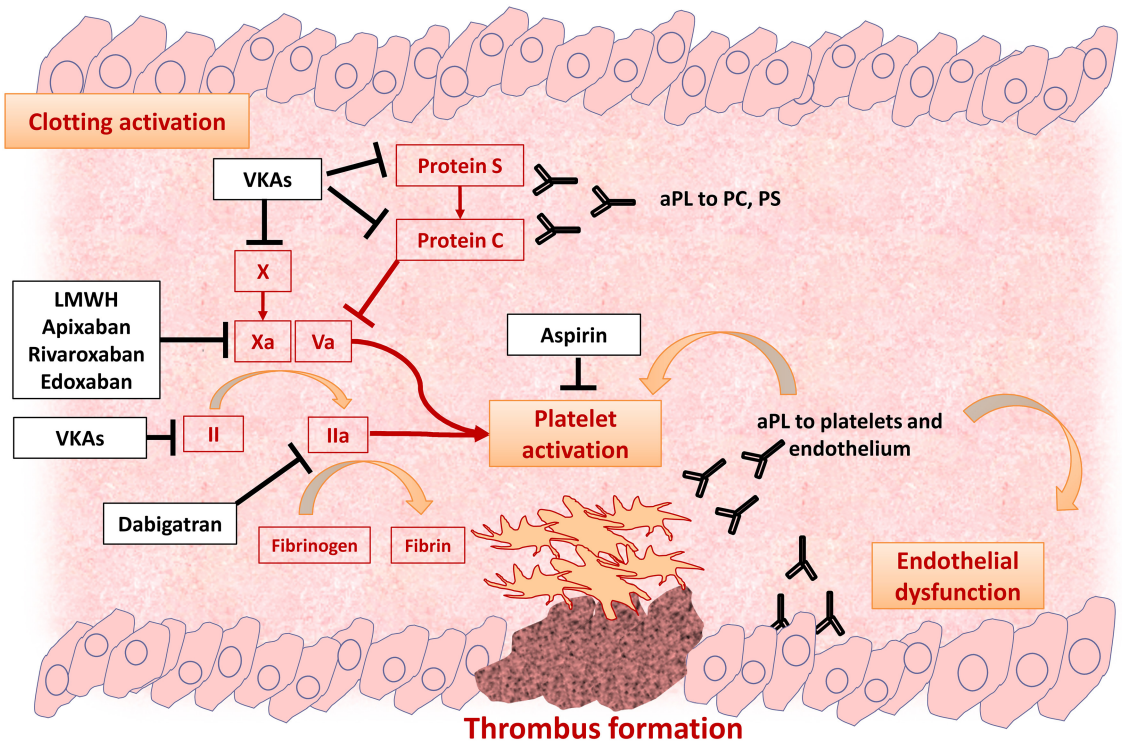

FIGURE 1 | Pathophysiology of thrombotic events in patients with antiphospholipid syndrome.

showed that the quality of RCT and *post-hoc* of RCT ranged from 8/14 to 10/14 mainly due to lack of blindness in treatment allocation, that is however, intrinsic in this type of studies comparing a dose-adjusted to a fixed-dose treatment (**Table 1**). The quality of case series was generally 4–5/9 with only two studies scoring 6/9 (31) and 7/9 (39) (**Table 1**). These results are essentially due to a poor description of statistical methods (some of these series were published in form of brief report or letter) and lack of consecutive recruitment of patients (**Table 1**).

Regarding the 3 cohort studies, they generally lacked a formal sample size justification, blind adjudication of event, exposure assessment only at baseline and did not report the rate of patients lost during follow-up (**Table 1**).

Women represented the majority of patients among the studies, and the mean age of the population range between 39.1 and 53.4 years. Clinical events for the initiation of anticoagulation were mainly represented by venous thromboembolism, but two RCTs included both arterial and venous thrombosis as clinical index event. Two studies included also patients with obstetrical APS (34, 35), however, DOACs are not recommended in obstetrical APS and in lactating women, as they have a variable excretion rate in human milk and data on their safety are still lacking (41).

Among DOACs, rivaroxaban was the most represented with 531 treated patients, followed by dabigatran with 90 patients and apixaban with 46 patients. All RCTs (28–30) compared rivaroxaban with VKAs, while a *post-hoc* analysis of RE-MEDY and RE-COVER trials compared dabigatran with VKAs (27).

Clinical Outcomes

The follow-up ranged from 7 to 5 years (**Table 2**). The efficacy endpoints were the recurrence of VTE or a composite of arterial and venous thrombosis; safety endpoints were major or clinically relevant bleedings.

In two RCTs (29, 30) rivaroxaban was associated with an increased risk of thrombotic events without an increased risk of bleeding. Of note, these studies included APS patients with both arterial and venous thrombotic events and a high proportion of patients with triple positivity.

The only study which showed an increased risk of bleeding included mostly APS women (>80%) with a high rate of heavy menstrual bleeding (HMB); while, no differences between two groups were reported regarding major, gastrointestinal or clinical relevant non-major bleeding (CRNMB) (32).

A *post-hoc* analysis of RE-MEDY and RE-COVER which compared dabigatran to VKAs (27) in patients with inherited disorders of whom APS represented the second most common

TABLE 1 | Quality assessment for included studies.

Items	RE-COVER(R), RE-COVER II, RE-MEDY (2016)* Goldhaber et al. (27)	RAPS (2016)* Cohen et al. (28)	TRAPS (2018)* Pengo et al. (29)	Ordi-Ros et al. (30)*	Malec et al. (31)**	Malec et al. (32)***	Legault et al. (33)***
1	Y	Y	Y	Y	Y	Y	Y
2	Y	Y	Y	Y	Y	Y	Y
3	NR	N	N	N	Y	NR	Y
4	N	N	N	N	N	Y	Y
5	N	N	N	N	Y	N	Y
6	Y	Y	N	N	Y	Y	Y
7	NR	Y	Y	N	Y	Y	Y
8	NR	Y	Y	Y	N	CD	CD
9	CD	CD	CD	CD	N	Y	Y
10	Y	Y	Y	Y	–	N	N
11	Y	Y	Y	Y	–	Y	Y
12	Y	Y	Y	Y	–	N	N
13	Y	Y	Y	Y	–	NR	Y
14	Y	Y	Y	Y	–	N	N
Total	8/14	10/14	9/14	8/14	6/9	7/14	10/14
Items	**Betancur et al. (34)****	**Haladyj and Olesinska (35)****	**Son et al. (36)****	**Sciascia et al. (37)****	**Noel et al. (38)****	**Resseguier et al. (39)****	**Sato et al. (40)*****
1	N	Y	N	Y	Y	Y	Y
2	Y	Y	N	Y	N	Y	Y
3	N	N	Y	N	N	N	NR
4	Y	Y	Y	Y	Y	Y	Y
5	Y	Y	Y	Y	Y	N	N
6	N	N	N	N	Y	Y	N
7	Y	Y	Y	N	Y	Y	Y
8	N	N	N	N	N	Y	CD
9	Y	N	N	N	N	Y	Y
10	–	–	–	–	–	–	N
11	–	–	–	–	–	–	Y
12	–	–	–	–	–	–	N
13	–	–	–	–	–	–	NR
14	–	–	–	–	–	–	Y
Total	5/9	5/9	4/9	4/9	5/9	7/9	7/14

**Quality Assessment of Controlled Intervention Studies. (1) Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT? (2) Was the method of randomization adequate (i.e., use of randomly generated assignment)? (3) Was the treatment allocation concealed (so that assignments could not be predicted)? (4) Were study participants and providers blinded to treatment group assignment? (5) Were the people assessing the outcomes blinded to the participants' group assignments? (6) Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)? (7) Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment? (8) Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower? (9) Was there high adherence to the intervention protocols for each treatment group? (10) Were other interventions avoided or similar in the groups (e.g., similar background treatments)? (11) Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants? (12) Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power? (13) Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)? (14) Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?*

***Quality Assessment Tool for Case Series Studies. (1) Was the study question or objective clearly stated? (2) Was the study population clearly and fully described, including a case definition? (3) Were the cases consecutive? (4) Were the subjects comparable? (5) Was the intervention clearly described? (6) Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants? (7) Was the length of follow-up adequate? (8) Were the statistical methods well-described? (9) Were the results well-described?*

****Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. (1) Was the research question or objective in this paper clearly stated? (2) Was the study population clearly specified and defined? (3) Was the participation rate of eligible persons at least 50%? (4) Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? (5) Was a sample size justification, power description, or variance and effect estimates provided? (6) For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? (7) Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? (8) For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? (9) Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? (10) Was the exposure(s) assessed more than once over time? (11) Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? (12) Were the outcome assessors blinded to the exposure status of participants? (13) Was loss to follow-up after baseline 20% or less? (14) Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?*

CD, cannot be determined; NA, not applicable; NR, not reported; N, no; Y, yes.

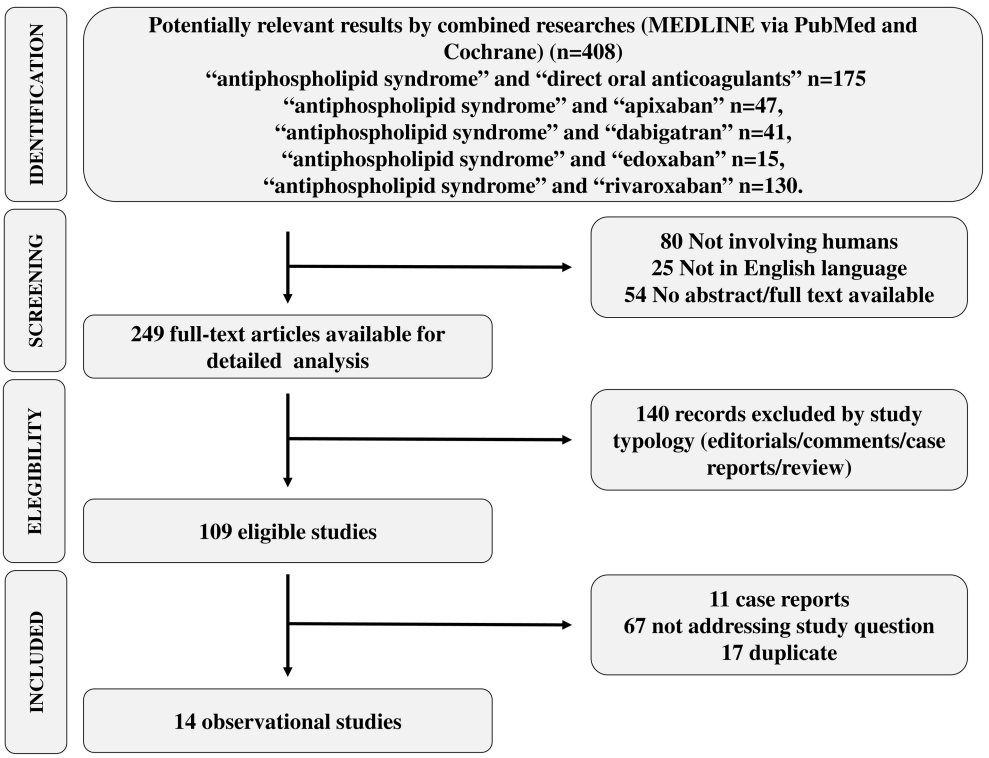

FIGURE 2 | PRISMA flow chart.

thrombophilia accounting for 20% of all patients (27), and a RCT (28), which compared rivaroxaban and VKAs showed similar safety and efficacy profiles between DOACs and VKAs (**Table 2**).

GUIDELINES RECOMMENDATIONS/CONSENSUS SUGGESTIONS

Based on the above discussed studies, different international thrombosis and cardiology societies provided discordant recommendations on the use of DOACs in patients with APS.

The grading system used to provide the level of evidence differed among guidelines and are reported in the footnote of the **Table 3**.

The 2019 European Society of Cardiology (ESC) guidelines recommend against the use of DOACs in APS patients, with no distinction among different DOACs, or between venous and arterial APS or among single, double or triple positive patients (**Table 3**). This recommendation seems however, to be based only on the results of the Trial on Rivaroxaban in AntiPhospholipid Syndrome (TRAPS) trial (29), which included triple positive thrombotic APS patients with both previous venous and arterial events, randomized to receive Rivaroxaban or conventional treatment. However, it should be noted that treatment of arterial events is not an indication to DOAC treatment. No mention is therefore given in case of venous or single/double positive APS patients. The results of this trial using Rivaroxaban were applied to all other DOACs.

Similarly, in the 2020 International Society on Thrombosis and Haemostasis (ISTH) guidance (46), DOACs are not considered as a valid option for any APS patient, with the only possibility of continuing DOAC in stable low-risk patients already on treatment, after shared informed discussion.

A more detailed indication on the use of DOACs is provided by the 2019 European League Against Rheumatism (EULAR) guidelines (47), which have taken into consideration the clinical phenotype of APS patients based on the presence of a venous or arterial event as indication to anticoagulation (**Table 3**). Thus, while DOACs and in particular Rivaroxaban, are contraindicated in APS patients with triple aPL positivity and/or an arterial event, its use may be considered in venous APS patients without triple aPL positivity (47). Another important difference between ESC and EULAR guidelines is that the latter consider the possibility that patients on VKAs may have low-quality therapy (i.e., low time in therapeutic range, TiTR) or may be intolerant to VKA treatment. In these cases, the use of DOACs may be considered (47).

A similar approach has been proposed by the 2020 British Society of Haematology (BSH) Guidelines, which suggest against the use of DOACs in arterial APS patients. In venous APS patients both triple and non-triple who are already on treatment

TABLE 2 | Characteristics of studies enrolling patients with APS treated with DOACs.

Author (year)	Design	Follow up (months)	Triple positive (%)	Study sample	Anticoagulant	Women (%)	Age (mean)	Index event	Safety endpoint	Efficacy endpoint
RE-COVER(R), RE-COVER II, RE-MEDY (2016) (27)	*Post-hoc* RCTs	NR	NR	151	Dabigatran: 71 VKA: 80	36.4	47.6	VTE	MB (ISTH criteria), CRB and any bleeding **Results:** Similar MB and CRBs. Less any bleeding with dabigatran (HR 0.50, 95%CI 0.26–0.95)	Recurrent VTE/VTE-related death **Results:** Similar VTE between dabigatran and warfarin (HR 0.43, 95%CI 0.08–2.38)
RAPS (2016) (28)	RCT	7.0	28.0	116	Rivaroxaban: 57 VKA: 59	72.4	48.5	VTE	MB, CRB, and minor bleedings **Results:** No MB or CRB occurred	Thromboembolism **Results:** No thrombotic events occurred
TRAPS (2018) (29)	RCT	20.4	100.0	120	Rivaroxaban: 59 VKA: 61	64.2	46.3	Arterial, venous, and/or biopsy-proven micro-thrombosis.	Arterial or venous thromboembolic events, MB, and vascular death **Results:** 13 total events (7 thrombotic and 6 MB): 11 (19%) in the rivaroxaban and 2 (3%) in the warfarin group Rivaroxaban: 4 IS and 3 MI, and 4 (7%) MB Warfarin: no thrombotic events and 2 (3%) MB. No death reported	
Ordi-Ros et al. (30)	RCT	36.0	60.5	190	Rivaroxaban: 95 VKA: 95	63.7	49.0	Arterial or venous thrombosis	MB **Results:** MB occurred in 6 patients (6.3%) in the rivaroxaban group and 7 (7.4%) in the VKA group (RR 0.86, 95%CI 0.30–2.46)	Venous and arterial thrombosis **Results:** 11 recurrent thrombosis in the rivaroxaban and 6 in the VKA group (RR 1.83, 95%CI, 0.71–4.76) More IS with rivaroxaban (RR 19.00, 95%CI, 1.12–321.9)
Malec et al. (31)	P Case series	22.0	28.6	56	Rivaroxaban: 49 Dabigatran: 4 Apixaban: 3	78.6	52.0	VTE	MB according to ISTH criteria **Results:** 2 severe bleedings	VTE **Results:** 6 (10.7%) VTE (5.8%/year)
Malec et al. (32)	P	51.0	26.1	176	Rivaroxaban: 36 Dabigatran: 4 Apixaban: 42 VKA: 94	83.0	44.5	VTE or arterial thrombosis	MB or CRB **Results:** DOACs increased risk of MB or CRNMB if menstrual bleeding were included (HR 3.63, 95%CI 1.53–8.63) GI bleeds and MB or CRNMB other than menstrual bleeding were similar between groups	Composite of VTE, cerebrovascular ischemic events or MI **Results:** Increased thrombosis with DOACs (HR 3.98, 95%CI 1.54–10.28) and recurrent VTE (HR 3.69, 95%CI 1.27–10.68) compared with VKAs
Legault et al. (33)	P	19.0	0.0	82	Rivaroxaban	47.6	53.4	VTE	MB Minor bleeding **Results:** There were no MB but 23 minor bleeding occurred	VTE, myocardial infarction, IS, and cardiovascular death **Results:** 4 thrombotic events (2 cerebrovascular and 2 VTE)

(Continued)

TABLE 2 | Continued

Author (year)	Design	Follow up (months)	Triple positive (%)	Study sample	Anticoagulant	Women (%)	Age (mean)	Index event	Safety endpoint	Efficacy endpoint
Betancur et al. (34)	Case series	19.0	12.5	8	Rivaroxaban: 7 Apixaban: 1	100.0	45.5	VTE (87.5%), PE (62.5%), and arterial thrombosis (75%), 25% obstetrical	–	Recurrence of thrombosis **Results:** There was no recurrence of thrombosis
Haladyj and Olesinska (35)	P Case series	20.0	17.4	23	Rivaroxaban	100.0	NR	8 arterial thrombosis, 9 VTE, 5 both	MB and minor bleeding **Results:** No MB or minor bleeding occurred	Arterial or venous thrombosis **Results:** 1 arterial thrombosis
Son et al. (36)	P Case series	11.4	41.7	12	Rivaroxaban	58.3	42.0	VTE and/or IS	–	Recurrent DVT **Results:** 2 patients had recurrent DVT
Sciascia et al. (37)	P Case series	10.0	NR	35	Rivaroxaban	68.6	47.0	Previous DVT (n: 24) and 11 DVT and PE	MB **Results:** No MB occurred	VTE **Results:** No VTE occurred
Noel et al. (38)	R Case series	19.0	26.9	26	Rivaroxaban: 15 Dabigatran: 11	53.8	39.1	Arterial and/or venous thrombosis, pregnancy morbidity	Bleeding events **Results:** 2 bleedings under Rivaroxaban: one hyper-menorrhea and one rectal bleeding	Thrombotic recurrence **Results:** One cutaneous microthrombosis under Rivaroxaban
Resseguier et al. (39)	R Case series	35.6	8.7	23	Rivaroxaban	56.5	41.0	VTE (*n*: 19), artery event (*n*: 2) or both (*n*: 1), and catastrophic APS (*n*: 1)	MB **Results:** No MB occurred	Arterial and venous thrombotic events **Results:** One patient developed PE
Sato et al. (40)	R	5 years	33.3	206	Factor Xa Inhibitors: 18 Warfarin: 36	86.0	42.8	34 arterial 32 VTE 11 pregnancy morbidity	Severe bleeding requiring hospitalization and/or blood transfusion **Results:** 1 and 2 cases of recurrences of thrombosis in the factor Xa Inhibitors and warfarin groups, respectively	Arterial/venous thrombosis **Results:** 6 and 8 cases of recurrences of thrombosis in the factor Xa Inhibitors and warfarin groups, respectively

CI, confidence interval; CRB, clinical relevant bleeding; CRNMB, clinical relevant non-major bleeding; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; GI, gastrointestinal; HR, hazard ratio; IS, ischemic stroke; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; MB, major bleeding; NR, not reported; P, prospective; PE, pulmonary embolism; R, retrospective; RCT, randomized clinical trial; RR, relative risk; VKA, vitamin K antagonist; VTE, venous thromboembolism.

TABLE 3 | International guideline recommendations/consensus suggestions on the use of DOACs in APS patients.

Guidelines	Recommendations	Level of evidence
	International guidelines on deep vein thrombosis/pulmonary embolism	
ESC 2019 (42)	Indefinite treatment with a VKA is recommended for patients with APS	Ib*
	DOACs are not recommended in patients with severe renal impairment, during pregnancy and lactation, and in patients with APS	IIIc*
ASH 2020 (43)	For patients with DVT and/or PE, the ASH guideline panel suggests using DOACs over VKAs (conditional recommendation based on moderate certainty in the evidence of effects). *Remarks: This recommendation may not apply to certain subgroups of patients, such as those with renal insufficiency (creatinine clearance, 30 mL/min), moderate to severe liver disease, or APS*	Remark. Evidence not provided
NICE 2020 (44)	Offer people with confirmed proximal deep vein thrombosis or pulmonary embolism and an established diagnosis of triple positive APS LMWH concurrently with a VKA for at least 5 days, or until the INR is at least 2.0 in two consecutive readings, followed by a VKA on its own	^
	International guidelines on antiphospholipid syndrome	
BSH Guidelines 2020 (45)	*Patients with arterial thrombosis* For anticoagulation for treatment and secondary prophylaxis of arterial thrombosis in patients with APS, we recommend VKAs and do not recommend DOACs	IB#
	Patients with triple positive APS and venous thrombosis We recommend against the initiation of DOACs for treatment or secondary prophylaxis in patients with venous thrombosis and known triple positive APS. For patients with triple positive APS who are currently on a DOAC, we recommend switching from the DOAC to a VKA after discussion with patients regarding the available evidence. *For those patients who do not wish to switch, we recommend continuation of the DOAC over no anticoagulation*	IB#
	Patients with non-triple positive APS and venous thrombosis There is insufficient evidence to make strong recommendations in this group of patients. We suggest against the initiation of DOACs for treatment or secondary prophylaxis in patients with venous thrombosis and known non-triple positive APS. *Patients who are already on a DOAC may continue or switch to a VKA after discussion with the patient taking into account their clinical history, treatment adherence and previous experience. For those patients who do not wish to switch, we recommend continuation of the DOAC over no anticoagulation*	IIC#
ISTH 2020 guidance (46)	*We recommend that for the treatment of thrombotic APS among patients with any of the following (termed "high-risk" APS patients)* (a) triple positivity, (b) arterial thrombosis, (c) small vessel thrombosis or organ involvement (d) heart valve disease according to Sydney criteria, VKA should be used instead of DOACs	Not provided
	We recommend that DOACs should not be used in APS patients with recurrent thrombosis while on therapeutic intensity VKA. In this circumstance, other therapeutic options may include an increased target INR range, treatment dose LMWH, or the addition of antiplatelet therapy	Not provided
	We recommend that DOACs should not be used in APS patients who are non-adherent to VKA. In this circumstance, other options may include education on adherence to VKA treatment along with frequent INR testing	Not provided
	In single or double positive non- "high risk" APS patients who have been on DOACs with good adherence for several months for a first episode of VTE, we recommend a discussion with the patient of options including perceived risks and uncertainties, in the spirit of shared decision-making and review of whether continued treatment with a DOAC is appropriate	Not provided
	In single- or double-positive non- "high-risk" APS patients with a single prior VTE requiring standard-intensity VKA, with allergy or intolerance to VKA or erratic INRs despite patient adherence, we suggest that alternative VKAs, if available, should be considered prior to consideration of a DOAC	Not provided
EULAR 2019 (47)	*In patients with definite APS and first venous thrombosis:* Rivaroxaban should not be used in patients with triple aPL positivity due to the high risk of recurrent events	1b/B§
	In patients with definite APS and first venous thrombosis: DOACs could be considered in patients not able to achieve a target INR despite good adherence to VKA or those with contraindications to VKA (e.g., allergy or intolerance to VKA)	5/D§
	In patients with definite APS and first arterial thrombosis: Rivaroxaban should not be used in patients with triple aPL positivity and arterial events	Ib/B§
	In patients with definite APS and first arterial thrombosis: Based on the current evidence, we do not recommend use of DOACs in patients with definite APS and arterial events due to the high risk of recurrent thrombosis	5/D§

APS, antiphospholipid antibody syndrome; ASH, American Society of Hematology; BSH, British Society for Haematology; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; ESC, European Society of Cardiology; EULAR, European League Against Rheumatism; INR, international normalized ratio; ISTH, International Society on Thrombosis and Haemostasis; LMWH, low-molecular weight heparin; NICE, National Institute for Health and Care Excellence; PE, pulmonary embolism; VKA, vitamin K antagonist; VTE, venous thromboembolism.

**ESC Committee for Practice Guidelines (CPG) policy.*

§Oxford Centre for Evidence-Based Medicine standards.

#Grading of Recommendations Assessment, Development and Evaluation (GRADE).

^Based on the Medicines and Healthcare products Regulatory Agency alert and the experience and opinion of the Guideline Committee.

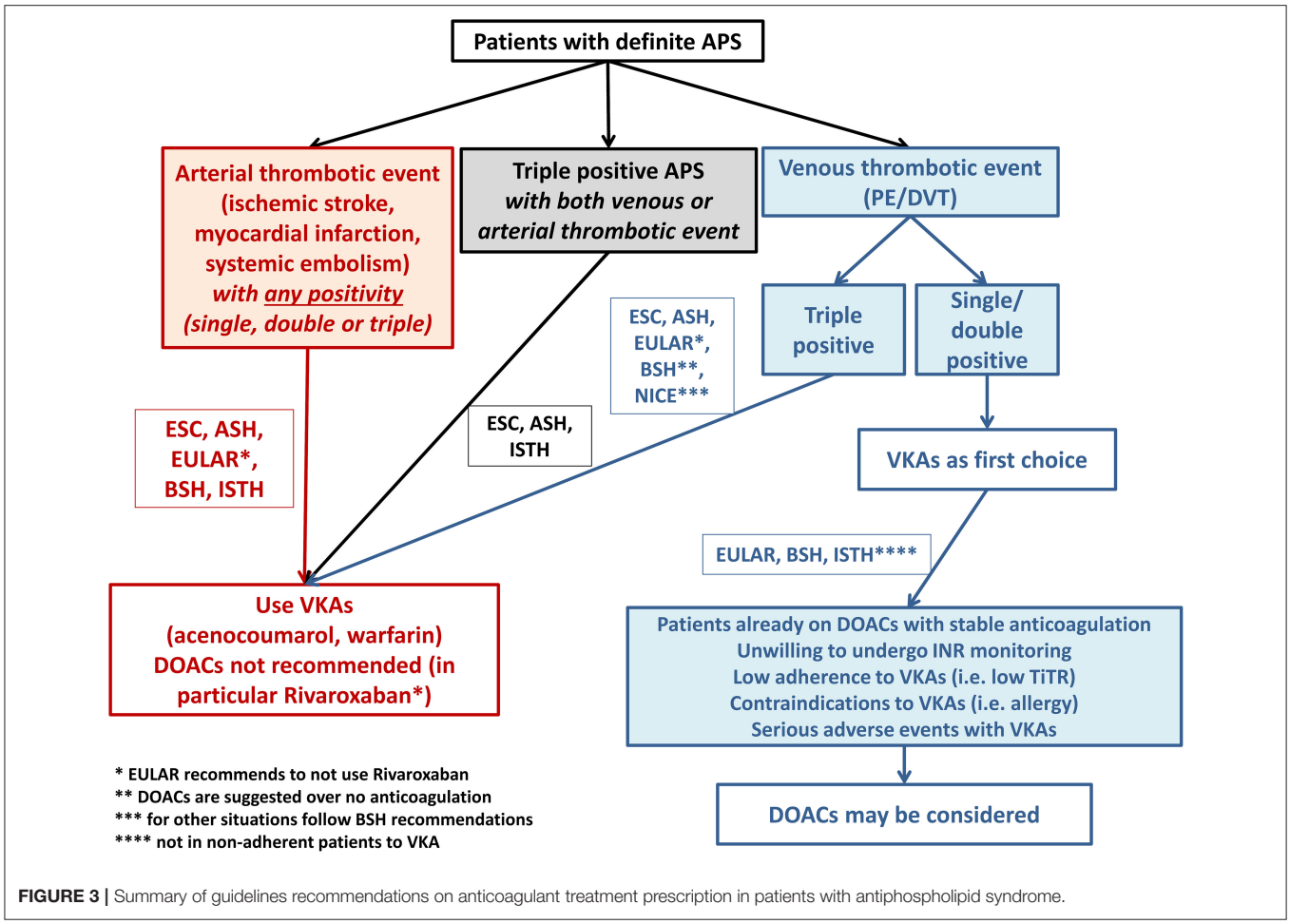

FIGURE 3 | Summary of guidelines recommendations on anticoagulant treatment prescription in patients with antiphospholipid syndrome.

with DOACs, treatment may be continued if patients refuse to switch to VKAs (45).

The 2020 American Society of Hematology (ASH) guidelines (43) state that APS patients are not optimal candidate for DOAC treatment, and suggest the use of low molecular weight heparin (LMWH) over DOAC in case of recurrent event under VKAs. However, the Authors acknowledge that this recommendation is based on very low certainty of the evidence of effects.

DISCUSSION/OBSERVATIONS

This systematic review of clinical studies showed that the safety and efficacy of DOACs may be highly dependent on clinical and immunological phenotype of APS patients. Of note, none of the studies including non-triple venous APS patients reported an excess of thrombotic recurrence, which was conversely more evident in studies including triple positive or arterial APS patients. It is therefore important to identify the clinical phenotype of patients with APS to establish in which subgroup the use of DOACs may be beneficial. In this context, a recent meta-analysis confirmed this approach showing a four-fold higher thrombotic risk in APS patients with triple positivity (56 vs. 23%; OR = 4.3, 95%CI 2.3–7.7, $p < 0.0001$) as well as in patients with a history of arterial thrombosis (32 vs. 14%; OR = 2.8, 95%CI 1.4–5.7, $p = 0.006$) on treatment with DOACs (12).

The results from these studies have been differently received by expert committees of international societies to provide clinical recommendations on the use of DOACs in this patient population. **Figure 3** summarizes current indications provided by international guidelines on the use of oral anticoagulants in patients with APS. While there is a general agreement on the contraindication on the use of DOACs, and in particular rivaroxaban, in patients with arterial APS and/or triple positivity, there are some differences regarding venous and non-triple APS patients.

Thus, while the ESC and ASH guidelines do not recommend the use of DOACs in any APS patients (with no level of evidence reported in the latter), there was an effort from EULAR, BSH, and ISTH to take into consideration the clinical phenotype of patients for choosing the most appropriate anticoagulant drug (**Figure 3**). These societies state that VKAs should always represent the first-choice treatment in venous non-triple APS but open to the possibility of using DOACs in some specific situations and in any cases after a shared informed decision with the patient. In particular, patients diagnosed with APS after VTE but who are

already on a stable anticoagulation with a DOAC may be kept on the same treatment, as the benefit of switching to VKAs may not be evident in this case. Similarly, patients with very low-quality anticoagulation by VKAs (i.e., TiTR <60%), experiencing INR instability and needing frequent INR checks may benefit more from a stable anticoagulation provided by fixed dose DOAC. Another group potentially suitable for DOAC treatment is represented by patients unwilling or unable to undergo INR monitoring as in the case of difficult access to healthcare facilities or impaired mobility, as treatment with DOAC may be beneficial over not treatment. Finally, patients with contraindications (i.e., allergy) or serious adverse events under VKA therapy may be considered for DOAC treatment. However, it should be noted that the indications provided by the ISTH is based on an expert consensus and no level of evidence for such recommendations is given.

Regarding the type of DOAC, rivaroxaban has been the most widely investigated drug, while the number of patients treated with dabigatran or apixaban is still low. A randomized trial investigating the efficacy and safety of Apixaban in APS patients is currently ongoing and has been modified to exclude patients with arterial thrombosis based on literature data (48); however, this study is actually closed. Patients who were enrolled are still being followed, although it is unclear if they are still being maintained on apixaban or not. No data regarding the use of edoxaban in this patient population are available.

Although DOACs do not require laboratory monitoring to ascertain their efficacy, the assessment of blood concentration of DOACs may turn particularly useful for patients with APS to verify if appropriate peak and trough concentrations are obtained after the drug administration. These values have been shown to correlate with bleeding or thrombotic complications (49). In this context, previous evidence showed that the twice-daily dosing regimens with Apixaban and Dabigatran are associated with less high peak or low trough concentrations (50). More importantly, these twice-daily drugs might guarantee a more stable anticoagulation level in APS patients, leaving patients less exposed to low trough concentrations which are associated with thrombotic events (51).

In conclusion, international guidelines agree on the exclusive use of VKAs in patients with arterial APS and triple positivity (**Figure 3**). Evidence on venous APS is weak and patients with single or double positivity may be candidate to DOACs, after a shared informed decision with patients, especially in patients who are not willing or have contraindications to VKAs. The lack of consensus among guidelines/consensus originate from the paucity of randomized studies and the lack of rigorous patients' stratification.

AUTHOR CONTRIBUTIONS

DP and DM: conceptualization and draft of the manuscript. VC and PP: design and revision of the manuscript. All authors provide approval for publication of the content.

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frontiers in Cardiovascular Medicine

MINI REVIEW
published: 04 October 2021
doi: 10.3389/fcvm.2021.714826

Pulmonary Artery Stump Thrombosis: To Treat or Not to Treat? The Question Is Still Open. Description of a Case and Review of the Literature

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OPEN ACCESS

Edited by:
Roberto Pola, Università Cattolica del Sacro Cuore, Italy

Reviewed by:
Iqbal Haider Jaffer, McMaster University, Canada
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Specialty section:
This article was submitted to Thrombosis, a section of the journal Frontiers in Cardiovascular Medicine

Received: *25 May 2021*
Accepted: *26 August 2021*
Published: *04 October 2021*

Citation:
Mirijello A, Santoliquido M, Piscitelli P, Borelli C, Serviddio G, Simeone A, Grandone E and De Cosmo S (2021) Pulmonary Artery Stump Thrombosis: To Treat or Not to Treat? The Question Is Still Open. Description of a Case and Review of the Literature. Front. Cardiovasc. Med. 8:714826. doi: 10.3389/fcvm.2021.714826

Pulmonary artery stump thrombosis (PAST) represents a possible complication after lung surgery. We report the case of a 59-year-old man who presented with dyspnoea about 4 years after right pneumonectomy due to squamous cell lung cancer. A CT-scan showed the presence of pulmonary artery stump thrombosis. Although there was no evidence of pulmonary embolism, given the clinical features and radiological shape of the thrombus, anticoagulation treatment with low-molecular-weight heparin was started with improvement of symptoms. The patient was discharged on anticoagulant treatment and a pulmonary CT-scan performed 4 months later showed an almost complete resolution of the PAST. Pathophysiological mechanisms of PAST are still unknown, although several hypotheses have been proposed. However, the decision to treat PAST with anticoagulants is still controversial. A review of literature will be provided in order to discuss risk factors, possible etiologies and to highlight clinical and radiological characteristics that could suggest to treat this condition, in particular when there is an increased risk of complications.

Keywords: anticoagulation, pneumonectomy, pulmonary embolism, thrombosis, pulmonary artery stump

INTRODUCTION

Pulmonary artery stump thrombosis (PAST) following pulmonary resection for lung cancer is a possible complication after lobectomy (1) or pneumonectomy (2), with an incidence of 12% (2) after this latter. Generally, PAST occurs early after surgery (3); nevertheless, a delayed presentation has been described, although sporadically (4–10). Pathophysiological mechanisms of PAST are not fully understood, although several hypotheses have been formulated, such as endothelial damage during surgery, hypercoagulability and blood flow stasis in the vascular stump. PAST is generally asymptomatic and incidentally detected at follow-up CT-scans; moreover, it is usually harmless (11). However, in a minority of cases, it could be complicated with pulmonary embolism to the contralateral lung (4), pulmonary hypertension (6) and death (8, 12–14). At present, the optimal treatment of PAST is still matter of debate.

Here we describe the late-occurrence of PAST in a patient treated with right pneumonectomy due to squamous cell lung carcinoma. Clinical features, possible causes and risk factors will be reported. Moreover, a review of the literature will be provided in order to discuss gray areas concerning treatment options and the choice to treat this specific case.

CASE PRESENTATION

In October 2020, a 59-year-old man was admitted to our Internal Medicine inpatients unit because of the persistence for about 2 weeks of dyspnoea, fatigue, and weight loss. The patient also reported right hypochondrium pain and loss of appetite. Past medical history was relevant for hypertension, type 2 diabetes and alcohol abuse (reported alcohol consumption: 3–5 drinks per day from the age of sixteen). In 2016 he was diagnosed with squamous cell lung carcinoma (stage T4N3M0) and treated with neoadjuvant polychemotherapy (cisplatine + vinorelbin) followed by right pneumonectomy. Despite a history of cancer, he was still an active smoker. His home therapy consisted of insulin and acetylsalicylic acid 100 mg/day.

At admission, blood pressure was 150/75 mmHg, heart rate 92 bpm, oxygen saturation 94% in room air, respiratory rate 20/min, body temperature was 36°C. Physical examination was non-significant apart from hepatomegaly. Results of laboratory tests, including blood gas analysis, at admission are shown in **Supplementary Table 1**. In particular, acute phase reactants (e.g., fibrinogen, C-reactive protein, ferritin), transaminases, cholestasis enzymes and D-dimer were altered. Hepatitis B and C markers were negative. Sars-CoV-2 nasopharyngeal swab was negative. Chest X-ray showed opacification and volume loss of right hemi-thorax with consensual mediastinal shift, according to history of previous pneumonectomy; no signs of pulmonary consolidation in the left lung. Abdominal US-scan showed hyperechogenicity of the liver compatible with steatosis and/or fibrosis and biliary sludge. No significant kidneys or spleen abnormalities nor ascites were found. The Esophago-Gastro-Duodenoscopy detected a grade B reflux disease (LA classification), congestive gastropathy and erosive bulb duodenitis. Basing on history, clinical features and Wells' score (0 points) (15), PE was unlikely. An echocardiography showed a normal left ventricle ejection fraction, no right ventricle overload nor pulmonary hypertension. To rule out cancer recurrence, total body CT-scan with contrast injection was performed. Chest CT images showed a pulmonary thrombus within the right main artery stump, not present 1 year earlier (**Figure 1A**). Doppler US-scan of lower limbs was normal. Anticoagulant treatment with enoxaparin 100 ui/kg/bid was started, together with proton pump inhibitor (PPI). Tests for inherited and acquired thrombophilia were negative as well as antibodies against Sars-Cov-2. Patient's symptoms gradually improved and he was discharged 7 days after PAST diagnosis with anticoagulant prescription. Contrast-enhanced CT scan performed 4 months later demonstrated an almost complete resolution of right pulmonary thrombosis (**Figure 1B**).

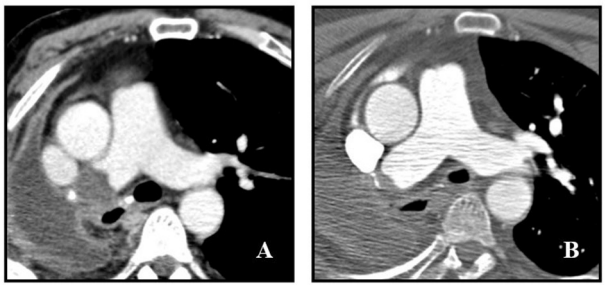

FIGURE 1 | Post-pneumonectomy thrombosis of right pulmonary artery stump. **(A)** Initial contrast-enhanced CT scan shows a large endoluminal filling defect in the right pulmonary artery stump. **(B)** Follow up contrast-enhanced CT scan obtained 4 months after **(A)** shows marked reduction of thrombus size with evidence of a small residual intraluminal defect adjacent to surgical clips.

DISCUSSION

PAST is a possible complication after lung surgery (2), generally occurring within 12 months (early PAST), even if a delayed presentation has also been described (late PAST) (4–10). Usually it is asymptomatic and incidentally detected during a follow-up CT-scan (3). However, English literature reports anecdotal cases of patients complaining of dyspnoea finally diagnosed with PAST (**Table 1**). At present, risk factors and mechanisms at the basis of this thrombotic event are still poorly understood. In a retrospective analysis of 648 oncologic surgeries for primary lung cancer, 25 (3.8%) PAST were found (3). Among them, elderly age, advanced cancer stage and neo-adjuvant chemotherapy could represent risk factors for its development (3). Regarding pathophysiological mechanisms for stump thrombosis, Virchow's triad has been indicated as one of the possible causes (3). On this connection, three processes could be hypothesized:

1. *Endothelial injury during surgery*. Complex surgeries and vascular manipulations increase the risk of endothelial damage, reducing the production of fibrinolytic activators with a consequent pro-coagulant state (16). For this reason, the technique with continuous ligature of the stump has been considered more appropriated than the transfixation one, obtaining a regular stump which decreases the probability of PAST. However, this mechanism could be mainly responsible for early PAST.
2. *Blood flow stasis of the vascular stump*. There is a correlation between stump's length and changes in blood flow dynamics (e.g., blood flow turbulence) (11). Basing on the retrospective revision of chest CT-scans of patients treated with pneumonectomy, Kim and co-workers (2) evidenced that the stump is longer after a right pneumonectomy than after a left pneumonectomy, and the thrombus was more frequently detected in the right (23.3%) than in the left (4.6%) stump. On the contrary Kwek and colleagues (11) found an almost equal incidence of thrombi between right and left stumps. Concerning lobectomy, left-sided thrombi were more common than right-sided one (3).

TABLE 1 | Cases of PAST reported in the English literature.

References	Gender	Age	Type of lung resection	Side	Symptoms	Timing	Lower limb Doppler US	Treatment	Resolution	Complications	Death
Barbetakis et al. (22)	Male	59	Lobectomy	Right	No	6 months	Negative	Heparin, then OAC for 6 months	Yes	No	No
Sato et al. (4)	Male	73	Pneumonectomy	Left	Chest discomfort	8 years	N.a.	Heparin	Yes	Controlateral pulmonary embolism (anticoagulant therapy was discontinued)	No
Thomas et al. (6)	Male	51	Pneumonectomy	Right	Astenia back pain dyspnoea	10 years	Deep venous thrombosis	Heparin	No	Multiple pulmonary emboli and pulmonary hypertension	Probably
Chuang et al. (12) n1	Female	29	Pneumonectomy	Right	Dyspnoea, tachycardia	8 months	N.a.	No	No	Infarction left lower lobe	Yes
Chuang et al. (12) n2	Male	65	Pneumonectomy	Right	Dyspnoea	24 h	N.a.	No	No	Emboli left lower lobe and lingular arteries	Yes
Gorospe Sarasúa (13)	Male	71	Pneumonectomy	Right	Dyspnea	5 month	/	Heparin	No	Death	Yes
Akcam et al. (9)	Male	73	Pneumonectomy	Left	No	3 years	Negative	Heparin, then warfarin	Yes	No	No
Joshi et al. (8)	Male	68	Pneumonectomy	Right	Pleuric chest pain	10 years	Negative	Heparin, then warfarin	No	Yes	Yes
Viola et al. (10)	Female	76	Lobectomy	Right	Dyspnoea	6 years		Rivaroxaban	No	/	No
Sawalha and Mador (5)	Male	67	Lobectomy	Right	No	2 years	Negative	Coumadin for 3 months	Yes	No	No
Kotoulas and Lachanis (23)	Male	53	Pneumonectomy	Right	No	3 months	Negative	Acenocumarol	Yes	No	No
Yoon et al. (7)	Female	75	Pneumonectomy	Right	Dyspnea	10 years	N.a.	Warfarin	Yes	Multiple small thrombi in left pulmonary artery	No
Gorospe et al. (14)	NA	NA	Lobectomy	Left	No	1 year	N.a.	Heparin	Yes	No	No
Dury et al. (24) (3 cases)	NA	NA	Pneumonectomy	/	/	/	/	No	/	No	No
Wechsler et al. (25)	Female	72	Lobectomy	Right	Shortness of breath, fatigue	11 months	Negative	No	No	No	No

3. *Hypercoagulability*. Increased platelet count and fibrinogen level at 7th and 14th day after lung surgery were observed as factors associated with higher thrombotic activity (17). In addition, other factors such as smoking (18), active cancer (19), and sepsis (20) are known to increase blood coagulability. To date, an association between PAST and inherited/acquired thrombophilia has never been described.

The need for anticoagulation in patients with PAST is still matter of debate. According to literature, early PAST is more likely to resolve spontaneously, regardless from anticoagulation, while late PAST usually shows a poor rate of resolution (21).

Among the 17 case reports of PAST reported in the English literature, seven of them were late PASTs (**Table 1**); all received anticoagulant therapy, the majority of which resolved.

Moreover, anticoagulation could be started according to the morphology of PAST at CT scan. Convex-shaped and floating PAST are considered more acute and at high-risk of embolization to the contralateral lung or of growth. On the contrary, concave-shaped thrombi are considered at lower risk of embolization and more "stable" (11). According to some authors, anticoagulation should be considered for convex thrombi or for a newly occurring PAST in the context of declining pulmonary status (8). Indeed, it is important to understand if PAST represents an *in situ* thrombosis, a cancer recurrence inside the vascular stump or an embolus from deep vein thrombosis (2); all of these could be indications for treatment. However, the incidence of PAST-associated PE is low (5). According to the available reports, one patient showed contralateral pulmonary embolism (4) and another one showed multiple pulmonary emboli with pulmonary hypertension (6); both of them had been treated, but just one solved (**Table 1**).

We reported the case of a patient complaining of dyspnoea, fatigue and abdominal pain, and weight loss. Since the presenting symptomatology was not specific for any particular disease, several examinations were performed. Chest X-ray did not show abnormalities in the left lung and, according to Wells' score, pre-test probability of PE was low. Abdominal symptoms and weight loss were consistent with chronic alcoholic liver disease, gastro-oesophagitis and duodenitis. Respiratory symptom was not justified by blood gas analysis, not showing respiratory failure. Finally, chest CT-scan evidenced the presence of PAST. According to CT-scan (**Figure 1A**), this was a newly evidenced late-occurring PAST with a convex-shaped thrombus in the right pulmonary artery stump with no evidence of PE. These characteristics, in conjunction with the presence of symptoms, surrounding inflammatory state, history of active smoking and previous chemotherapy led us to the decision to start anticoagulation. The CT-scan performed 4 months later found an almost complete resolution of the clot (**Figure 1B**).

CONCLUSIONS

PAST represents a possible complication after lung surgery, in particular after right pneumonectomy. Local and systemic factors seem to be involved in its pathophysiology, although the exact mechanisms are not completely understood. Generally, PAST represents an occasional finding at follow-up CT scan and it is asymptomatic; sometimes, patients could complain of dyspnoea, fatigue and chest discomfort. The choice to prescribe anticoagulants should be based on the risk of complications, such as contralateral pulmonary embolism, worsening lung function and death. At present, literature data on factors potentially favoring embolization are few and decision-making algorithms are lacking. It is conceivable that the evidence of convex-shaped thrombi and patient's thrombotic risk could represent the most important factors suggesting the need for anticoagulation. In any case, the choice for optimal treatment duration and follow-up should be evaluated case by case.

ETHICS STATEMENT

Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

AM, MS, PP, and EG managed the patient during hospitalization. AM, MS, and PP thought about the study rationale. CB and AS reviewed radiological images. GS and SD reviewed collected data. AM, MS, PP, EG, and SD wrote the first draft. All Authors read, had the possibility to modify and approved the final draft of the paper.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.714826/full#supplementary-material

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frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 14 October 2021
doi: 10.3389/fcvm.2021.737551

Nomogram to Predict Left Atrial Thrombus or Spontaneous Echo Contrast in Patients With Non-valvular Atrial Fibrillation

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Specialty section:
This article was submitted to Thrombosis, a section of the journal Frontiers in Cardiovascular Medicine

Received: 07 July 2021
Accepted: 21 September 2021
Published: 14 October 2021

Citation:
Li Z, Liu Q, Liu F, Hidru TH, Tang Y, Cong T, Gao L, Yang X and Xia Y (2021) Nomogram to Predict Left Atrial Thrombus or Spontaneous Echo Contrast in Patients With Non-valvular Atrial Fibrillation. Front. Cardiovasc. Med. 8:737551. doi: 10.3389/fcvm.2021.737551

Background: The predictive power of the $CHADS_2$ and CHA_2DS_2-VASc scores for the presence of Left atrial thrombus (LAT)/ spontaneous echo contrast (SEC) in non-valvular atrial fibrillation (NVAF) is modest. The aim of this analysis is to define clinical and ultrasonic variables associated with LAT/SEC and to propose nomograms for individual risk prediction.

Methods: Data on 1,813 consecutive NVAF patients who underwent transesophageal echocardiography (TEE) from January 2016 to January 2021 were collected. The univariate and multivariate logistic regression analyses were used to construct a nomogram. We examined the predictive ability of the risk scores by calculating the area under the curve (AUC). Moreover, the performance of the nomogram was assessed with respect to calibration, discrimination, and clinical usefulness.

Results: LAT/SEC was found in 260 (21.0%) and 124 (21.6%) patients in the training and validation cohorts, respectively. On multivariate analysis, independent factors for LAT/SEC were Age, left atrial diameter (LAD), left ventricular ejection fraction (LVEF), hypertension (HTN), previous stroke or transient ischemic attack, Non-paroxysmal AF and a nomogram was built based on these variables. The calibration curve for the probability of LAT/SEC showed good prediction agreement with actual observation. The nomogram achieved good concordance indexes of 0.836 and 0.794 in predicting LAT/SEC in the training and validation cohorts, respectively. Decision curve analysis demonstrated that the nomogram would be clinically useful.

Conclusions: In this study, a nomogram was constructed that incorporated six characteristics of NVAF patients. The nomogram may be of great value for the prediction of LAT/SEC in NVAF patients.

Keywords: left atrial thrombus, spontaneous echo contrast, atrial fibrillation, nomogram, risk score

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with a 5-fold risk for stroke (1). Recent evidence stated left atrial thrombus (LAT) and left atrial spontaneous echo contrast (LASEC) as risk factors of cardiogenic embolism in atrial fibrillation patients (2). Although transesophageal echocardiography (TEE) is still considered the gold standard to exclude LA/LAA thrombus, TEE requires special skills for proper performance and interpretation. Additionally, it is a relatively invasive test, usually performed with the patient under conscious sedation. Therefore, a potentially non-invasive and efficacious method allowing identification of LAT/SEC with reliability and accuracy comparable to TEE would be of significant clinical value.

The current guidelines for anticoagulant therapy for stroke prevention in NVAF depend on $CHADS_2$ and CHA_2DS_2-VASc scores (3). However, the predictive power of the $CHADS_2$ and CHA_2DS_2-VASc scores for the presence of LAT in NVAF is not satisfactory (c-statistics 0.55∼0.70) (4, 5). Thrombus can be found even in some patients with low CHA2DS2-VASc scores (6). As such, it is of scientific interest to establish a stronger predictive model that incorporates factors associated with LAT/SEC based on clinical and ultrasonic data.

A powerful model that estimates LAT/SEC presence can assist cardiologists to identify high-risk patients and lead to a rational therapeutic choice. As a result, many efforts on the peri-procedural estimation of LAT/SEC have been made previously (5, 7). However, there is still no accurate model to predict LAT/SEC. Owing to this lack of a specific and practical predictive method, the development of a predictive model that incorporates factors associated with LAT/SEC based on peri-procedural clinicopathologic data becomes desirable.

In this study, we applied nomogram analysis, which can provide individualized, evidence-based, and highly accurate risk estimation. To our knowledge, we have established the first nomogram for peri-procedural LAT/SEC risk estimation in NVAF. The objectives of this study include to (1) investigate the predictive power of the $CHADS_2$ and CHA_2DS_2-VASc scores for the presence of LAT/SEC, (2) identify the clinical predictors of LAT/SEC, and (3) establish nomogram for LAT/SEC risk estimation in NVAF.

METHODS

Study Participants

We retrospectively enrolled 1,899 consecutive patients with non-valvular AF who underwent a TEE from January 2016 to January 2021 in the First Affiliated Hospital of Dalian Medical University (FAHDMU). Patients who were referred for catheter ablation or direct current cardioversion underwent transesophageal echocardiography (TEE) were eligible for this study. Patients with organic valvular heart diseases, rheumatic heart disease, prosthetic valve placement, malignant tumor were excluded. Likewise, individuals with missing/incomplete echocardiography or laboratory data were excluded from the analysis. Finally, 1,813 eligible patients were randomly assigned into the training cohort ($n = 1{,}239$) and validation cohort ($n = 574$). The study was approved by the first affiliated hospital of the Dalian medical University institutional review board, and the requirement for informed consent was waived. The research was conducted in accordance with the Helsinki declaration guidelines and all procedures listed here were carried out in compliance with the approved guidelines.

Definition of the Explanatory Variables

Data on demographics, medical history, and laboratory data, and medications were collected from the electronic medical record of FAHDMU. All anticoagulants were administered at least 5–7 days until the TEE day. Diabetes mellitus was defined as a fasting glucose level ≥126 mg/dL (or non-fasting glucose ≥200 mg/dL), a physician diagnosis of diabetes, or use of diabetes medications (8). Congestive heart failure was defined as clinical heart failure (stage C or D) according to the ACC/AHA guidelines (9). Prevalent coronary artery disease (CAD) was defined by a history of physician-diagnosed myocardial infarction, coronary artery bypass surgery, or coronary angioplasty. Hypertension (HTN) was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg at two or more visits or a past medical history of hypertension (10). The definition and classification of AF were according to the published guideline (3). Non-paroxysmal AF was composed of persistent, long-standing persistent, and permanent AF.

Assessment of CHADS2 and CHA2DS2-VASc Score and Risk Classification

$CHADS_2$ score was determined by assigning 1 point each for the presence of congestive heart failure (CHF), hypertension, age ≥ 75 years, and diabetes and by assigning 2 points for the previous stroke/transient ischemic attack (TIA). The CHA_2DS_2-VASc score was determined by assigning 1 point each for the presence of CHF, hypertension, age 65–74 years, diabetes, and vascular disease (peripheral artery disease or myocardial infarction) and by assigning 2 points each for age ≥ 75 years and previous stroke/TIA (11, 12). Current guidelines recommend anticoagulation for all patients with documented atrial fibrillation and a CHA_2DS_2-VASc score of 2 or greater in men and 3 or greater in women (3). Therefore, we classified men with a CHA_2DS_2-VASc score of 0–1 or women with a CHA_2DS_2-VASc score of 0–2 as low risk.

Ultrasound Evaluation

All patients routinely underwent transthoracic echocardiography and TEE before catheter ablation or direct current cardioversion. Transthoracic echocardiography was performed with a Vivid 7 ultrasound system (GE Healthcare, Waukesha, WI, USAGE Vingmed Ultrasound) and an M3S probe for the subjects in partial left decubitus. TEE was performed with an HP Sonos5500 color Doppler flow imager using a multi-planar transesophageal ultrasound probe frequency of 4–7 MHz and suitable gain adjustment. The probe was advanced to the mid-esophagus, 25–35 cm from the incisor teeth. A multi-axial scan was performed on the horizontal section of the left heart to display the LAA

and then a 0–180° continuous scan was performed at different angles and depths to maximize visualization of the structure of the LAA and its internal echoes. Before the patients underwent the TEE examination, the procedure was explained in detail, and written informed consent was obtained from all patients. Thrombus was defined as a circumscribed, uniformly echo dense mass distinct from the underlying left atrial endocardium and pectinate muscles detected in more than 1 imaging plane. Spontaneous echocardiographic contrast (SEC) was defined as dynamic "smoke-like" echoes with a characteristic swirling motion that could not be eliminated despite optimized gain settings (2). All measurements were performed and interpreted by experienced physicians who were blind to the study.

Statistical Analysis

Continuous data were expressed as mean (SD) and compared using an unpaired, 2-tailed *t*-test, or Mann–Whitney test. The categorical data were presented as count and percentage and analyzed by χ^2 test or Fisher exact test. Prior to the data analysis, patients with NVAF were divided into the following two groups according to their AF status: patients with paroxysmal AF and patients with Non-paroxysmal AF.

The significance of each variable in the training cohort was assessed by univariate logistic regression analysis for investigating the independent risk factors of the presence of LAT/SEC. All variables associated with LAT/SEC at a significant level were candidates for stepwise multivariate analysis. Further, a nomogram was formulated based on the results of multivariate logistic regression analysis using the rms package of R, version 4.0 (http://www.r-project.org/). The nomogram is based on proportionally converting each regression coefficient in multivariate logistic regression to a 0–100-point scale. The effect of the variable with the highest β coefficient (absolute value) is assigned to 100 points. The points of the independent variables were added to derive total points, which were converted to predicted probabilities. The predictive performance of the nomogram was evaluated by concordance index (C-index) and calibration with 1,000 bootstrap samples to decrease the overfit bias. Decision curve analysis was conducted using the R library rmda package to determine the clinical usefulness of the nomogram by quantifying the net benefit at different threshold probabilities in the primary dataset.

TABLE 1 | Baseline characteristics.

Variable	Cohort		*P*-value
	Training (n = 1,239)	Validation (n = 574)	
Age, years	62.6 (9.5)	62.6 (9.3)	0.987
Male sex, *n* (%)	811 (65.5)	356 (62.0)	0.171
Medical history			
HTN, *n* (%)	767 (61.9)	361 (62.9)	0.725
T2DM, *n* (%)	297 (24.0)	140 (24.4)	0.893
Previous stroke/TIA, *n* (%)	248 (20.0)	96 (16.7)	0.11
Vascular disease, *n* (%)	39 (3.1)	14 (2.4)	0.494
Non-paroxysmal AF, *n* (%)	445 (35.9)	206 (35.9)	1
CAD, *n* (%)	402 (32.4)	174 (30.3)	0.394
$CHADS_2$ Score	1.39 (1.17)	1.34 (1.13)	0.415
CHA_2DS_2-VASc score	2.46 (1.45)	2.38 (1.43)	0.25
laboratory data			
eGFR, ml/(min 1.73 m^2)	90.1 (18.8)	90.7 (19.0)	0.527
Uric acid, μmol/L	366.99 (87.77)	368.09 (91.70)	0.807
PT-INR	1.21 (0.50)	1.27 (0.58)	0.019
Echocardiographic parameters			
LAT/SEC, *n* (%)	260 (21.0)	124 (21.6)	0.812
LAD, mm	39.2 (4.5)	39.1 (4.6)	0.729
LVEDD, mm	47.9 (4.3)	47.9 (4.2)	0.81
LVEF, %	56.5 (4.9)	56.3 (5.2)	0.443
Medication			
Statin, *n* (%)	752 (60.7)	334 (58.2)	0.336
Amiodarone, *n* (%)	908 (73.3)	432 (75.3)	0.404
Antiplatelet, *n* (%)	378 (30.5)	159 (27.7)	0.245

CAD, coronary artery disease; HTN, Hypertension; LAD, left atrium diameter; LAT, left atrial thrombus; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; SEC, spontaneous echo contrast; T2DM, Type 2 diabetes mellitus; TIA, transient ischemic attack.

TABLE 2 | Univariate and multivariate logistic regression analysis of LAT/SEC presence based on peri-procedural data in the training cohort.

Variable	Univariate analysis		Multivariate analysis	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Age, years	1.03 (1.02–1.05)	<0.001	1.04 (1.02–1.06)	0.001
Male sex	0.95 (0.72–1.27)	0.748		
Medical history				
HTN	1.68 (1.25–2.27)	0.001	1.44 (1.02–2.06)	0.041
T2DM	1.13 (0.82–1.54)	0.445		
Previous stroke/TIA	1.94 (1.41–2.65)	<0.001	1.79 (1.23–2.60)	0.002
Vascular disease	1.93 (0.95–3.74)	0.058		
Non-paroxysmal AF	3.58 (2.7–4.77)	<0.001	2.76 (1.99–3.85)	0.001
CAD	1.34 (1.01–1.78)	0.042		
laboratory data				
eGFR, ml/(min 1.73 m^2)	0.99 (0.98–0.99)	<0.001		
Uric acid, μmol/L	1.02 (1.01–1.04)	0.028		
PT-INR	1.5 (1.17–1.91)	0.001		
Echocardiographic parameters				
LAD, mm	1.27 (1.23–1.32)	<0.001	1.21 (1.16–1.26)	0.001
LVEDD, mm	1.09 (1.06–1.13)	<0.001		
LVEF, %	0.89 (0.86–0.91)	<0.001	0.92 (0.89–0.94)	0.001
Medication				
Statin	1.05 (0.79–1.39)	0.754		
Amiodarone	1.21 (0.88–1.67)	0.24		
Antiplatelet	1.02 (0.75–1.36)	0.918		

CAD, coronary artery disease; HTN, Hypertension; LAD, left atrium diameter; LAT, left atrial thrombus; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; SEC, spontaneous echo contrast; T2DM, Type 2 diabetes mellitus; TIA, transient ischemic attack.

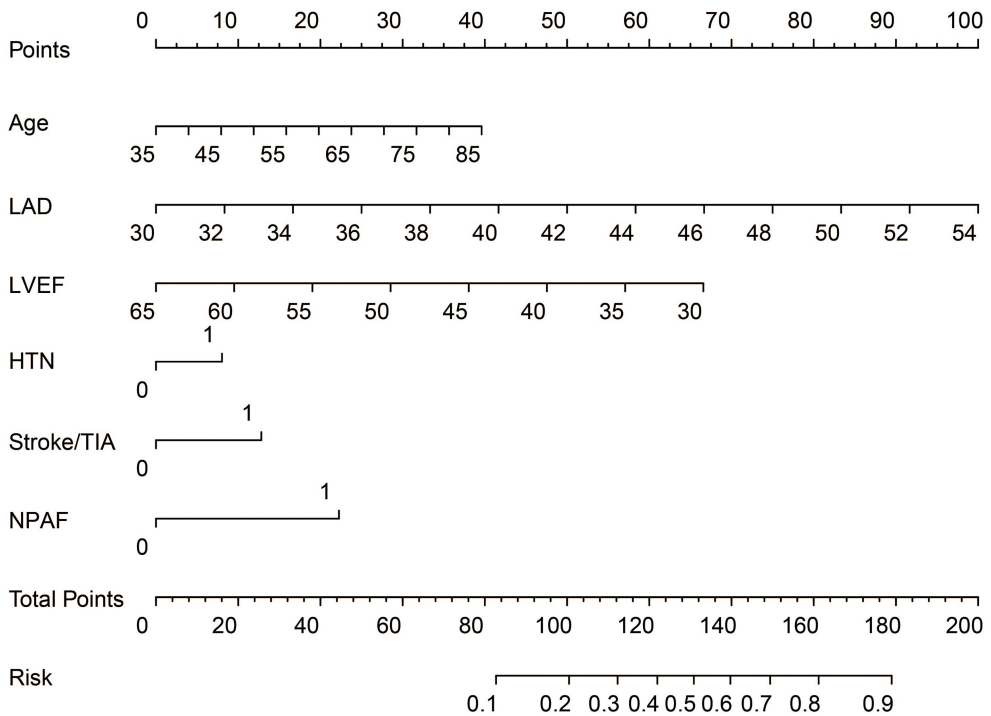

FIGURE 1 | Nomogram for peri-procedural estimation of LAT/SEC risk in NVAF patients. HTN, Hypertension; LAD, left atrium diameter; LVEF, left ventricular ejection fraction; NPAF, Non-paroxysmal AF.

Receiver operating characteristic curve analysis was used to investigate the optimal cutoff values that were determined by maximizing the Youden index (sensitivity + specificity – 1). The accuracy of the optimal cutoff value was assessed by the sensitivity, specificity, predictive values, and likelihood ratios. $P<.05$ was considered statistically significant. All analyses were performed using R software, version 4.0.

RESULTS

During the study period, 1,813 consecutive NVAF patients were collected. The patients were divided into the training (1,239, 68.3%) and validation cohorts (574, 31.7%). The baseline data were similar between the training and validation cohorts. The mean age of the participants was 62.6 ± 9.4 years. Of the total participants, 64.4% were males. LAT/SEC was found in 260 (21.0%) and 124 (21.6%) patients in the training and validation cohorts, respectively. The clinical and demographic characteristics of the patients are presented in **Table 1**.

The results of the univariate and multivariate logistic analysis are presented in **Table 2**. In the LAT/SEC group, patients had a higher prevalence of hypertension, prior stroke/TIA, non-paroxysmal AF, CAD, and larger left atrial diameter. Likewise, the LAT/SEC group had higher values of $CHADS_2$ and CHA_2DS_2-VASc scores, but lower left ventricular ejection fraction and estimated glomerular filtration rate. However, the prevalence of vascular disease and diabetes mellitus was similar in the two groups. The multivariate analysis showed that risk factors such as age (OR = 1.04, 95% CI: 1.02–1.06, and $P = 0.001$), LAD (OR = 1.21, 95% CI: 1.16–1.26, and $P = 0.001$), LVEF (OR = 0.92, 95% CI: 0.89–0.94, and $P = 0.001$), previous stroke/transient ischemic attack (OR = 1.79, 95% CI: 1.23–2.60, and $P = 0.002$), hypertension (OR = 1.44, 95% CI: 1.02–2.06, and $P = 0.041$) and non-paroxysmal AF (OR = 2.76, 95% CI: 1.99–3.85, and $P = 0.001$) remained independently associated with LAT/SEC.

ROC curve analysis was used to investigate the predictive power of the $CHADS_2$ and CHA_2DS_2-VASc scores concerning LAT/SEC. The results showed that the c-statistic of the $CHADS_2$ and CHA_2DS_2-VASc scores were 0.608 and 0.606, respectively. Furthermore, we developed a LAT/SEC risk estimation nomogram based on the results of the multivariate logistic analysis (**Figure 1**). The bootstrap validation method was used to internally validate the resulting model.

The nomogram demonstrated a very good predictive power in estimating the risk of LAT/SEC, with an unadjusted C index of 0.836. Besides, calibration plots graphically showed good agreement on the presence of LAT/SEC between the risk estimation by the nomogram and TEE confirmation. In the validation cohort, the nomogram displayed a C index of 0.794 for the estimation of LAT/SEC risk. Also, our result indicates that the observed frequencies and the estimated probability of LAT/SEC presence showed a good calibration curve for the risk estimation (**Figures 2A–D**). The decision curve shows the clinical usefulness of the nomogram (**Figures 2E,F**). In this analysis,

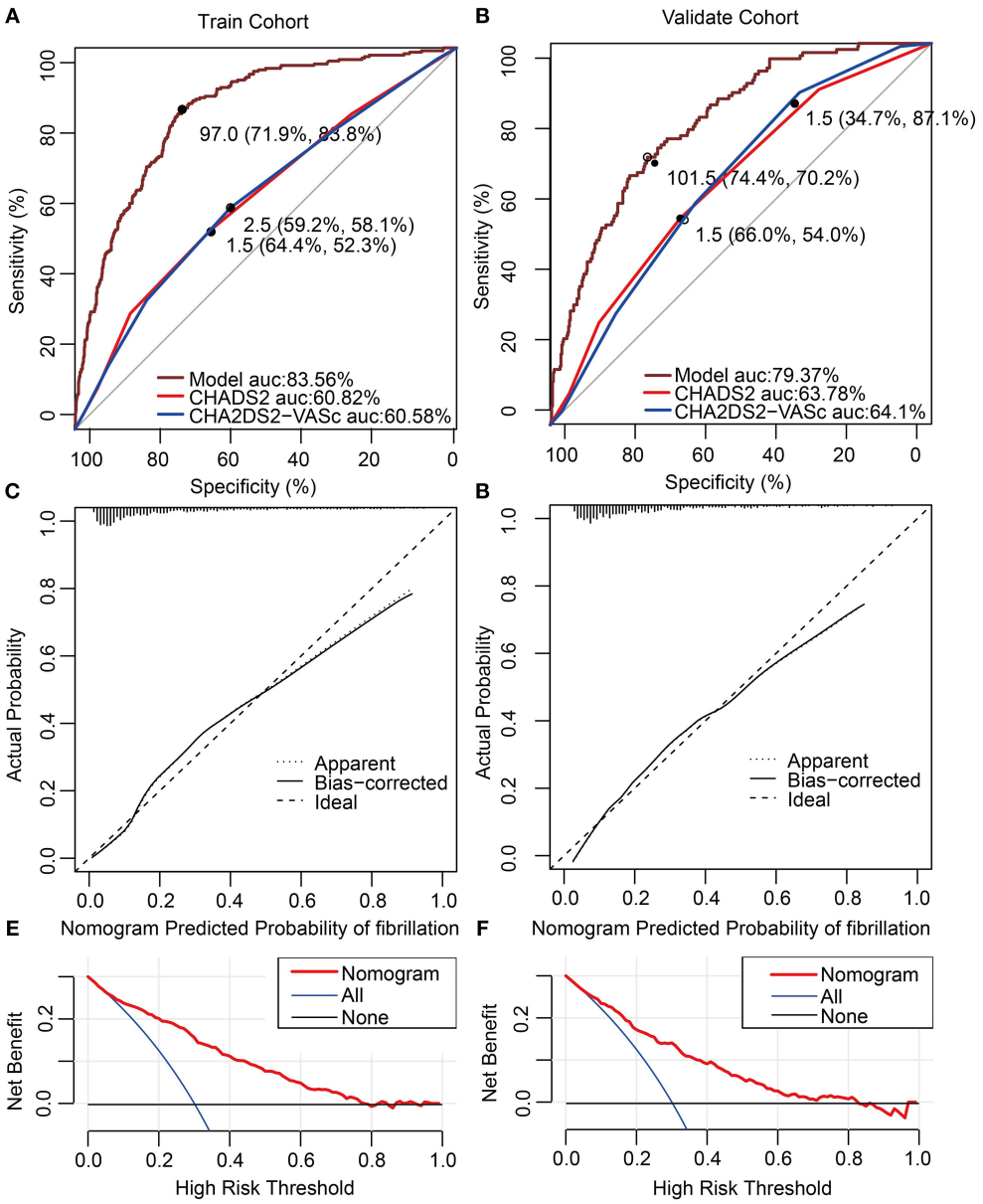

FIGURE 2 | (A,B) Receiver operating characteristic curve for models in predicting LAT/SEC in the training cohort and validation cohort. **(C)** Calibration curves for the nomogram in the training cohort. The dotted line represents the entire cohort ($n = 1,239$), and the solid line is the result after bias-correction by bootstrapping (1,000 repetitions), indicating nomogram performance (boot mean absolute error = 0.027). **(D)** Calibration curves for the nomogram in the validation cohort. The dotted line represents the entire cohort ($n = 574$), and the solid line is the result after bias-correction by bootstrapping (1,000 repetitions), indicating nomogram performance (boot mean absolute error = 0.020). **(E,F)** Decision curve analysis for the nomogram in the training cohort and validation cohort. The decision curve of the nomogram is composed of an *X*-axis which represents continuum of potential thresholds for LAT/SEC risk and a *Y*-axis which represents the net benefit which is obtained by dividing the net true positives by the sample size. The "All" curve shows the net benefit if all patients subject to transesophageal echocardiography (TEE). The "None" line shows the net benefit if no patient subject to TEE. The "Nomogram" curve shows the net benefit if it is used to select patients for TEE. For example, if the personal threshold probability of a patient was 40%, the net benefit would be 0.1 when using the nomogram to decide whether to conduct TEE examination, which means that there are 10 net detected LAT/SEC per 100 patients.

the final decision curve showed that for a threshold probability between 10 and 80%, the model had positive net benefit.

The optimal cutoff value of the total nomogram scores was determined to be 97.0. The sensitivity, specificity, positive predictive value, and negative predictive value were 83.8, 71.9, 44.2, and 94.4%, respectively in the training cohort, and 70.2, 74.4,43.1, and 90.1%, respectively in the validation cohort (**Table 3**).

TABLE 3 | Accuracy of the prediction score of the nomogram for estimating the risk of LAT/SEC.

Variable	Nomogram		$CHADS_2$ score		CHA_2D_2VASc score	
	Training cohort	Validation cohort	Training cohort	Validation cohort	Training cohort	Validation cohort
AUC	0.84	0.79	0.61	0.64	0.61	0.64
Cutoff score	97.0	101.5	1.5	1.5	2.5	1.5
Specificity, %	71.9	74.4	64.4	66.0	59.2	34.7
Sensitivity, %	83.8	70.2	52.3	54.0	58.1	87.1
NPV, %	94.4	90.1	83.6	83.9	84.2	90.7
PPV, %	44.2	43.1	28.0	30.5	27.5	26.9

AUC, Area under ROC curve; NPV, Negative predictive value; PPV, Positive predictive value; ROC, receiver operating characteristic.

DISCUSSION

The present study that established the first nomogram for LAT/SEC risk estimation in patients with NVAF found that a new model composed of age, LAD, LVEF, previous stroke or transient ischemic attack, HTN and non-paroxysmal AF had a better performance for the prediction of LAT/SEC compared to $CHADS_2$ and CHA_2DS_2-VASc scores.

The prevalence of LAT/SEC for patients with AF varied in previous studies (2, 4, 13). In our study, the prevalence of LAT/SEC was 21.2% in NVAF population. In the present study, two variables that are not included in the CHA_2DS_2-VASc score were found to be the top predictors of LAT/SEC. Two predictors include LAD and non-paroxysmal AF. Therefore, it may be reasonable to consider NVAF patients with the enlarged left atrium and non-paroxysmal AF as candidates for more intensive medical follow-up. The association between these factors and LAT/SEC has also been reported in previous studies (7, 14–16). For instance, left atrial enlargement has been shown to associate with LAT/SEC, which is a surrogate marker of stroke risk (14, 17). Earlier evidence also reported that the possibility of thrombus formation increases with an enlarged LA cavity (14, 18). Although many mechanisms can explain the association between left atrial enlargement and thrombus formation, the mechanism that involves changes in left atrial hemodynamics, such as the existence of turbulences, reduced flow velocity, increased blood stasis and endothelial injury could be speculated as plausible mechanisms (19).

As earlier mentioned, non-paroxysmal AF remained a significant predictor for LAT/SEC in our study. Although the current ESC guidelines do not list AF type or AF burden among factors affecting the probability of LAA thrombus formation, few studies have shown that persistent or permanent AF carries a higher risk of stroke than paroxysmal AF (20). Relative to paroxysmal AF, non-paroxysmal AF shows greater structural remodeling and endocardial fibroelastosis of the atria and appendage, both of which are likely to contribute to thrombus formation (21, 22).

In our study, there were still 103 (14.9%) patients with LAT/SEC among the low-risk group (classified based on CHA_2DS_2-VASc score). In addition, the c-statistics of the $CHADS_2$ and CHA_2DS_2-VASc scores were 0.608 and 0.606, respectively, suggesting $CHADS_2$ and CHA_2DS_2-VASc scores had relatively weaker predictive performance in discriminating LAT/SEC compared to the new model. There could be two reasons that contribute to the observed phenomenon. Firstly, the models share the same risk factor with atherosclerosis. Consequently, $CHADS_2$ and CHA_2DS_2-VASc scores may predict stroke through the mechanism of atherosclerosis but not *via* mechanisms that involve cardiogenic embolism. Secondly, these risk scores do not incorporate other risk factors that are highly linked to thrombo-embolic risks, such as echocardiographic components, biochemical concentrations, and coagulation parameters that are known for predisposing stasis of blood within the left atrium and appendage.

In this study, our multivariate analysis revealed several predictors of LAT/SEC. By combining these predictors of LAT/SEC, we constructed a nomogram model. Interestingly, the newly constructed model demonstrated a strong discriminatory performance to identify patients with increased risk of LAT/SEC. The prognostic relevance of such a model of clinical risk factors has not been prospectively studied in the past. According to our results, the discriminatory performance of the new composition score was even stronger than $CHADS_2$ and CHA_2DS_2-VASc scores. For clinical use of the model, we recommend 97.0 as the cutoff value, and patients with a score of 97.0 or more should be considered as a high-risk group for LAT/SEC. Based on these predictions from the nomogram, the new model might serve as a substitute of TEE for NVAF patients who cannot tolerate TEE and provide references about whether to stop anticoagulants after procedural in the follow-up.

Our study has some limitations. First, this analysis was based on data from a single institution, thus it is necessary to validate the results from other centers. Second, this analysis is a retrospective study, some specific markers which might be associated with LAT/SEC such as left atrial appendage morphology, markers of endothelial dysfunction, and inflammation were not included in the nomogram. Moreover, the current study lacks data on left atrial volume, a more accurate marker to assess left atrial size. Third, the nomogram achieved a good predictive accuracy, with a cutoff point of 97.0, however, it demonstrated a significant proportion of false-positive and

false-negative rates in the training (28.1 and 16.2%, respectively) and validation cohort (25.6 and 29.8%, respectively), which indicates replication of such study is of crucial importance in the future study to confirm the power of the utilized model in clinical decision making. Finally, the present study included only NVAF patients who underwent TEE before ablation or cardioversion intervention, therefore our results may be limited to NVAF patients who are candidates for ablation or cardioversion interventions.

CONCLUSIONS

Our study showed that Age, LAD, LVEF, HTN, previous stroke or transient ischemic attack, and Non-paroxysmal AF were the risk factors of LAT/SEC from AF patients. By combining these risk factors of LAT/SEC, a nomogram was constructed. The model provides an optimal peri-procedural estimation of LAT/SEC risk in patients with non-valvular atrial fibrillation.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the First Affiliated Hospital of the Dalian Medical University Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

XY and YX designed this study. ZL, QL, and YT were in charge of data analysis and data collection. ZL drafted the article. FL and TH did the critical revision of article. TC and LG conducted the data collection. All authors have read and approved the final manuscript.

ACKNOWLEDGMENTS

We would like to acknowledge Yidu cloud (Beijing) Technology Ltd. for their worthy cooperation in data searching, extraction, and processing.

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frontiers in Cardiovascular Medicine

SYSTEMATIC REVIEW
published: 15 October 2021
doi: 10.3389/fcvm.2021.757188

Reappraisal of Non-vitamin K Antagonist Oral Anticoagulants in Atrial Fibrillation Patients: A Systematic Review and Meta-Analysis

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OPEN ACCESS

Edited by:
Roberto Pola,
Università Cattolica del Sacro Cuore, Italy

Reviewed by:
Håkan Wallen,
Karolinska Institutet (KI), Sweden
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Specialty section:
This article was submitted to Thrombosis, a section of the journal Frontiers in Cardiovascular Medicine

Received: *11 August 2021*
Accepted: *21 September 2021*
Published: *15 October 2021*

Citation:
Liu F, Yang Y, Cheng W, Ma J and Zhu W (2021) Reappraisal of Non-vitamin K Antagonist Oral Anticoagulants in Atrial Fibrillation Patients: A Systematic Review and Meta-Analysis. Front. Cardiovasc. Med. 8:757188. doi: 10.3389/fcvm.2021.757188

Background: Recent observational studies have compared effectiveness and safety profiles between non-vitamin K antagonist oral anticoagulants (NOACs) and warfarin in patients with atrial fibrillation (AF). Nevertheless, the confounders may exist due to the nature of clinical practice-based data, thus potentially influencing the reliability of results. This systematic review and meta-analysis were conducted to compare the effect of NOACs with warfarin based on the propensity score-based observational studies vs. randomized clinical trials (RCTs).

Methods: Articles included were systematically searched from the PubMed and EMBASE databases until March 2021 to obtain relevant studies. The primary outcomes were stroke or systemic embolism (SSE) and major bleeding. Hazard ratios (HRs) and 95% confidence intervals (CIs) of the outcomes were extracted and then pooled by the random-effects model.

Results: A total of 20 propensity score-based observational studies and 4 RCTs were included. Compared with warfarin, dabigatran (HR, 0.82 [95% CI, 0.71–0.96]), rivaroxaban (HR, 0.80 [95% CI, 0.75–0.85]), apixaban (HR, 0.75 [95% CI, 0.65–0.86]), and edoxaban (HR, 0.71 [95% CI, 0.60–0.83]) were associated with a reduced risk of stroke or systemic embolism, whereas dabigatran (HR, 0.76 [95% CI, 0.65–0.87]), apixaban (HR, 0.61 [95% CI, 0.56–0.67]), and edoxaban (HR, 0.58 [95% CI, 0.45–0.74]) but not rivaroxaban (HR, 0.92 [95% CI, 0.84–1.00]) were significantly associated with a decreased risk of major bleeding based on the observational studies. Furthermore, the risk of major bleeding with dabigatran 150 mg was significantly lower in observational studies than that in the RE-LY trial, whereas the pooled results of observational studies were similar to the data from the corresponding RCTs in other comparisons.

Conclusion: Data from propensity score-based observational studies and NOAC trials consistently suggest that the use of four individual NOACs is non-inferior to warfarin for stroke prevention in AF patients.

Keywords: anticoagulants, atrial fibrillation, propensity score, outcomes, meta-analysis

INTRODUCTION

Atrial fibrillation (AF), the most common arrhythmia in clinical practice, increases the five-fold risk of ischemic stroke and two-fold for all-cause mortality (1, 2). Before 2010, warfarin was primarily used to prevent stroke in AF patients, but there is a limited range for treatment due to the regular monitoring of the international normalized ratio (INR), and the dosage is adjusted frequently (3). Subsequently, non-vitamin K oral anticoagulants (NOACs), including direct thrombin inhibitor (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) are recommended as the preferred drugs for stroke prevention among nonvalvular AF patients (4–6). Compared with warfarin, NOACs do not require anticoagulation monitoring, have easier dosing regimens, and have fewer food and drug interactions (7).

Previous randomized clinical trials (RCTs) have shown that the efficacy and safety of the NOACs are superior or non-inferior to warfarin in AF patients. Specifically, compared with warfarin, dabigatran is associated with lower rates of stroke and systemic embolism (SSE) and a similar rate of major bleeding (8), apixaban has decreased rates of SSE and MB (9), rivaroxaban has non-inferior rates of SSE and a similar rate of major bleeding (10), and edoxaban has non-inferior rates of SSE and a lower rate of major bleeding (11). Although RCTs could ensure the balance of results between different patient groups and get a fair evaluation of the trial treatment effect, they limit the assessment of the risks and benefits of interventions for all the populations when these interventions are used in real-world settings. By contrast, observational studies could infer a wider range of patient characteristics and evaluate a broader range of outcomes over a more extended period (12, 13). More recently, many observational studies have been published to compare the effectiveness and safety of NOACs vs. warfarin in AF patients. However, the obvious confounders and significant biases may exist in several observational studies due to the nature of clinical practice-based data, thus potentially influencing the reliability of findings.

An effective method to evaluate interventions' effectiveness in typical clinical settings can be provided by the propensity score (PS) (14). Observational studies using the PS method may alter the target population by changing the distribution of patient baseline characteristics that facilitate analysis. Therefore, the PS analysis can be used to reduce biases in comparisons between the targeted populations and controls. In the present meta-analysis, we aimed to compare the effectiveness and safety profiles between NOACs and warfarin based on the PS-based observational studies, and further test whether the pooled results of high-quality observational studies were consistent with data from the corresponding RCTs.

METHODS

This systematic review and meta-analysis were carried out based on the Cochrane Handbook for systemic reviews. The results were presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. Ethical approval was not provided because we only included the published studies.

We performed a systematic search in detail on the PubMed and EMBASE databases until March 2021 to obtain all the relevant studies. To obtain a balanced covariate distribution between groups of NOACs and warfarin, we included observational articles that applied the PS-based methods. In addition, 4 RCTs of NOACs vs. warfarin were also selected (dabigatran [RE-LY], rivaroxaban [ROCKET AF], apixaban [ARISTOTLE], and edoxaban [ENGAGE AF-TIMI 48]). The primary outcomes were SSE and major bleeding. Data extraction was conducted independently by two researchers. The hazard ratios (HR) and 95% confidence intervals (CIs) were considered as the effect sizes, and the pooled by the random-effects model. To test the stability of the results, we re-conducted the analysis using the fixed-effects model, inverse variance heterogeneity (IVhet), and quality effects (QE) models. Detailed information including eligibility criteria, literature search, study selection, and data extraction, quality assessment, and statistical analysis was provided in **Supplementary Materials**.

All the statistical analyses were carried out by Review Manager 5.3 software (the Cochrane Collaboration 2014. Nordic Cochrane Centre Copenhagen, Denmark), the Stata software (version 16.0, Stata Corp LP, College Station, TX), and MetaXL (version 5.3).

RESULTS

Study Selection

The flow chart of document retrieval is presented in **Supplementary Figure 1**. A total of 1,139 studies from two electronic databases were under-identification. A total of 782 studies remained after duplication removal, and then 57 studies were left based on the screenings of titles/abstracts. Among the 57 studies undergoing the full-text screenings, 33 of them were excluded due to the following reasons: (1) 23 studies used overlapping databases; (2) 3 studies included single-center patients, and the sample size was less than 1,000; (3) 5 studies reported the comparisons between combined NOACs vs. warfarin, or did not regard warfarin as the reference; (4) 2 studies did not use the PS-based methods to match baseline patient characteristics. Finally, 24 studies (3, 7–11, 15–32) (20 observational cohort studies and 4 RCTs) were included in our current meta-analysis.

Baseline Characteristics of the Included Studies

The baseline characteristics of the included RCTs are shown in **Supplementary Table 1**. Detailed information was categorized into different groups based on the dose of NOACs. Baseline characteristics of the 20 observational studies are shown in **Table 1**. Although some studies extracted data from the same database, they analyzed different kinds of NOACs, included diverse study periods, or included different outcomes for analysis. For instance, both Gupta et al. (25) and Villines et al. (26) obtained data from the US Department of Defense, but the study periods ranged from 2013 to 2015 for Gupta et al., and from 2009 to 2012 for Villines et al. All the included studies

TABLE 1 | Baseline characteristics of included observational studies.

Included studies	Location	Data source	Comparisons	Sample size (n)*	Age (y)*	Female (%)*	Follow-up (months)*	Outcomes in the analysis	PS methods
Mitsuntisuk et al. (15)	Thailand	REAL-T AF trial, 01/2012–04/2018; age≥18 years; retrospective	DA vs. WAR RIV vs. WAR API vs. WAR	405/605 441/605 604/605	71.63/68.40	48.21/50.25	26.44/33.84	SSE, MB, IS, all-cause death, ICH, GIB	IPTW
Nielsen et al. (16)	Denmark	Three Danish nationwide databases, 08/2011–02/2016; retrospective	DA vs. WAR RIV vs. WAR API vs. WAR	4400/38893 8875/38893 3476/38893	80.54/71.00	55.41/40.40	27.60	SSE, MB, IS, all-cause death	IPTW
Larsen et al. (17)	Denmark	Three Danish nationwide database, 08/2011–10/2015; retrospective	DA vs. WAR RIV vs. WAR API vs. WAR	6349/35436 12701/35436 7192/35436	69.65/72.40	37.82/41.20	22.80	SSE, MB, IS, all cause-death, ICH	IPTW
Kohsaka et al. (18)	Japan	MDV, 03/2011–07/2018, retrospective	DA vs. WAR RIV vs. WAR API vs. WAR EDO vs. WAR	22752/19059 8003/19059 12592/19059 17481/19059	76.08/76.10	38.74/38.80	24.00	SSE, MB, IS, ICH, GIB	IPTW
Lee et al. (19)	Korea	Korean Health Insurance Review and Assessment database, 01/2015–12/2017, retrospective	DA vs. WAR RIV vs. WAR API vs. WAR EDO vs. WAR	35965/25420 17745/25420 22177/25420 15496/25420	70.93/71.20	44.36/45.50	-	MB, IS, ICH, GIB	IPTW
Cha et al. (20)	Korea	NHIS, 01/2014–12/2015, retrospective	DA vs. WAR RIV vs. WAR API vs. WAR	5681/23222 3741/23222 2189/23222	70.08/68.82	45.27/43.10	5.97/18.12	IS, all-cause death, ICH	PSM
Bang et al. (21)	Korea	Korea's nationwide health insurance claims database, 01/2015–11/2016, retrospective	DA vs. WAR RIV vs. WAR API vs. WAR	-	-	-	-	SSE, MB, ICH, GIB	IPTW
Chan.et al. (22)	Taiwan	Taiwan's National Health Insurance Research Database, 06/2012–12/2017, retrospective	DA vs. WAR RIV vs. WAR API vs. WAR EDO vs. WAR	4577/19761 9952/19761 33022/19761 22371/19761	74.7/74.6 74.8/74.6 74.7/74.6 74.7/74.6	42.8/43.3 42.4/43.3 42.5/43.3 42.6/43.3	16	SSE, MB, IS, ICH, GIB	IPTW
Laliberte et al. (23)	USA	SHS Patient Transactional Datasets, 05/2011–07/2012, retrospective	RIV vs. WAR	3654/14616	73.30/73.70	51.00/51.50	2.77/3.77	SSE, MB, IS, ICH, GIB	PSM
Wanat et al. (24)	USA	GE Centricity EMR database, 01/2012–12/2016, retrospective	API vs. WAR	10189/10189	72.10/72.20	46.90/46.60	12.00	SSE	PSM

(Continued)

TABLE 1 | Continued

Included studies	Location	Data source	Comparisons	Sample size (n)*	Age (y)*	Female (%)*	Follow-up (months)*	Outcomes in the analysis	PS methods
Gupta et al. (25)	USA	DOD, 01/01/2013–30/09/2015, retrospective	DA vs. WAR RIVvs. WAR API vs. WAR	3691/3691 8226/8226 7607/7607	76.03/76.07	41.31/41.20	5.60/5.03	SSE, MB, IS, ICH, GIB	PSM
Villines et al. (26)	USA	DOD, 10/2009–07/2012, retrospective	DA vs. WAR	12793/12793	73.80/74.00	41.20/41.10	9.91/7.24	MB, IS, all-cause death, ICH, GIB	PSM
Russo-Alvarez et al. (27)	USA	CCHS, 01/2012–07/2016, retrospective	RIV vs. WAR	472/472	73.60/73.60	38.80/36.40	-	MB	PSM
Adeboyeje et al. (28)	USA	HIRE, 11/2010–02/2015, retrospective	DA vs. WAR RIVvs. WAR API vs. WAR	8539/23431 3689/23431 8398/23431	70.00/70.00	41.07/40.90	6.05/9.50	MB, ICH, GIB	IPTW
Chang et al. (29)	USA	IMS Health LifeLink Health Plan Claims Database, 10/2010–03/2012, retrospective	DA vs. WAR RIV vs. WAR	4907/39607 1649/39607	60.89/57.40	36.08/46.90	1.95/1.57	GIB	PSM
Lip et al. (3)	USA	US Centers for Medicare and Medicaid Services Medicare data and 4 commercial claims database, 01/01/2013–30/09/2015 retrospective	DA vs. WAR RIV vs. WAR API vs. WAR	100977/100977 36990/36990 125068/125068	75.45/75.48	47.11/47.00	4.51/5.27	SSE, MB, IS, ICH, GIB	PSM
Hernandez et al. (30)	USA	CMS, 10/2010–10/2011, retrospective	DA vs. WAR	1302/8102	75.10/75.60	57.90/59.00	5.90/7.60	MB, ICH, GIB	IPTW
Huybrechts et al. (31)	USA	MarketScan and Optum, 10/2010–09/2015, prospective	DA vs. WAR RIV vs. WAR API vs. WAR	29448/29448 35520/35520 19588/19588	69.88/69.78	38.95/38.42	-	SSE, MB, IS, all-cause death, ICH, GIB	PSM
Bradley et al. (7)	USA	SDD, 12/2012–06/2018, age≥21 years, retrospective	API vs. WAR	55038/55030	71.30/71.30	39.30/39.20	-	IS, ICH, GIB	PSM
Go et al. (32)	USA	SDD, 11/2010–05/2014, age≥21 years, retrospective	DA vs. WAR	25289/25289	68.48.68.34	36.10/35.70	4.10/3.40	IS, ICH, GIB	PSM

*****Data after PSM or IPTW.*

MDV, Medical Data Vision Co Ltd; NHIS, Korean National Health Insurance Service database; SHS, Symphony Health Solutions' (SHS) Patient Transactional Datasets; DOD, US Department of Defense; CCHS, Cleveland Clinic Health System; HIRE, HealthCore Integrated Research Environment; CMS, Centers for Medicare and Medicaid Services; SDD, the Sentinel Distributed Database;DA, dabigatran; RIV, rivaroxaban; API, apixaban; EDO, edoxaban; WAR, warfarin; SSE, stroke or systemic embolism; MB, major bleeding; IS, ischemic stroke; ICH, intracranial hemorrhage; GIB, gastrointestinal bleeding; PS, Propensity Score; PSM, propensity score matching; IPTW, inverse probability of treatment weighting; NA, diagnostic not available; SD, standardized difference.

applied the PS-based methods to balance the covariates between groups [propensity score matching [PSM], $n = 11$ (3, 7, 20, 23–27, 29, 31, 32), and inverse probability of treatment weighting [IPTW], $n = 9$ (15–19, 21, 22, 28, 30)]. For the PS diagnostics, 14 studies used standardized differences, and 6 studies failed to report any further diagnostic use.

The results of the risk of bias assessment for RCTs are shown in **Supplementary Table 2**, suggesting low risks in biases. The methodological quality assessment of observational cohorts was carried out by the NOS tool (**Supplementary Table 3**). All articles scored 7 or more points indicating relatively high quality.

Comparisons Between Individual NOAC and Warfarin

Based on the observational studies, the crude event rates and pooled HRs (based on random-effects model) of the outcomes between each NOAC vs. warfarin are summarized in **Table 2**.

Primary Outcomes Between Each NOAC vs. Warfarin

As presented in **Figure 1**, compared with warfarin, dabigatran was associated with reduced risks of SSE (2.08 vs. 2.89%; HR, 0.82 [95% CI, 0.71–0.96]) and major bleeding (2.65 vs. 4.14%; HR, 0.76 [95% CI, 0.65–0.87]). The results of rivaroxaban vs. warfarin are shown in **Figure 2**. Compared with warfarin use, the use of rivaroxaban was markedly associated with a reduced risk of SSE (1.37 vs. 2.29%; HR, 0.80 [95% CI, 0.75–0.85]). Meanwhile, it presented a comparable risk of major bleeding (3.31 vs. 4.14%; HR, 0.92 [95% CI, 0.84–1.00]) between rivaroxaban vs. warfarin. As shown in **Figure 3**, the use of apixaban vs. warfarin was related to reduced risks of SSE (1.08 vs. 2.47%; HR, 0.75 [95% CI, 0.65–0.86]) and major bleeding (2.12 vs. 4.35%; HR, 0.61 [95% CI, 0.56–0.67]). As shown in **Supplementary Figure 2**, compared with warfarin use, the use of edoxaban was significantly associated with decreased risks of SSE (1.16 vs. 3.84%; HR, 0.71 [95% CI, 0.60–0.83]) and major bleeding (0.88 vs. 2.80%; HR, 0.58 [95% CI, 0.45–0.74]).

Secondary Outcomes Between NOAC vs. Warfarin

Compared with warfarin, dabigatran was associated with reduced risks of ischemic stroke (HR, 0.93 [95% CI, 0.86–1.00]) and intracranial hemorrhage (HR, 0.46 [95% CI, 0.38–0.55]), but had similar risks of all-cause death and gastrointestinal bleeding (**Supplementary Figure 3**). As for rivaroxaban vs. warfarin shown in **Supplementary Figure 4**, it was associated with reduced risks of ischemic stroke (HR, 0.84 [95% CI, 0.79–0.90]) and intracranial hemorrhage (HR, 0.69 [95% CI, 0.63–0.76]), but had comparable risks of all-cause death and gastrointestinal bleeding. The use of apixaban vs. warfarin was significantly associated with reduced risks of ischemic stroke (HR, 0.73 [95% CI, 0.62–0.86]), intracranial hemorrhage (HR, 0.62 [95%

TABLE 2 | Pooled HRs of the effectiveness and safety outcomes between NOACs vs. warfarin in patients with AF.

	SSE	Major bleeding	Ischemic stroke	All-cause death	Intracranial hemorrhage	Gastrointestinal bleeding
DA vs. WAR						
No. of effect estimates	9	13	11	5	13	12
Crude event rates	2.08 vs. 2.89%	2.65 vs. 4.14%	1.46 vs. 2.14%	4.34 vs. 8.55%	0.29 vs. 0.81%	1.26 vs. 1.57%
HRs and 95% CIs	0.82 (0.71–0.96)	0.76 (0.65–0.87)	0.93 (0.86–1.00)	0.75 (0.53–1.04)	0.46 (0.38–0.55)	0.97 (0.80–1.17)
P-value	0.01	0.0001	0.06	0.08	<0.00001	0.73
I^2 statistic	82%	91%	25%	91%	66%	93%
RIV vs. WAR						
No. of effect estimates	10	13	10	4	11	10
Crude event rates	1.37 vs. 2.29%	3.31 vs. 4.14%	1.36 vs. 2.18%	8.60 vs. 11.69%	0.47 vs. 0.89%	1.72 vs. 1.83%
HRs and 95% CIs	0.80 (0.75–0.85)	0.92 (0.84–1.00)	0.84 (0.79–0.90)	1.02 (0.77–1.36)	0.69 (0.63,0.76)	0.96 (0.82,1.12)
P-value	<0.00001	0.06	<0.00001	0.88	<0.00001	0.62
I^2 statistic	15%	83%	29%	94%	27%	89%
API vs. WAR						
No. of effect estimates	10	11	10	4	11	9
Crude event rates	1.08 vs. 2.47%	2.12 vs. 4.35%	0.85 vs. 1.96%	3.24 vs. 10.41%	0.27 vs. 0.80%	0.78 vs. 1.73%
HRs and 95% CIs	0.75 (0.65–0.86)	0.61 (0.56–0.67)	0.73 (0.62–0.86)	0.77 (0.39–1.54)	0.62 (0.50–0.75)	0.63 (0.54–0.73)
P-value	<0.0001	<0.00001	0.0002	0.46	<0.00001	<0.00001
I^2 statistic	88%	73%	83%	97%	75%	84%
EDO vs. WAR						
No. of effect estimates	2	3	3	-	2	3
Crude event rates	1.16 vs. 3.84%	0.88 vs. 2.80%	1.17 vs. 2.83%	-	0.22 vs. 1.10%	0.62 vs. 1.66%
HRs and 95% CIs	0.71 (0.60–0.83)	0.58 (0.45–0.74)	0.67 (0.59–0.76)	-	0.60 (0.25–1.44)	0.65 (0.41–1.04)
P-value	<0.0001	<0.0001	<0.00001	-	0.25	0.07
I^2 statistic	0%	68%	0%	-	95%	90%

SSE, stroke or systemic embolism; DA, dabigatran; RIV, rivaroxaban; API, apixaban; EDO, edoxaban; WAR, warfarin; HR, hazard ratio; CI, confidence interval.

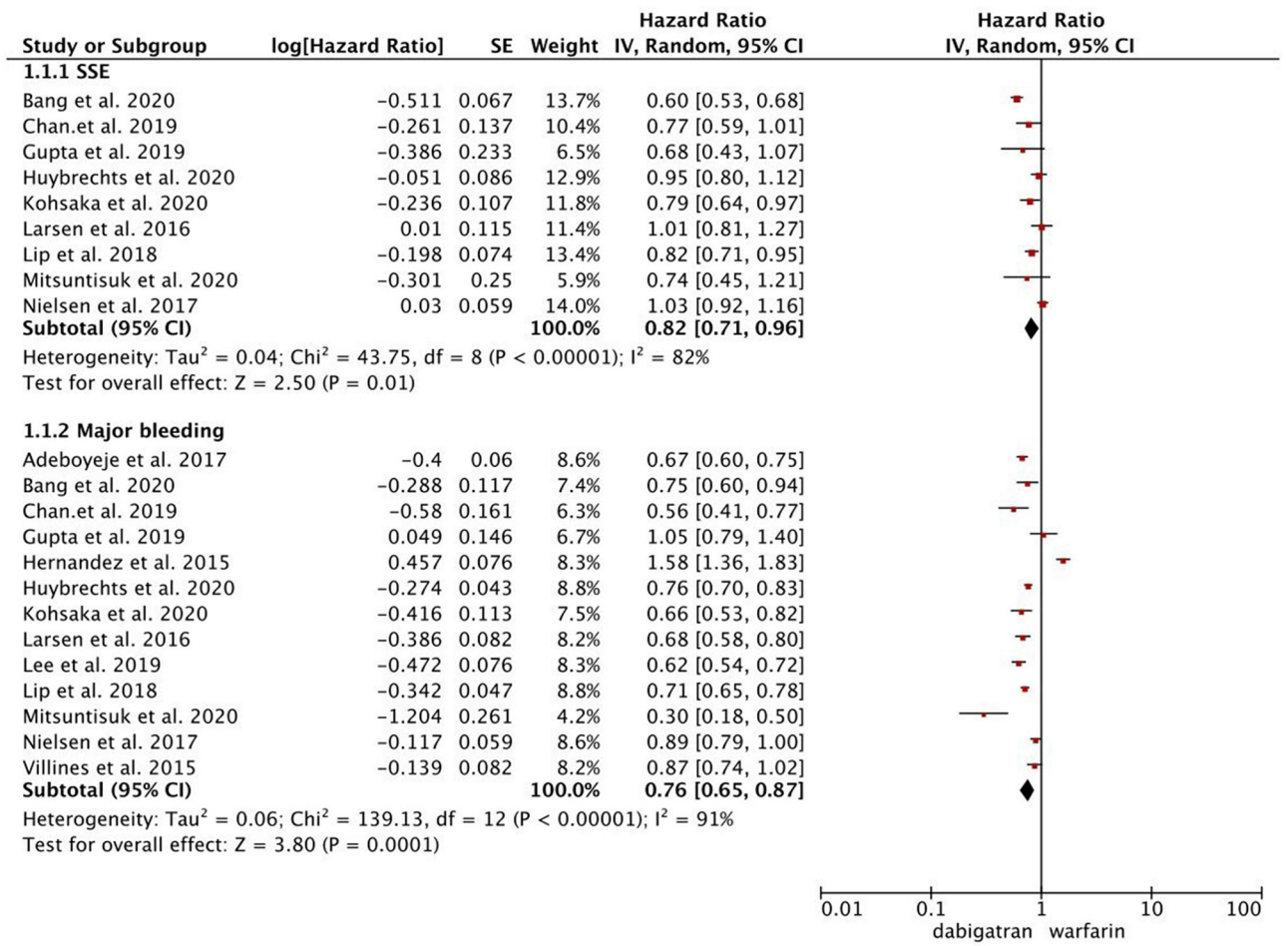

FIGURE 1 | Comparing the primary outcomes including SSE and MB of dabigatran vs. warfarin. SSE, stroke or systemic embolism; MB, major bleeding; HR, hazard ratio; CI, confidence interval; SE, standard error; IV, inverse of the variance.

CI, 0.50–0.75]), and gastrointestinal bleeding (HR, 0.63 [95% CI, 0.54–0.73]), but displayed no difference in all-cause death (**Supplementary Figure 5**). The use of edoxaban vs. warfarin was related to a decreased risk of ischemic stroke (HR, 0.67 [95% CI, 0.59–0.76]), whereas similar risks were observed in intracranial hemorrhage and gastrointestinal bleeding between the two study groups (**Supplementary Figure 2**).

Sensitivity Analysis and Subgroup Analysis

In the sensitivity analysis, the results of the primary outcomes from the IVhet or QE models (**Supplementary Figures 6–9**) were similar to those from the primary analysis using the random-effects model. In addition, the results did not change substantially when we re-conducted the analyses using the fixed-effects model (**Supplementary Table 4**).

As shown in **Supplementary Table 4**, the subgroup analyses concerning the primary outcomes suggested no significant interactions grouped by the NOAC-dose and follow-up period. For the subgroup analysis based on the regions, Asians showed fewer risks of SSE and major bleeding than non-Asians in the group of dabigatran vs. warfarin. In the group of rivaroxaban vs. warfarin, Asians showed fewer risks of major bleeding compared with non-Asians. In the group of apixaban vs. warfarin, the risk of SSE was significantly lowered in Asians compared with non-Asians. There were not enough studies for the subgroup analyses between edoxaban vs. warfarin.

Summary Effect Estimates Between Observational Studies and RCTs

Comparative effect estimates of NOACs vs. warfarin between observational studies and RCTs are shown in **Table 3**. For the primary outcomes, dabigatran 150 mg vs. warfarin had a significantly lower risk of major bleeding in the observational studies (HR, 0.72 [95% CI, 0.66–0.78]) than that in the RE-LY trial (HR, 0.93 [95% CI, 0.81–1.07]) ($P_{\text{interaction}} = 0.002$). In other comparisons, the pooled effects of the observational studies were consistent with data from the corresponding NOAC trials.

For the secondary outcomes, dabigatran 110 mg vs. warfarin demonstrated a higher risk of all-cause death in observational studies (HR, 1.05 [95% CI, 0.99–1.12]) than that in the

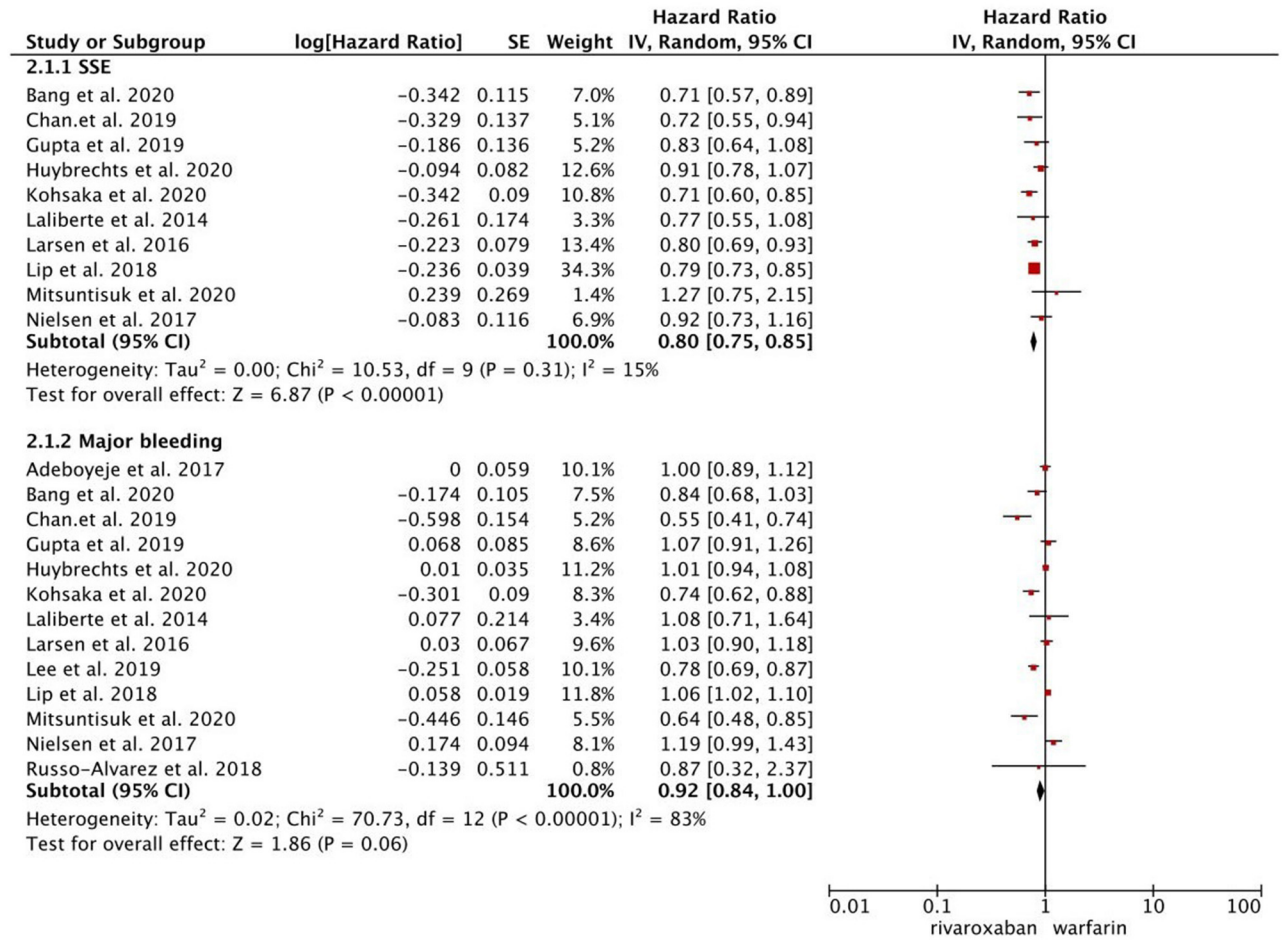

FIGURE 2 | Comparing the primary outcomes including SSE and MB of rivaroxaban vs. warfarin. SSE, stroke or systemic embolism; MB, major bleeding; HR, hazard ratio; CI, confidence interval; SE, standard error; IV, inverse of the variance.

RE-LY trial (HR, 0.91 [95% CI, 0.80–1.03]) ($P_{interaction}$ = 0.04). Dabigatran 150 mg vs. warfarin showed a lower risk of gastrointestinal bleeding in observational studies (HR, 1.03 [95% CI, 0.83–1.28]) compared with that in the RE-LY trial (HR, 1.50 [95% CI, 1.19–1.89]) ($P_{interaction}$ = 0.02). The pooled HR of apixaban 5/2.5 mg vs. warfarin for gastrointestinal bleeding was significantly lower in observational studies (HR, 0.58 [95% CI, 0.43–0.77]) compared to that of the ARISTOTLE trial (HR, 0.89 [95% CI, 0.70–1.15]) ($P_{interaction}$ = 0.03). Meanwhile, all the effect estimates of rivaroxaban vs. warfarin were similar between observational studies and the ROCKET AF trial, whereas no enough studies assessed the secondary outcomes of edoxaban vs. warfarin between observational studies and the ENGAGE AF-TIMI 48 trial.

Publication Bias

For the observational studies, there were no potential publication biases when inspecting the funnel plots of the primary outcomes (**Supplementary Figures 10–13**). In addition, the Begg's and Egger's tests also proved no significant publication biases (all $P > 0.1$; **Supplementary Table 5**). For the secondary outcomes, the Egger's test showed a potential publication bias in intracranial hemorrhage of the dabigatran vs. warfarin group, and ischemic stroke of the rivaroxaban vs. warfarin group. Nevertheless, the results from the trim-and-fill analysis suggested no trimming performed, and the corresponding pooled results were not changed. For the RCTs, there was no need for publication bias analysis because only four NOAC trials were included.

DISCUSSION

In the current meta-analysis, we compared the studied outcomes between NOACs and warfarin by only included the PS-based observational studies. Based on the observational studies, the results from different pooled models consistently suggested that compared with warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban were associated with a reduced risk of SSE, whereas dabigatran, apixaban, and edoxaban but not rivaroxaban was associated with a decreased risk of major bleeding. We further tested whether the pooled results of high-quality observational

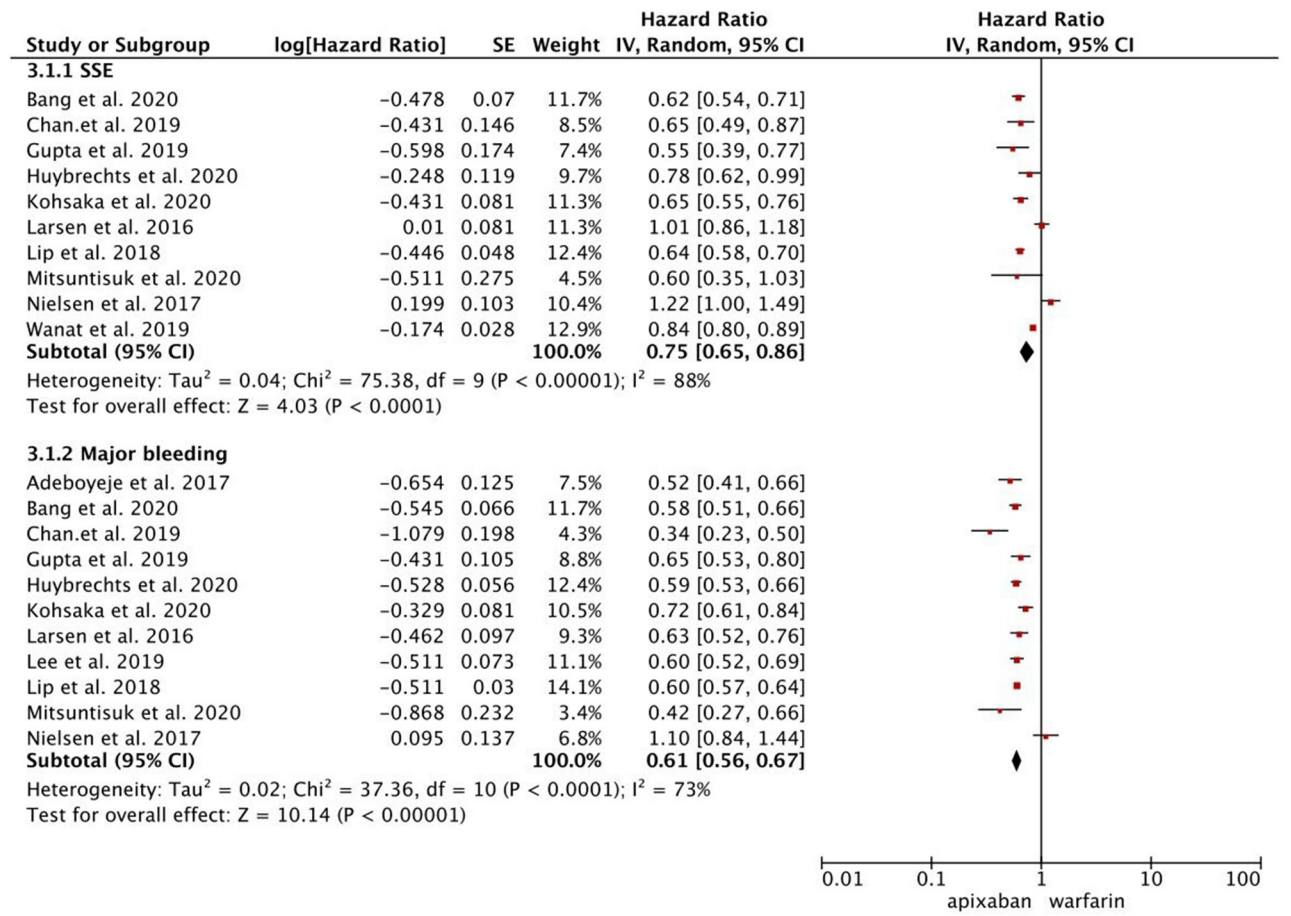

FIGURE 3 | Comparing the primary outcomes including SSE and MB of apixaban vs. warfarin. SSE, stroke or systemic embolism; MB, major bleeding; HR, hazard ratio; CI, confidence interval; SE, standard error; IV, inverse of the variance.

studies were consistent with data from the corresponding RCTs. The risk of major bleeding with dabigatran 150 mg was significantly lower in observational studies than that in the RE-LY trial, whereas the pooled results of observational studies were consistent with data from the corresponding RCTs in other comparisons for both SSE and major bleeding.

Over the past few decades, vitamin K antagonists such as warfarin have been confirmed to be effective for preventing stroke in AF patients (33). However, the shortcomings of warfarin mainly include slow onset time, the significantly varied dose-response relationship among patients, narrow therapeutic window, and frequent interactions with other drugs, potentially limiting its clinical applications (34). Nowadays, there is increasing use of NOACs because they could be more effective, easier to control, and safer than warfarin (7). Previous NOAC trials (RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE-AF TIMI 48) suggested that NOACs were comparable to warfarin in efficacy, but NOACs significantly reduced the risk of bleeding. Based on data of NOAC trials, current guidelines have recommended NOACs as the first-line drugs for the prevention of thrombogenesis and stroke in patients with nonvalvular AF (5). Although, RCTs have always been hailed as the gold standard for clinical efficacy evaluation, their results may not be well applicable in practice. At this time, observational studies can be a useful complement (35).

Nowadays, clinical practice-based data are increasingly used to evaluate the effectiveness and safety profiles of NOACs compared to warfarin. Xue et al. (34) compared the overall effectiveness and safety outcomes of three NOACs (dabigatran, rivaroxaban, and apixaban) with warfarin in Asians with AF. Based on the real-world studies, the authors demonstrated that in Asians with AF, the use of NOACs could have potential advantages in all the effectiveness and safety profiles when compared to warfarin irrespective of the type and drug doses. Nevertheless, the heterogeneous real-world studies without proper methods to balance the covariate distribution could be influenced by the potential confounders (36), thus potentially influencing the reliability of results. The PS methods including PSM and IPTW are the most frequently used methods to deal with this issue. The PS methods comprehensively consider all measured characteristic variables, especially confounding factors, making the matched sample more similar to the population of an RCT. PSM can match the treatment and non-treatment group based on the PS from low to high, and thus it can control multiple

TABLE 3 | Comparing total effect estimates of NOACs vs. warfarin between observational studies and RCTs.

	Dabigatran vs. Warfarin				Rivaroxaban vs. Warfarin		Apixaban vs. Warfarin		Edoxaban vs. Warfarin	
	Dabigatran 110 mg		Dabigatran 150 mg		Rivaroxaban 15/20 mg		Apixaban 2.5/5 mg		Edoxaban 60 mg	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Primary outcomes SSE										
Observational	0.94 (0.76,1.16)	0.83	0.82 (0.68,0.98)	0.14	0.78 (0.72,0.84)	0.18	0.68 (0.54,0.84)	0.29	0.76 (0.39,1.47)	0.72
RCT*	0.91 (0.74,1.11)		0.66 (0.53,0.82)		0.88 (0.74,1.03)		0.79 (0.66,0.95)		0.86 (0.74,1.01)	
MB										
Observational	0.77 (0.53,1.10)	0.83	0.72 (0.66,0.78)	0.002	1.07 (1.03,1.13)	0.70	0.59 (0.51,0.67)	0.11	0.81 (0.15,4.39)	0.99
RCT*	0.80 (0.69,0.93)		0.93 (0.81,1.07)		1.04 (0.90,1.20)		0.69 (0.60,0.80)		0.80 (0.71,0.91)	
Secondary outcomes IS										
Observational	0.96 (0.77,1.21)	0.39	0.99 (0.83,1.20)	0.009	0.91 (0.79,1.04)	0.8	0.72 (0.57,0.91)	0.21	-	-
RCT*	1.11 (0.89,1.40)		0.76 (0.60,0.98)		0.94 (0.75,1.17)		0.92 (0.74,1.34)		-	
All-cause death										
Observational	1.05 (0.99,1.12)	0.04	0.65 (0.54,0.79)	0.05	1.19 (0.78,1.80)	0.15	0.77 (0.39,1.54)	0.69	-	-
RCT*	0.91 (0.80,1.03)		0.88 (0.77,1.00)		0.85 (0.70,1.03)		0.89 (0.80,1.00)		-	
ICH										
Observational	0.51 (0.30,0.86)	0.15	0.43 (0.33,0.57)	0.77	0.61 (0.47,0.81)	0.7	0.61 (0.45,0.81)	0.1	-	-
RCT*	0.31 (0.20,0.47)		0.40 (0.27,0.60)		0.67 (0.47,0.93)		0.42 (0.30,0.58)		-	
GIB										
Observational	0.77 (0.49,1.21)	0.18	1.03 (0.83,1.28)	0.02	1.29 (1.05,1.58)	0.45	0.58 (0.43,0.77)	0.03	-	-
RCT*	1.10 (0.86,1.41)		1.50 (1.19,1.89)		1.42 (1.22,1.66)		0.89 (0.70,1.15)		-	

** Corresponding RCTs for the dabigatran group, rivaroxaban group, apixaban group and edoxaban group are RE-LY (8), ROCKET-AF (10), ARISTOTLE (9) and ENGAGE AF-TIMI 48 [11], respectively.*

NOAC, non-vitamin K antagonist oral anticoagulant; RCT, randomized controlled trials; HR, hazard ratio; CI, confidence interval; SSE, stroke or systemic embolism; MB, major bleeding; IS, ischemic stroke; ICH, intracranial hemorrhage; GIB, gastrointestinal bleeding.

confounders at the same time by only using the matching of PS (37). IPTW is capable of eliminating confounders by conforming to the distribution of PS in each group (37). However, PSM and IPTW are often failed to be properly conducted (36). Therefore, to further improve the reliability of the study outcomes and reduce the influence of confounding factors, PS diagnostics such as standardized differences, C-statistic, and eye-balling could be conducted after PSM or IPTW. Standardized differences are an attribute of the sample, independent of the sample size. It is easy to compute and understand and is the most commonly used diagnostic method to measure the balance of covariate distribution between treatment groups (36, 38). In our current analysis, all of the 20 observational studies applied PSM or IPTW to balance the covariates between NOACs and warfarin regimen group. For the PS diagnostics, 14 studies used standardized differences, and 6 studies failed to report any further diagnostic use.

Reaching an agreement between RCTs and observational studies can greatly improve the accuracy of the results and offer more confidence in the reference of clinical routine practice. It is still known that whether the findings of observational studies were consistent with data from the NOAC trials. Siontis et al. (35) compared the consistency between RCTs and observational studies of the profiles of NOACS and warfarin. The authors found that the effect of NOACs and warfarin were consistent between RCTs and observational studies for most outcomes. However, some exceptions appeared in the dabigatran vs. warfarin group. The RE-LY trial found an increased risk of myocardial infarction in patients treated with dabigatran 150 mg compared with patients using warfarin, whereas the reverse outcomes were found in observational studies. Also, significantly higher risks of major and gastrointestinal bleeding were found in observational studies when compared to the RE-LY trial in the dabigatran group. Conversely, the data of the RE-LY trial demonstrated a lower rate of SSE compared with that of the observational studies. However, Siontis et al. did not describe the baseline characteristics of the treated and non-treated groups in detail, nor did they clarify the statistical methods used in the included studies. Lacking rigorous study design and statistical analysis could make the results easily affected by confounding bias, and thus reduced its reliability. Given these issues, we decided to conduct a more comprehensive meta-analysis by only included the PS-based observational studies. In our analysis, the results of the effectiveness and safety profiles are largely in agreement with some discrepancies that mainly happened in the dabigatran vs. warfarin group. The results of the consistency between the observational studies and RCTs of Siontis et al. are quite similar to our study.

LIMITATIONS

There were still several limitations in this meta-analysis. First, most of the observational studies included were retrospective, and therefore, the association between the drug and the event outcomes rather than their causal relationships were

evaluated. Second, despite the detailed information extracted from the included studies, there were still some articles that lack major data (e.g., drug dosage, follow-up period of NOAC treatment) which may provide potential uncertainties to the results. Third, several important cardiovascular events including myocardial infarction were not included in our analysis due to a lack of data. Fourth, in this meta-analysis, we did not include observational studies that only focused on the special populations with AF. Nevertheless, we have previously discussed the effect of NOACs in the special AF populations (e.g., chronic kidney disease, hypertrophic cardiomyopathy, peripheral artery disease, prior stroke) (39–42). Finally, although we included comparisons of outcomes between edoxaban and warfarin, we still failed to assess the results for some outcomes due to insufficient data.

CONCLUSION

This meta-analysis suggested that the use of NOACs for stroke prevention in AF was non-inferior or even superior to warfarin based on data from PS-based observational studies. The consistency between the observational studies and corresponding RCTs further confirmed this view.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

This study was funded by National Natural Science Foundation of China (8210020907), China National Postdoctoral Program for Innovative Talents (BX20200400), and China Postdoctoral Science Foundation (2020M673016).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.757188/full#supplementary-material

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frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 18 October 2021
doi: 10.3389/fcvm.2021.752468

Apixaban vs. Warfarin in Atrial Fibrillation Patients With Chronic Kidney Disease

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Edited by:
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Specialty section:
This article was submitted to Thrombosis, a section of the journal Frontiers in Cardiovascular Medicine

Received: 03 August 2021
Accepted: 21 September 2021
Published: 18 October 2021

Citation:
Fu C-M, Li L-C, Lee Y-T, Wang S-W and Hsu C-N (2021) Apixaban vs. Warfarin in Atrial Fibrillation Patients With Chronic Kidney Disease. Front. Cardiovasc. Med. 8:752468. doi: 10.3389/fcvm.2021.752468

Background and Objectives: Real-world evidence of apixaban treatment in patients with chronic kidney disease remains scarce. This study aimed to compare the relative risk of stroke or systemic embolism (SE) and major bleeding between apixaban and warfarin in atrial fibrillation (AF) patients with different degrees of kidney function.

Design, Setting, Participants, and Measurements: We evaluated newly diagnosed AF patients between 2004 and 2018, who were receiving apixaban or warfarin. Electronic medical record data were collected from a large healthcare delivery network in Taiwan. The outcomes of hospitalization for stroke/SE and major bleeding were compared with propensity-score matched apixaban and warfarin cohorts. Stratified analyses according to initial apixaban dose (standard dose of 10 mg/day vs. lower dose of 2.5–5.0 mg/day) and baseline estimated glomerular filtration rate were performed.

Results: Each cohort involved 1,625 matched patients. Apixaban was significantly associated with a lower risk of stroke/SE (adjusted hazard ratio [aHR]: 0.74; 95% confidence interval [CI]:0.57–0.97; $p = 0.03$). The risk of major bleeding was not increased whether in standard doses (aHR: 0.66; 95% CI: 0.45–0.96; $p = 0.03$) or reduced doses (aHR, 0.84; 95% CI, 0.63–1.12; $p = 0.23$) of apixaban. Regarding kidney function, apixaban reduced the risk of stroke/SE by 37% in those with an eGFR of <30 ml/min/1.73 m^2 (aHR: 0.63; 95% CI: 0.40–0.98; $p = 0.04$).

Conclusions: Compared to warfarin, apixaban is associated with a reduced risk of stroke/SE and is consistent with a subset of AF patients with eGFR <30 ml/min/1.73 m^2. Both standard and reduced doses of apixaban showed lower risk of major bleeding than those of warfarin.

Keywords: apixaban, warfarin, chronic kidney disease, atrial fibrillation (AF), ischemic stroke, bleeding, thromboembolism

INTRODUCTION

Atrial fibrillation (AF) as the most common cardiac arrhythmia (1) and contributes significantly to cerebral ischemic stroke and other severe thromboembolic events. To prevent these severe complications, current guidelines stipulate that high-risk AF patients (CHA_2DS_2–VASc scores $\geq$2) should be prescribed direct oral anticoagulants (DOACs) rather than vitamin K antagonists (2–5). Patients with chronic kidney disease (CKD) have a 2- to 3-fold higher prevalence of AF than the general population (6–8). In addition, CKD itself contributes to a pro-thrombotic state, which increases the risks of ischemic stroke or systemic embolism (9–11). The risk of thromboembolic events is even worse in CKD patients receiving renal replacement therapy (11, 12). Furthermore, patients with an estimated glomerular filtration rate (eGFR) of $<$ 30 mL/min/1.73 m^2 have a higher risk of bleeding compared to those with an eGFR of between 30 and 60 mL/min/1.73 m^2 and those with an eGFR $\geq$ 60 mL/min/1.73 m^2 while receiving oral anticoagulant (OAC) therapy (12–14). Importantly, most pivotal studies of DOACs excluded patients with advanced CKD and end-stage kidney disease (ESKD). Thus, real-world evidence is needed to optimize the prevention of thromboembolism, and still minimize the risk of bleeding in patients with abnormal kidney function.

A patient's kidney function is one of the factors that influences OAC selection (15, 16), and warfarin is often prescribed in patients with CKD. Apixaban is currently the only approved DOAC for AF patients with serum creatinine clearance (CrCl) of $<$15 mL/min; however, approval was based on a pharmacokinetic study of only eight patients with CKD on dialysis (17). Furthermore, treatment outcomes of apixaban in ESKD patients have been reported (18, 19). A study using 2010–2015 Renal Data System in the United State (USRDS) data found that although apixaban has no benefit on stroke/systemic embolism (SE) prevention, it is associated with a significantly lower risk of major bleeding compared to warfarin (18). Another study using USRDS data (2012–2015) compared apixaban with no anticoagulation in patients with chronic dialysis and AF, and found that apixaban treatment was not associated with risk reductions in both ischemic stroke and fatal or intracranial bleeding (19). Given that these studies mainly focused on the necessity of anticoagulation in the chronic dialysis population, the usefulness of apixaban treatment in CKD patients without dialysis treatment is still unclear. Thus, this study aimed to compare the relative risk of stroke or SE and major bleeding between apixaban and warfarin in AF patients with different degrees of kidney disease.

MATERIALS AND METHODS

Study Design and Data Source

This was a retrospective cohort study of adult patients with non-valvular AF or atrial flutter. Data were obtained from the Chang Gung Research Database (CGRD), a de-identified, electronic health records database of patient information from the healthcare delivery system in Taiwan. The CGRD contains International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification *(*ICD-9/10-CM*)* codes, Healthcare Common Procedure Coding System codes, Anatomical Therapeutic Chemical Classification System codes, and laboratory test results in emergency departments and in-and-outpatient settings (**Supplementary Table 1**). The data sets and have been described previously (20, 21).

This study was approved by the Institutional Review Board of Chang Gung Medical Foundation at Taipei, Taiwan (approval number 201900901B0) and was conducted according to the tenets of the Declaration of Helsinki. The need for informed consent was waived owing to the retrospective nature of the study.

Patients

We evaluated AF patients who were newly diagnosed between January 1, 2004, and December 21, 2018, in whom apixaban or warfarin therapy had been initiated. The inclusion criteria were having a diagnosis of AF before the index date (the date of apixaban or warfarin initiation) and at least one or more admissions within at least 12 months before the index date (**Figure 1**). Patients were excluded if they had any of the following: OAC treatment (warfarin, apixaban, dabigatran, rivaroxaban, edoxaban) within 3 months before the index date, missing serum creatinine (SCr) results, moderate or severe mitral stenosis, valve replacement, peritoneal dialysis, or kidney transplantation. The patient selection criteria are detailed in **Figure 1**, **Supplementary Table 1**. The patients were identified using ICD-9/10-CM codes on at least two outpatient visits with an interval of more than 28 days or on one post-discharge follow-up within the study period. The first apixaban or warfarin prescription date in the outpatient setting was designated as the index date for patients without any other OAC treatment.

Outcome Measures

Effectiveness was evaluated according to the incidence of stroke or SE as outcome measure, while safety was evaluated according to the incidence of major bleeding, including any intracranial hemorrhage but not traumatic hemorrhage, intraabdominal, gastrointestinal bleeding, hematuria, or bleeding at other sites (**Supplementary Table 1**) (22). The outcomes of interest were defined according to discharge diagnosis in the as-treated cohort. All patients were followed up from the index date to the first event of interest, discontinuation date of apixaban or warfarin, medication switch date, in-hospital death, loss to follow-up ($\geq$365 days without any medical encounters before the end date of the database), or the data cut-off date (December 31, 2018), whichever came first.

Statistical Analysis

The patients were matched using propensity scores (PS) to minimize selection bias (23, 24). Each patient's PS was calculated based on the following characteristics: demographic data, such as age and sex; individual disease condition in the Charlson Comorbidity Index (25); eGFR; hypertension; major bleeding; medications; CHA_2DS_2-VASc score and HAS-BLED score. The

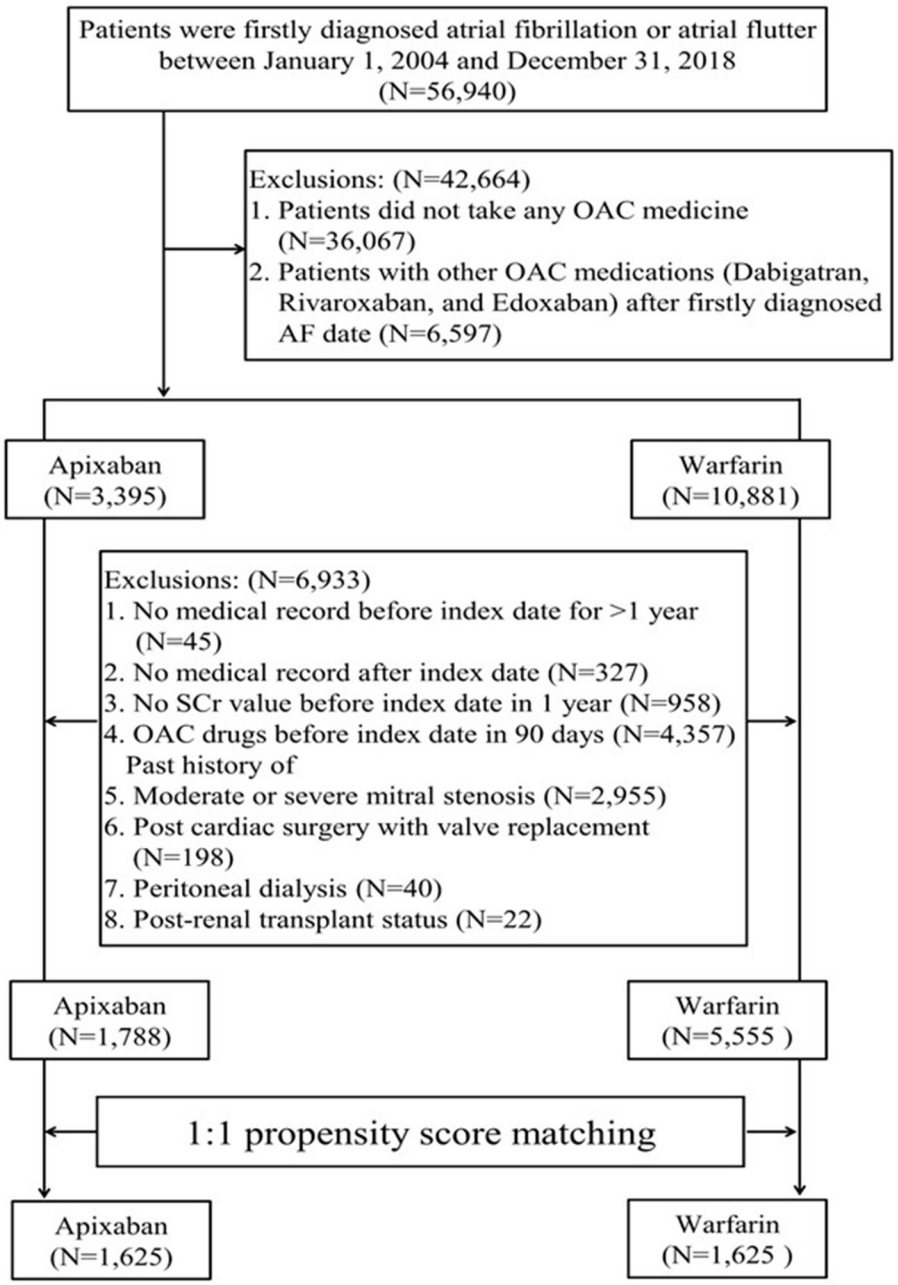

FIGURE 1 | Patient inclusion flowchart.

covariates for the PS matching model are presented in **Table 1**, **Supplementary Table 1**. Patients who were prescribed apixaban or warfarin were matched in a 1:1 ratio using a greedy algorithm (26). The distributions of PS was assessed, and the covariate balance between treatment groups were determined using the standardized mean differences (SMD) with a threshold of <10% (27). The relative risk of stroke/SE and major bleeding between apixaban and warfarin was evaluated using Cox proportional hazards models separately, and adjusted for covariates listed in **Table 1**.

Subgroup analysis according to the apixaban dose (standard dose [10 mg/day] vs. reduced dose [2.5–5.0 mg/day]) was conducted using the Cox proportional hazards model to evaluate the dose relationship with the heterogeneity of treatment effects. Subgroup analysis according to baseline eGFR (≥60 ml/min/1.73 m^2 (mild CKD), 59.9–30.0 ml/min/1.73 m^2 (moderate CKD),

TABLE 1 | Baseline patient characteristics by treatment group before and after propensity score matching.

	Before propensity score matching			After propensity score matching		
	Warfarin (*n* = 5,555)	**Apixaban (*n* = 1,788)**	**SMD**	**Warfarin (*n* = 1,625)**	**Apixaban (*n* = 1,625)**	**SMD**
Age group, years, *n* (%)						
<40	122 (2.20)	12 (0.67)	0.129	11 (0.68)	12 (0.74)	0.007
40–64	1,882 (33.88)	250 (13.98)	0.480	257 (15.82)	245 (15.08)	0.020
65–74	1,578 (28.41)	537 (30.03)	0.036	503 (30.95)	504 (31.02)	0.001
≥75	1,973 (35.52)	989 (55.31)	0.406	854 (52.55)	864 (53.17)	0.012
Sex, *n* (%)						
Male	3,335 (60.04)	1,023 (57.21)	0.057	926 (56.98)	938 (57.72)	0.015
Female	2,220 (39.96)	765 (42.79)	0.057	699 (43.02)	687 (42.28)	0.015
Baseline eGFR, ml/min/1.73 m^2, *n* (%)						
≧90	1,001 (18.02)	286 (16.00)	0.054	286 (17.60)	277 (17.05)	0.015
60–89.9	2,262 (40.72)	739 (41.33)	0.012	678 (41.72)	674 (41.48)	0.005
45–59.9	1,066 (19.19)	386 (21.59)	0.060	337 (20.74)	357 (21.97)	0.030
30–44.9	617 (11.11)	246 (13.76)	0.080	193 (11.88)	198 (12.18)	0.010
15–29.9	298 (5.36)	115 (6.43)	0.045	117 (7.20)	103 (6.34)	0.034
<15	311 (5.60)	16 (0.89)	0.268	14 (0.86)	16 (0.98)	0.013
Charlson comorbid conditions, *n* (%)						
Acute myocardial infarction	354 (6.37)	103 (5.76)	0.026	94 (5.78)	95 (5.85)	0.003
Congestive heart failure	1,857 (33.43)	568 (31.77)	0.036	537 (33.05)	519 (31.94)	0.024
Peripheral vascular diseases	245 (4.41)	44 (2.46)	0.107	29 (1.78)	44 (2.71)	0.062
Cerebral vascular accident	2,013 (36.24)	589 (32.94)	0.069	505 (31.08)	525 (32.31)	0.026
Dementia	135 (2.43)	51 (2.85)	0.026	49 (3.02)	48 (2.95)	0.004
Pulmonary disease	1,031 (18.56)	291 (16.28)	0.060	261 (16.06)	277 (17.05)	0.027
Connective tissue disorder	26 (0.47)	17 (0.95)	0.058	14 (0.86)	14 (0.86)	0.000
Peptic ulcer	766 (13.79)	291 (16.28)	0.070	270 (16.62)	266 (16.37)	0.007
Liver diseases	553 (9.95)	120 (6.71)	0.118	117 (7.20)	116 (7.14)	0.002
Diabetes	1,563 (28.14)	537 (30.03)	0.042	470 (28.92)	477 (29.35)	0.010
Diabetes with complications	375 (6.75)	193 (10.79)	0.143	145 (8.92)	143 (8.80)	0.004
Paraplegia	249 (4.48)	98 (5.48)	0.046	87 (5.35)	82 (5.05)	0.014
Renal disease	762 (13.72)	424 (23.71)	0.258	311 (19.14)	316 (19.45)	0.008
Cancer	340 (6.12)	187 (10.46)	0.158	147 (9.05)	151 (9.29)	0.009
Severe liver diseases	18 (0.32)	6 (0.34)	0.002	6 (0.37)	5 (0.31)	0.011
Metastatic cancer	59 (1.06)	30 (1.68)	0.053	25 (1.54)	28 (1.72)	0.015
Hypertension	3,612 (65.02)	1,314 (73.49)	0.184	1,186 (72.98)	1,177 (72.43)	0.012
Prior major bleeding	1,147 (20.65)	582 (32.55)	0.272	479 (29.48)	484 (29.78)	0.007
Prior medication uses						
Lipid-lowering agent	905 (16.29)	485 (27.13)	0.265	409 (25.17)	408 (25.11)	0.001
Glucose-lowering agent	1,088 (19.59)	403 (22.54)	0.073	342 (21.05)	340 (20.92)	0.003
Anti-hypertension	3,857 (69.43)	1,394 (77.96)	0.195	1,262 (77.66)	1,246 (76.68)	0.024
Anti-platelet agent	2,433 (43.80)	753 (42.11)	0.034	708 (43.57)	690 (42.46)	0.022
Aspirin	2,029 (36.53)	560 (31.32)	<0.0001	583 (35.88)	512 (31.51)	-
Clopidogrel	552 (9.94)	261 (14.6)	<0.0001	171 (10.52)	238 (14.65)	-
Ticagrelor	12 (0.22)	14 (0.78)	<0.0001	3 (0.18)	11 (0.68)	-
Others	264 (4.75)	67 (3.75)	0.112	72 (4.43)	60 (3.69)	-
Amiodarone	841 (15.14)	355 (19.85)	0.124	302 (18.58)	301 (18.52)	0.002
Digoxin	839 (15.10)	150 (8.39)	0.210	149 (9.17)	146 (8.98)	0.006
NSAIDs	568 (10.23)	200 (11.19)	0.031	189 (11.63)	185 (11.38)	0.008
Gastric antacids	922 (16.60)	506 (28.30)	0.283	421 (25.91)	423 (26.03)	0.003
Mean value (SD)						
CHA_2DS_2-VASc score	3.40 (1.84)	3.92 (1.70)	0.293	3.81 (1.69)	3.83 (1.68)	0.011
HAS-BLED score	2.55 (1.43)	3.02 (1.36)	0.333	2.92 (1.36)	2.92 (1.34)	0.003

SMD, standardized mean difference; SD, standard deviation; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NSAID: non-steroidal anti-inflammatory drug.

and <30 ml/min/1.73 m^2 (advanced CKD) was also performed to evaluate the influence of kidney function on the effectiveness of apixaban and warfarin. Baseline eGFR was calculated based on the mean serum creatinine (SCr) level within 3 months prior to the index date and using the Modification of Diet in Renal Disease (MDRD) equation (28): 175 × SCr (mg/dL)$^{-1.154}$ × age (years)$^{-0.203}$ × 0.742 (if female). Furthermore, hospital admissions for pneumonia or hip fracture were regarded as negative control outcomes (19) to ensure the robustness of the study results. We hypothesized that pneumonia and hip fracture had the same exposure risk in the apixaban and warfarin groups. All statistical analyses were performed using SAS 4.0 (Cary, NC, USA). A two-sided *P*-value of <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 56,940 patients with AF or atrial flutter diagnosis were identified. Out of them, 7,343 patients who were administered warfarin (n = 5555) or apixaban (n = 1788) were initially evaluated (**Figure 1**). Before matching, the apixaban group were more likely to be older (mean age: 75.16 ± 10.63 years vs. 68.72 ± 12.47 years) at the index date and had higher CHA_2DS_2-VASc (3.92 ± 1.70 vs. 3.4 ± 1.84) and HAS-BLED (3.02 ± 1.36 vs. 2.55 ± 1.43) scores. Further, comorbid kidney disease was more prevalent in the apixaban group than in the warfarin group (23.71 vs. 13.72%). However, the baseline mean eGFR was similar between the two groups.

After matching, the PS distributions were compatible and baseline characteristics were similar in the matched cohort, with each group involving 1,625 patients. The SMDs of all variables were <0.1 (**Table 1**). The mean age at the initiation of apixaban or warfarin was 74–75 years. In total, 131 patients (8.06%) in the warfarin group and 119 patients (7.32%) in the apixaban group had advanced CKD (i.e., eGFR <30 ml/min/1.73 m^2). Among the patients who received apixaban, 710 patients (56.31%) and 913 (43.69%) patients received a reduced and standard dose, respectively. The reduced and standard dose subgroups had a mean age of 78.5 years and 70 years, respectively (**Supplementary Table 2**). The patient characteristics before and after PS matching are shown in **Table 1**.

Study Outcomes

The rates of stroke/SE, major bleeding, and in-hospital mortality are presented in **Table 2**. Compared to the warfarin group, the apixaban group showed significantly lower incidence rates of stroke/SE (10.77 vs. 7.08%, $p < 0.001$), major bleeding (11.26 vs. 7.51%, $p < 0.001$), and in-hospital any-cause death (5.84 vs. 3.94%, $p = 0.01$). The Kaplan-Meier curves (**Figures 2A,C**) also showed significant between-group differences in the cumulative incidence of stroke and major bleeding (log-rank $p = 0.01$ and $p = 0.03$, respectively). Among the 250 patients with eGFR < 30 ml/min/1.73 m^2 (**Figures 2B,D**), those treated with apixaban tended to have fewer events of stroke/SE and major bleeding (log-rank $p = 0.09$ and $p = 0.06$, respectively). Meanwhile, there was no significant between-group difference in the rate of in-hospital any-cause death.

Stroke/Systemic Embolism

Cox proportional hazards regression analysis showed that apixaban treatment was associated with a lower risk of ischemic stroke/SE than warfarin treatment (adjusted hazard ratio [aHR]: 0.74; 95% confidence interval [CI]: 0.57–0.97; $p = 0.03$) (**Figure 3A**, **Supplementary Table 2**). The relative effect on ischemic stroke/SE prevention was not influenced by the apixaban dose (standard dose: aHR, 0.71; 95% CI, 0.50–1.01; p

TABLE 2 | Study outcomes in the matched cohort and in the advanced CKD subgroup.

	Apixaban-warfarin matched cohort (n = 3,250)				Baseline eGFR < 30 (n = 250)			
	Event	**Warfarin**	**Apixaban**	***p*-value**	**Event**	**Warfarin**	**Apixaban**	***p*-value**
Stroke/systemic embolism, *n* (%)	290	175 (10.77)	115 (7.08)	0.0002	21	15 (11.45)	6 (5.04)	0.0681
Ischemic or uncertain stroke	222	111 (6.83)	111 (6.83)	1.0000	16	10 (7.63)	6 (5.04)	0.4031
Systemic embolism	77	72 (4.43)	5 (0.31)	<.0001	6	6 (4.58)	0 (0.00)	
Major bleeding, *n* (%)	305	183 (11.26)	122 (7.51)	0.0002	44	30 (22.90)	14 (11.76)	0.0209
Intracranial	66	36 (2.22)	30 (1.85)	0.4556	6	4 (3.05)	2 (1.68)	0.4788
Ocular	5	3 (0.18)	2 (0.12)	0.6545	0	0 (0.00)	0 (0.00)	
Intraabdominal	2	2 (0.12)	0 (0.00)		0	0 (0.00)	0 (0.00)	
Hematuria	20	12 (0.74)	8 (0.49)	0.3696	2	1 (0.76)	1 (0.84)	0.9456
Gastrointestinal	213	128 (7.88)	85 (5.23)	0.0023	36	25 (19.08)	11 (9.24)	0.0269
Other sites	8	7 (0.43)	1 (0.06)	0.0337	1	1 (0.76)	0 (0.00)	
Other outcomes, *n* (%)								
In-hospital death, *n* (%)	159	95 (5.85)	64 (3.94)	0.0117	24	13 (9.92)	11 (9.24)	0.8554
Pneumonia	302	175 (10.77)	127 (7.82)	0.0037	34	19 (14.50)	15 (12.61)	0.6618
Hip fracture	26	17 (1.05)	9 (0.55)	0.1152	4	3 (2.29)	1 (0.84)	0.3616

eGFR, estimated glomerular filtration rate, ml/min/1.73 m^2.

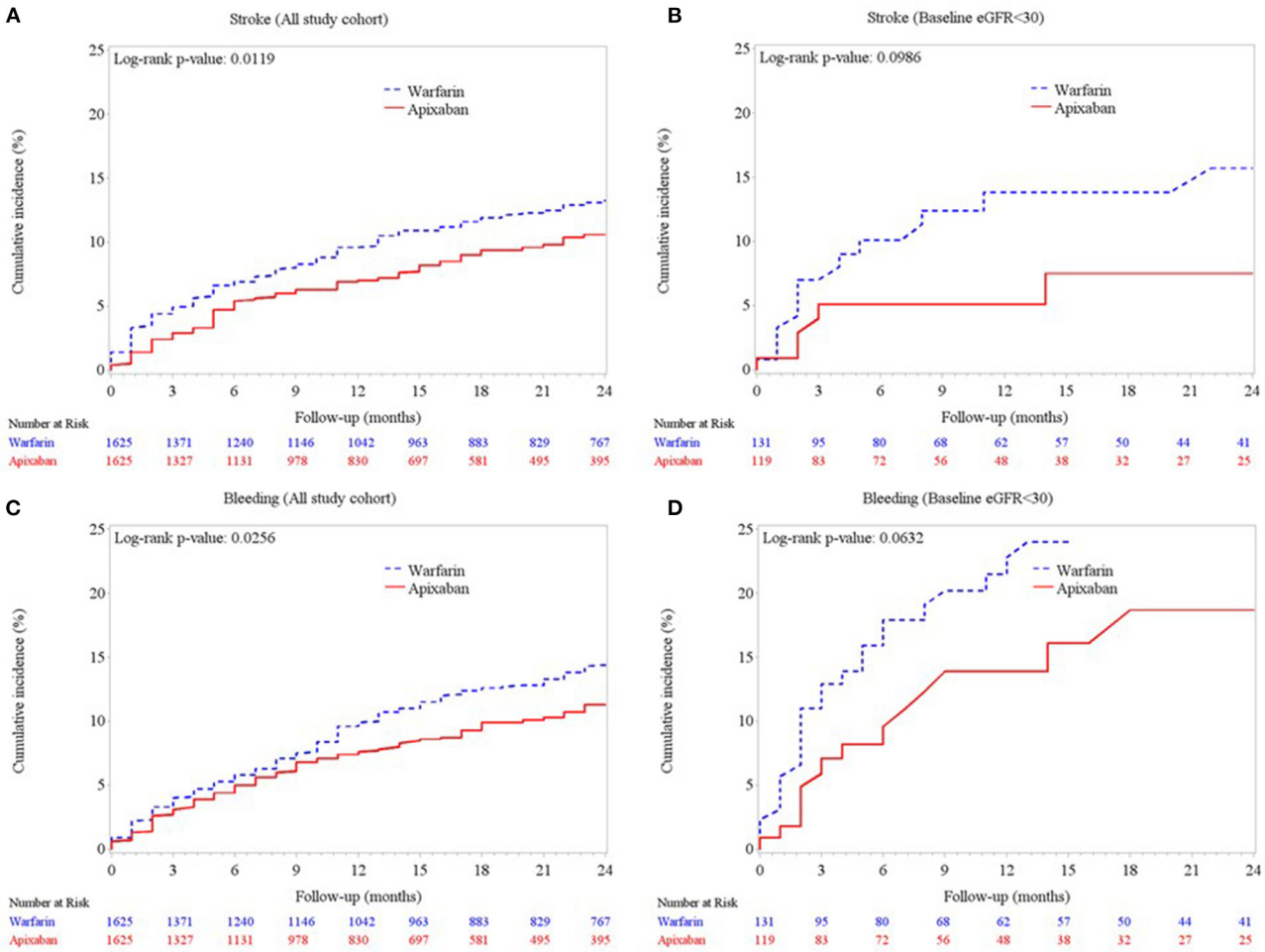

FIGURE 2 | Cumulative incidences of **(A)** ischemic stroke/systemic embolism in the matched cohort, **(B)** ischemic stroke/systemic embolism in the subgroup of patients with advanced CKD (eGFR <30 ml/min/1.73 m^2), **(C)** major bleeding in the matched cohort, and **(D)** major bleeding in the subgroup of patients with eGFR<30 ml/min/1.73 m^2.

= 0.06; reduced dose: aHR, 0.77; 95% CI, 0.57–1.05; $p = 0.09$) (**Table 3**, **Supplementary Table 2**)

Major Bleeding

In the entire cohort, gastrointestinal bleeding was high in both the apixaban and warfarin groups (5.23 vs. 7.88%), following by intracranial bleeding (1.85 vs. 2.22%) and hematuria (0.49 vs. 0.74%) in **Table 2**. Apixaban reduced the risk of major bleeding by 22%, but the difference did not reach statistical significance (aHR, 0.78; 95% CI, 0.60–1.00; $p = 0.05$). The standard dose of apixaban significantly lowered the risk of major bleeding (aHR, 0.66; 95% CI, 0.45–0.96; $p = 0.03$) than warfarin, but the reduced dose of apixaban didn't exhibit significantly difference in major bleeding (aHR, 0.84; 95% CI, 0.63–1.12; $p = 0.23$) (**Table 3**, **Supplementary Table 3**).

Kidney Function

The results according to the eGFR classification were consistent with the main analysis (**Figures 3A,B**). In the advanced CKD subgroup, apixaban initiation was significantly associated with a lower risk of stroke/SE (aHR: 0.63; 95% CI: 0.40–0.98, $p = 0.04$), but not for major bleeding (aHR: 0.71; 95% CI: 0.49–1.03; $p = 0.70$). Meanwhile, there was no significant difference in the risk of stroke/SE or major bleeding outcomes between apixaban and warfarin in the mild and moderate CKD subgroups. Further stratified analyses to investigate the impact of apixaban dose on the association between kidney function and risk of major bleeding showed inconclusive findings because there was no event in the advanced CKD subgroup (**Table 3**).

Other Subgroup and Sensitivity Analyses

The relative effects of apixaban according to a history of stroke and CHA_2DS_2-VASc score at baseline (<4 and ≥4), prior major bleeding, and HAS-BLED score at baseline (<3 and ≥3) are shown in **Figures 3A,B**. In general, apixaban was associated with more favorable outcomes than warfarin in patients without a history of stoke, CHA2DS2-VASc score <4, without history of

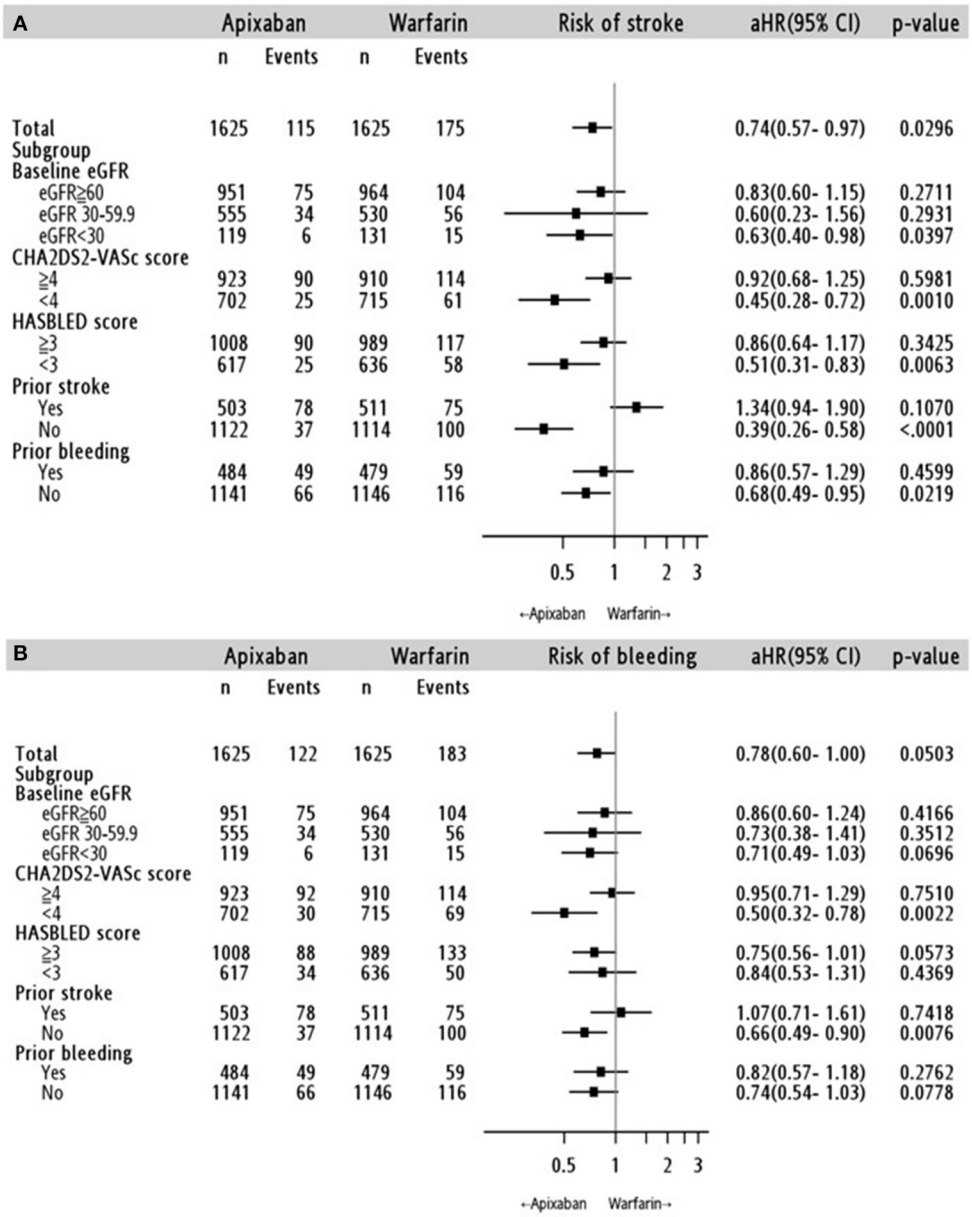

FIGURE 3 | Stratified analyses for the risk of **(A)** ischemic stroke/systemic embolism and **(B)** major bleeding in the apixaban-warfarin matched cohort. aHR: adjusted hazard ratio; 95% CI, 95% confidence interval; eGFR: estimated glomerular filtration rate (ml/min/1.73 m^2).

major bleeding, and with a HAS-BLED score <3. In addition, the choice of OAC did not increase the risk of pneumonia (aHR: 0.99; 95% CI: 0.76–1.28; $p = 0.91$) and hip fracture (aHR: 0.71; 95% CI: 0.29-1.76; $p = 0.44$) (**Supplementary Table 4**).

DISCUSSION

Real-world evidence on the benefit of apixaban in AF patients with CKD without dialysis is limited. This study found that apixaban lowers the risk of ischemic stroke or SE by 26% in AF patients with CKD and by 37% in those with advanced CKD. Meanwhile, although the rate of major bleeding was lower in the apixaban group than it was in the warfarin group, the difference was not statistically significant in the overall cohort and across the eGFR groups. Subgroup analysis according to apixaban doses showed that a standard dose of 10 mg/day was associated with a 34% lower risk of major bleeding.

The first real-word study on apixaban vs. warfarin use in CKD patients was published in 2017. The study, which included 146 patients with CrCl <25 mL/min or serum creatinine >2.5 mg/dL, found no significant differences with respect to major bleeding or thromboembolic events between apixaban and

TABLE 3 | Study outcomes by apixaban dose.

	Apixaban (reduced dose)* vs. Warfarin			Apixaban (standard dose)* vs. Warfarin		
	aHR	**95% CI**	***p-value***	**aHR**	**95% CI**	***p-value***
Stroke/SE						
Overall	0.77	(0.57, 1.05)	0.0955	0.71	(0.50, 1.01)	0.0575
Baseline eGFR group						
≧60	0.86	(0.57, 1.27)	0.3304	0.82	(0.54, 1.20)	0.3175
30–59.9	0.68	(0.42, 1.09)	0.2522	0.48	(0.20, 1.00)	0.0605
<30	0.66	(0.23, 1.65)	0.7231	-	-	-
Major bleeding						
Overall	0.84	(0.63, 1.12)	0.2286	0.66	(0.45, 0.96)	0.0287
Baseline eGFR group						
≧60	1.03	(0.67, 1.57)	0.5912	0.70	(0.43, 1.11)	0.0856
30–59.9	0.72	(0.47, 1.07)	0.1758	0.69	(0.36, 1.21)	0.2677
<30	0.81	(0.41, 1.53)	0.3807	-	-	-

**Apixaban standard dose: 10 mg/day, reduced dose: 2.5–5 mg/day; -: aHR was not available because no event was observed in the advanced CKD subgroup (eGFR < 30 ml/min/1.73 m^2). aHR: adjusted hazard ratio; 95% CI, 95% confidence interval; eGFR: estimated glomerular filtration rate (ml/min/1.73 m^2).*

warfarin treatments (29). A recent subgroup analysis from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial also showed no significant difference in stoke or SE prevention and all-cause mortality between apixaban and warfarin in patients with CrCl 25–30 mL/min (30). A US Medicare population cohort of 22,739 AF patients with group 3, 4, and 5 CKD compared apixaban, rivaroxaban, and dabigatran with warfarin in CKD patients and found that apixaban was associated with the lowest risk of stroke/SE (31). However, most of the patients (>80%) had group 3 CKD (eGFR between 30 and 59), and the patients were identified using diagnostic codes, limiting the generalizability of the findings to the advanced CKD patients. In the present study, the incidence rate of ischemic stroke/SE in patients with advanced CKD is comparable to that in previous observational studies (18, 29). The relatively large sample size of CKD patients in the present study and the data from a national representative database provide robust real-world evidence on the relative effect of apixaban in comparison to that of warfarin on stroke/SE prevention in a heterogeneous CKD population.

The apixaban dose is an important influencing factor of its efficacy and safety in patients with CKD. Although the apixaban label indicates a dose of 5 mg twice daily for non-valvular AF, patients are recommended to take apixaban 2.5 mg twice daily if they meet at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, and serum creatinine ≥1.5 mg/dL (32). In the secondary analyses of the ARISTOTLE trial, the risk of stroke/SE was 23% lower in standard dose apixaban (5 mg twice daily) than in warfarin, whereas there was no significant difference between reduced dose apixaban and warfarin (33). With respect to major bleeding, the risk was lower in apixaban than in warfarin irrespective of the apixaban dose, with the benefit being more profound in patients who were older, weighed less, and had serum creatinine ≥1.5 mg/dL (or lower CrCl) (30). Apixaban was also reported to be associated with lower rates of major bleeding than warfarin among patients with CrCl of 25–30 ml/min (30). Overall, data from the ARISTOTLE trial support that standard dose apixaban (5 mg twice daily) has a better pharmacokinetic distribution in patients with CrCl 25–30 ml/min than in those with higher CrCl (>30 ml/min) (30). The findings collectively suggest that the standard dose of apixaban may be safe in patients with CKD.

Given the low rate of OAC use in patients with eGFR <15 ml/min/1.73 m^2 in the current study, we were unable to evaluate the relative benefits and disadvantages of apixaban in comparison to those of warfarin. However, the results support that the risk of stroke/SE was lower in apixaban treatment than in warfarin treatment in patients with eGFR <30 ml/min/1.73 m^2, and apixaban was more beneficial in patients with low eGFR values than in those with high eGFR values, consistent with previous findings (30, 34). However, the effect of apixaban dose on the association between kidney function and risk of stroke/SE and major bleeding was not clarified in the present study.

The ARISTOLE trial suggested that apixaban was not inferior to warfarin as it had a mean time in therapeutic range (TTR) of 62% and an international normalized ratio (INR) of 2.0–3.0 (4). A subanalysis of the ARISTOTLE trial showed relatively lower mean TTR in East Asians (mean 27.2 ± 11.07) compared to those of non-East Asians (30.1 ± 14.29), and the duration with an international normalized ratio (INR) of <2 was longer in East Asians (28.6%) than in non-East Asians (18%) (35). Furthermore, the level of TTR varies between different countries (44–77%), and according to a dabigatran multinational trial, the mean TTR was lowest (44%) in Taiwan (36). In the present study, the mean INR was 1.97 (±1.01) during the total follow up period among patients with at least one INR values in the warfarin group (n = 1,511), and these patients had a higher rate of intracranial hemorrhage compared to those of patients in the apixaban group. The high rate of intracranial hemorrhage in patients with a lower INR compared to those of controls is similar to the findings in Asian patients in the apixaban (35) and dabigatran multinational trials (36).

The effectiveness and safety of using warfarin is associated with its optimum therapeutic INR control. We noted a high rate of systematic embolism in patients treated with warfarin with great INR fluctuations from the mean value of 3.14 (±1.67) to 1.72 (±0.72) over the follow-up period (**Supplementary Figure 1**). The high variability of INR may be because of poor adherence or difficult management in some warfarin users (35, 37). Low intensity of anticoagulation is a common practice in Taiwan. Regarding the interpretation of these study results, it is important to address the differences in the relative effect of DOACs vs. warfarin between Asian and non-Asian populations (35, 36).

Of note, gastrointestinal bleeding and intracranial hemorrhage were the most common major bleedings in this study cohort, and this is consistent with the reports of a population-based observational study in Taiwan (1.81 per 100 person-years for gastrointestinal bleeding, 1.53 per 100 person-years for intracranial hemorrhage) (38). The population-based

observational study and the meta-analyses of multinational randomized trials suggested that all DOACs can reduce overall major bleeding risk, but only apixaban was superior to warfarin in terms of fewer rates of major bleeding (39) or gastrointestinal bleeding (38). The reason for the differences in the risk of gastrointestinal bleeding between DOACs requires further research (40). In the present study, only patients with standard-dose apixaban (vs. warfarin) revealed statistically significant reduction in overall major bleeding. Further research into precise apixaban dosing could support the use of apixaban as an alternative to warfarin in patients with chronic kidney disease and atrial fibrillation.

The present study has limitations. First, like other retrospective studies, biases due to residual confounding may not have been eliminated. The present study applied hospitalization for pneumonia and hip fracture as negative control outcomes to ensure the robustness of the relative effects of apixaban in comparison to those of warfarin. There were no associations between both negative control outcomes and treatment choices, which indicated that there was no evidence for unmeasured confounding bias. Second, there was a high proportion of patients who received reduced-dose apixaban. This could be because the patients were older, had worse kidney function, and a higher HAS-BLED score (**Supplementary Table 5**), as is characteristics of the Asian population (41, 42). Reduced-dose DOACs is common in real-world practice, especially in Asians (43–45). Third, the results may be applicable only in Taiwanese or Asian populations and have limited generalizability to the overall population of CKD patients. However, the clinical practice pattern in the study setting is likely to follow international clinical guidelines and could help improve understanding of the benefit/disadvantage of anticoagulation in patients with kidney dysfunction. Further, we measured kidney function using the Taiwan version of the MDRD formula (28), as is routine practice in Taiwan. MDRD-based eGFR values could be not the same as CrCl in ARISTOTLE trial (46). The current study findings may help establish the appropriate apixaban dose in high-risk patients, such as those with advanced CKD and the elderly, according to kidney function estimated with the MDRD formula.

In conclusion, the risk of stroke/SE is lower in AF patients receiving apixaban treatment than in those receiving warfarin treatment, and the benefits of apixaban are also noted in patients with advanced CKD (eGFR <30 ml/min/1.73 m^2). Further, compared to warfarin, both standard and reduced dose of apixaban do not increase the risk of major bleeding. Our findings highlight the importance of appropriate anticoagulation treatment in patients with AF and kidney disease.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Chang Gung Medical Foundation at Taipei, Taiwan. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

C-MF, L-CL, and C-NH: conceptualization and wrote manuscript—original draft preparation. C-MF and C-NH: formal analysis, methodology, funding acquisition. All authors: investigation, validation, visualization, wrote manuscript—review, and editing.

FUNDING

This work was supported by the Ministry of Science and Technology, Taiwan, under Grants MOST 107-2622-E-182A-001-CC3 and 109-2622-E-182A-001-CC3 (recipient: C-NH), and Kaohsiung Chang Gung Memorial Hospital, Taiwan under Grant CFRPG8J0041 (recipient: C-MF) and CMRPG8E0463 (recipient: C-NH).

ACKNOWLEDGMENTS

The authors thank Mrs. Chun-Hua Liao and Ying-Jen Hsu from the Department of Management of Information Systems, Chang Gung Memorial Foundation, for their technical assistance with electronic health records acquisition and data retrieval. We thank Ms. Hsiao-Ching Kuo from the Department of Pharmacy, Kaohsiung Chang Gung Memorial Hospital for the assistance on data management and statistical analysis.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.752468/full#supplementary-material

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frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 28 October 2021
doi: 10.3389/fcvm.2021.729298

SOFA Score as a Reliable Tool to Detect High Risk for Venous Thrombosis in Patients With Critical Stage SARS-CoV-2

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Background: Severe acute respiratory syndrome from coronavirus-2 (SARS-CoV-2) has been associated with an increased risk of venous thromboembolism (VTE). Different anticoagulation protocols have been applied in several studies in the absence of clear evidence. A reliable deep venous thrombosis (DVT) indicator in critical patients with SARS-CoV-2 could guide the anticoagulation treatment; however, it has not yet been identified, and clinical applicability of the most common markers is debatable. The aim of our study was to determine the actual incidence of DVT in critically ill SARS-CoV-2 patients and to find a reliable tool to identify patients who might benefit from therapeutic-intensity anticoagulation.

Methods: From March 1, 2020 to May 31, 2020, all patients admitted to the intensive care unit (ICU) for SARS-CoV-2 at Ospedale Regionale di Locarno, Locarno, Switzerland, were prospectively enrolled and screened daily with ultrasound for DVT. Following international consensus, a higher-intensity thromboprophylaxis was administered to all patients who were not at increased risk for bleeding. Sepsis-induced coagulopathy (SIC) and sequential organ failure assessment (SOFA) scores were calculated and time-to-DVT event in a COX proportional-hazard regression model was performed. A receiver operating characteristic (ROC) curve was used to determine sensitivity and specificity and the Youden's Index to establish the best threshold.

Results: A total of 96 patients were enrolled. Deep venous thrombosis was detected in 37% of patients. Sepsis-induced coagulopathy and SOFA scores were both correlated to DVT. A SIC score of 1 vs. ≥2 showed a close association with DVT, with sensitivity, specificity, and positive and negative predictive values of 90.0, 48.1, and 49.1, and 89.7%, respectively. Most significantly though, a SOFA score of 1 or 2 points was shown to be the most accurate value in predicting the absence of DVT, indicating no need for therapeutic-intensity anticoagulation. Its sensitivity, specificity, and positive and negative predictive values were 87.9, 100, and 100, and 93.7%, respectively. The D-dimer test showed lower sensitivity and specificity whereas platelet count and aPTT were not found to be correlated to DVT.

OPEN ACCESS

Edited by:
Roberto Pola, Università Cattolica del Sacro Cuore, Italy

Reviewed by:
Younes Zaid, Université de Montréal, Canada
Angelo Porfidia, Catholic University of the Sacred Heart, Italy

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Specialty section:
This article was submitted to Thrombosis, a section of the journal Frontiers in Cardiovascular Medicine

Received: *22 June 2021*
Accepted: *28 September 2021*
Published: *28 October 2021*

Citation:
Prouse G, Ettorre L, Mongelli F, Demundo D, van den Berg JC, Catanese C, Fumagalli L, Usai C, Spinedi L, Riva F, Bertoni MV and Giovannacci L (2021) SOFA Score as a Reliable Tool to Detect High Risk for Venous Thrombosis in Patients With Critical Stage SARS-CoV-2. Front. Cardiovasc. Med. 8:729298. doi: 10.3389/fcvm.2021.729298

Conclusions: Patients with SOFA scores of 1 or 2 are at low risk of developing DVT and do not require therapeutic-intensity anticoagulation. Conversely, patients with scores ≥3 are at high risk of developing DVT.

Keywords: SARS-CoV-2, venous thromboembolism, deep vein thrombosis (DVT), anticoagulation (AC), SOFA score, SIC score, D-dimer (DD)

INTRODUCTION

The link between a severe inflammatory state and coagulopathy has been established (1). This is particularly true for severe acute respiratory syndrome from coronavirus-2 (SARS-CoV-2), in which the severe acute respiratory syndrome has been consistently linked to an increased risk of venous thromboembolism (VTE) with endothelial dysfunction potentially playing a significant additional role (2–4). Venous thromboembolism has been associated with unfavorable outcomes, with some reports describing up to 40% mortality (5). This is why several different anticoagulation protocols have been suggested in a widespread effort among scientists worldwide (6, 7). Most of these protocols, however, lack validation and are based on studies that adopted inconsistent prophylactic regimens, especially throughout the early phases of the pandemic (5, 8, 9). Despite widespread use of regular and higher-intensity thromboprophylaxis in severe cases in the later phases of the pandemic, a high incidence of thrombotic events was still observed (4, 10–12). This suggests that there may be a subgroup of critical SARS-Co-V2 patients who might benefit from therapeutic-intensity anticoagulation before the onset of thrombotic complications. To this end, although many hematological manifestations have been described in patients affected by SARS-CoV-2 (13), there still is no consensus on which are most effective to predict deep vein thrombosis (DVT) and pulmonary embolism (PE).

Our aim is to determine the parameters that can be best used to detect critical patients at high-risk for venous thrombosis and PE.

METHODS

Study Design and Enrollment

This study was approved by the ethics committee (Comitato Etico Cantonale del Ticino, Switzerland, BASEC 2020-01354 CE 3659). All patients requiring admission to the intensive care unit (ICU) due to Covid-19 infection at Ospedale Regionale di Locarno, Locarno, Switzerland, between March 1, 2020, and May 31, 2020, were prospectively included. No patients were excluded. During the Covid-19 outbreak, this hospital has been identified as the designated hospital, treating all Covid-19 patients referred to the public hospitals network in southern Switzerland. Covid-19 infection was diagnosed with either the Xpert®X Press SARS-CoV-2 or the Viasure SARS-CoV-2 S gene. In-house PCR testing was conducted on all non-nasopharyngeal specimens with Roche reagents and primers (TIB Molbiol) using Applied Biosystems® 7500 Fast (ThermoFisher Scientifics). All patients underwent daily ultrasound screening of upper and lower limbs and of jugular veins bilaterally until thrombosis was identified. Only occlusive or sub occlusive thrombosis with clear mural involvement where considered. In case of prolonged need for prone position care, the jugular vein screening was not carried out. The ultrasound screening was continued after ICU discharge only in patients who underwent tracheostomy and were subsequently transferred to an intermediate care ward on mechanical ventilation.

Epidemiological, demographic, clinical, treatment, and outcome data were collected in a dataset. The primary endpoint was the incidence of DVT and the secondary endpoint was to evaluate the diagnostic power to predict DVT of platelet count, aPTT, D-dimer, INR, sepsis-induced coagulopathy (SIC) score, sequential organ failure assessment (SOFA) score, and simplified acute physiology score (SAPS II). The SOFA scores were recorded for all patients daily. The Glasgow Coma Scale evaluation was based on preintubation observation in all mechanically ventilated patients (14, 15). The SIC scores were retrospectively calculated. In patients who developed DVT, the last SIC and SOFA scores before the event were considered, whereas in patients in whom no DVT was detected, the highest scores during ICU stay were used. SAPS II score at ICU admission was used for all patients. SIC and SOFA scores were analyzed in order to find the most useful threshold to detect patients who were at high risk for DVT, and who could benefit from full-dose anticoagulation, and those who were at very low risk and who may not require full-dose treatment.

Treatment Protocol

All patients admitted to the ICU without clinical and radiological evidence of VTE who were not on previous anticoagulation therapy and who were not considered at increased risk for hemorrhage were treated with higher-intensity thromboprophylaxis using low-molecular-weight heparin or unfractionated heparin (UFH) adapted to weight and glomerular filtration rate, as shown in **Table 1**. Therapeutic-intensity anticoagulation was initiated when evidence of VTE was found (**Table 2**).

Patients on previous oral anticoagulants were switched to therapeutic-intensity anticoagulation with low-molecular-weight

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; aPTT, activated partial thromboplastine time; INR, international normalized ratio; PLT, platelet count; SIC, sepsis induced coagulopathy; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score; ICU, intensive care unit; UFH, unfractionated heparin; ROC, receiver operating characteristic; AUC, area under curve; OR, odds ratio; CI, confidence interval; BMI, body mass index; IQR, interquartile range.

TABLE 1 | Weight and GFR adapted higher-intensity thromboprophylaxis.

eGFR	Weight <80 kg	Weight ≥80 kg
≥30 ml/min/1.73 m^2	Enoxaparin 40 mg sc **2/day**	Enoxaparin 60 mg sc **2/day**
<30 ml/min/1.73 m^2 and/or hemofiltration	Unfractioned heparin sc 5,000 UI **3/day**	

TABLE 2 | Weight and GFR adapted therapeutic-intensity anticoagulation.

eGFR	Weight <80 kg	Weight ≥80 kg
≥30 ml/min/1.73 m^2	Enoxaparin 60 mg sc **2/day**	Enoxaparin 80 mg sc **2/day**
<30 ml/min/1.73 m^2 and/or hemofiltration	**Preferentially IV UFH**, *anti-Xa target 0.3–0.5 U/mL* Alternatively: UFH sc 15,000 UI **2/day,** *anti-Xa target 0.3–0.5 U/mL*	

heparin or UFH, and those at increased risk for bleeding received standard-dose thromboprophylaxis (enoxaparin, 40 mg/day or UFH, 5,000 UI/twice daily). Only patients with an absolute contraindication, such as relevant active bleeding, were excluded from antithrombotic treatment.

Statistical Analysis

We used MedCalc Statistical Software version 19.4.0 (MedCalc Software Ltd., Ostend, Belgium; https://www.medcalc.org; 2020). Descriptive statistics were presented as absolute frequencies for categorical variables and mean with SD for continuous variables. The comparisons of dichotomous values were performed using the chi-squared test, whereas continuous variables between groups were compared using the Mann–Whitney test (16). For D-dimers, international normalized ratio, platelet count, SOFA and SAPS II scores, a receiver operating characteristic (ROC) curve (17) was used to calculate area under the ROC curve (AUC) sensitivity and specificity. The Youden's index was used to establish the best threshold on the ROC curve (18). A Cox proportional-hazards model was used to identify factors associated with time-to-DVT events, to test SIC and SOFA scores in regards to DVT and to provide hazard ratio (HR) and 95% confidence interval (CI). K-Fold Cross Validation method (K = 5) was used to create multiple validation subsets of our data sample and to assess our prediction model reliability. Subgroup analyses were performed to test the diagnostic power of SIC and SOFA scores in patients not on anticoagulation treatment prior to admission. The threshold of statistical significance was $P < 0.05$.

RESULTS

Of 450 patients admitted for Covid-19 infection, 96 required intensive care and were included in this study. Median age was 69.1 years (IQR 61.1–75.0); 69 (71.9%) were male; and 74 (77.1%) had at least one comorbidity. Median BMI was 29.6 kg/m^2 (IQR 26.6–32.4), with 31.7 in the DVT group and 28.9 in the non-DVT group ($P = 0.009$). Median length of ICU stay was 19 days (IQR 12–25) in the DVT group and 9 days (IQR 3–19) in the non-DVT group ($P = 0.004$). A total of 84 patients (87.5%) required invasive mechanical ventilation. Additional details are shown in **Table 3**. The overall median time of DVT development after ICU admission was 12.5 days (IQR 8.5–20.0).

Ultrasound screening carried out in all critical SARS CoV-2 patients detected DVT in 37% of cases. A total of 55 patients were on higher-intensity thromboprophylaxis, whereas 16 patients were on therapeutic-intensity anticoagulation, and 24 patients on regular-dose thromboprophylaxis because of increased risk for bleeding. One patient presented with concomitant subdural hematoma at admission and received no antithrombotic treatment. Details on anticoagulation treatment and prophylaxis are shown in the **Figure 1**.

Nine patients had bleeding events, three were major bleedings of which two were fatal. Eight of these nine patients were on therapeutic-intensity anticoagulation and one was on higher-intensity prophylaxis.

The ROC analysis resulted not significant in predicting the presence of DVT for D-dimers, platelet count, International normalized ratio, and SAPS II score (**Figures 2A–D**). Conversely, SOFA score showed an AUC of 0.981 ($p < 0.001$) (**Figure 3**). With a SOFA score threshold ≥2 points, we found the test to have a sensitivity of 97.0% and a specificity of 93.3%, while with a threshold ≥3 points the sensitivity was 87.9% and specificity 100%. SIC scores ≥2 showed the best association with DVT, with sensitivity, specificity, and positive and negative predictive values of 90.0, 48.1, and 49.1 and 89.7%, respectively. There were no patients with a SIC score of 0. The K-Fold Cross Validation Method confirmed the high diagnostic power of the SOFA score prediction model. Sensitivity, specificity and positive and negative predictive values were, respectively, 88.3, 100.0, 93.8, and 100.0%.

The Cox proportional-hazard regression analysis was carried out including eight different factors potentially associated to time-to-DVT event (i.e., age, sex, BMI, SOFA score, comorbidities, anticoagulation intensity, d-dimer level, length of ICU stay). In the regression model four factors associated with DVT were retained: age (HR 0.954, 95%CI 0.914–0.997, $p = 0.034$), sex (HR 0.400, 95%CI 0.164–0.976, $p = 0.044$), SOFA score (HR 1.871, 95%CI 1.574–2.225, $p < 0.001$), and anticoagulation intensity (HR 0.407, 95%CI 0.219–0.758, $p = 0.005$) (**Figure 4**).

DISCUSSION

Although the danger associated with hypercoagulability in patients with severe SARS-Co-V2 has been observed repeatedly and is well-accepted, three fundamental questions remain uncertain: What is the real incidence of DVT and PE in this subset of patients?; Which prophylactic and anticoagulation strategies should be applied?; and Which are the most reliable markers that allow detection of patients who may benefit from anticoagulation treatment while avoiding overtreatment in patients at very low risk of developing VTE?. Numbers reported in different studies to address the first question are

TABLE 3 | Patient characteristics and primary clinical outcomes.

	DVT group *n* = 36	No DVT group *n* = 60	*P*
Age, years (IQR)	70.3 (62.5–74.6)	68.8 (60.6–75.2)	0.748
Sex, male (%)	23 (63.9)	46 (76.7)	0.179
Comorbidities			
Cardiovascular disease, *n* (%)	9 (25.0)	21 (35.0)	0.309
Hypertension, *n* (%)	14 (38.9)	35 (58.3)	0.066
Pulmonary disease, *n* (%)	5 (13.9)	9 (15.0)	0.882
Renal disease, *n* (%)	2 (5.6)	8 (13.3)	0.229
Presence of a solid tumor, *n* (%)	1 (2.8)	1 (1.7)	0.714
Diabetes, *n* (%)	7 (19.4)	17 (28.3)	0.333
Dementia, *n* (%)	1 (2.8)	1 (1.7)	0.714
Immunosuppressive status, *n* (%)	2 (5.6)	1 (1.7)	0.292
BMI, kg/m^2 (IQR)	31.7 (29.7–39.1)	28.9 (25.8–30.4)	**0.009**
Active smoking, *n* (%)	3/18 (16.7)	1/16 (6.2)	0.354
Vital signs on admission			
Systolic blood pressure, mmHg (IQR)	136 (123–148)	129 (120–141)	0.210
Hearth rate, BPM (IQR)	87 (74–95)	84 (71–96)	0.576
Temperature, °C (IQR)	37.6 (36.9–38.3)	37.6 (36.8–38.1)	0.759
Respiratory rate, breaths per minute (IQR)	22 (19-24)	24 (20-30)	0.161
Days positive test to ICU admission	2.0 (1.0–5.5)	3.5 (0–6.0)	0.848
Length of ICU stay, days (IQR)	19 (12–25)	9 (3–19)	**0.004**
Early Warning Score, points (IQR)	4 (3–6)	5 (3–9)	0.122
SAPS II, median (IQR)	42 (37–48)	41 (36–54)	0.762
SIC score, points (IQR)	2 (2)	2 (1–2)	**0.015**
SOFA score, points (IQR)	5 (3–7)	1 (1)	**<0.001**
INR, median (IQR)	1.2 (1.1–1.25)	1.2 (1.1–1.3)	0.638
LDH_{max}, median (IQR)	790.5 (604–1115)	722 (486–870)	0.112
ALT_{max}, median (IQR)	50 (30–103)	42 (34–78)	0.501
AST_{max}, median (IQR)	76 (55–121)	44 (31–71)	**0.010**
aPTT, sec. (IQR)	33.5 (30–46.25)	35 (30–55.5)	0.356
PLT, n x 10^9/L (IQR)	328 (236–552)	403.5 (217–559)	0.510
Mechanical ventilation, n (%)	34 (94.4)	50 (83.3)	0.113
Anticoagulation regimens			
- None, *n* (%)	0	1 (1.7)	**0.032**
- Simple prophylaxis, *n* (%)	28 (77.8)	29 (48.3)	
- High prophylaxis, *n* (%)	4 (11.1)	20 (33.3)	
- Anticoagulation, *n* (%)	4 (11.1)	10 (16.7)	
Mortality, *n* (%)	12 (33.3%)	24 (38.3%)	0.354

Continue variables are expressed as median with interquartile range (IQR) in parentheses, frequencies are expressed as absolute number with percentage in parentheses. DVT, deep vein thrombosis; BPM, beats per minute; °C, Celsius degrees; BMI, body mass index; SAPS, simplified acute physiology score; SIC, sepsis induced coagulopathy; SOFA, sequential organ failure assessment; INR, International Normalized Ratio; aPTT, activated partial thromboplastin time; PLT, platelet count; ICU, intensive care unit. Bold values are the statistically significative ones.

of limited value to determine the actual incidence of DVT or PE, because most diagnostic tests were carried out only in patients who showed clinical symptoms (2). This approach is understandable given the fact that extensive screening of COVID patients for DVT potentially exposes operators to an increased risk of infection if serious precautions are not taken. During this medical emergency, when resources are often depleted, it could be argued that carrying out routine screening of all critical patients poses too high a risk of infecting medical staff and is too time consuming (19). Moreover, in terms of cost effectiveness, an analysis of systematic daily ultrasound screening should be carried out (20). Conversely, the difficulty in detecting minor PE in the subset of severe SARS-CoV-2 patients subjected to mechanical ventilation potentially leaves some events unrecognized. It is therefore impossible to determine the real incidence of PE or *in situ* pulmonary artery thrombosis. In some case series, despite VTE was not clinically suspected before death, an occlusion of the pulmonary artery has been

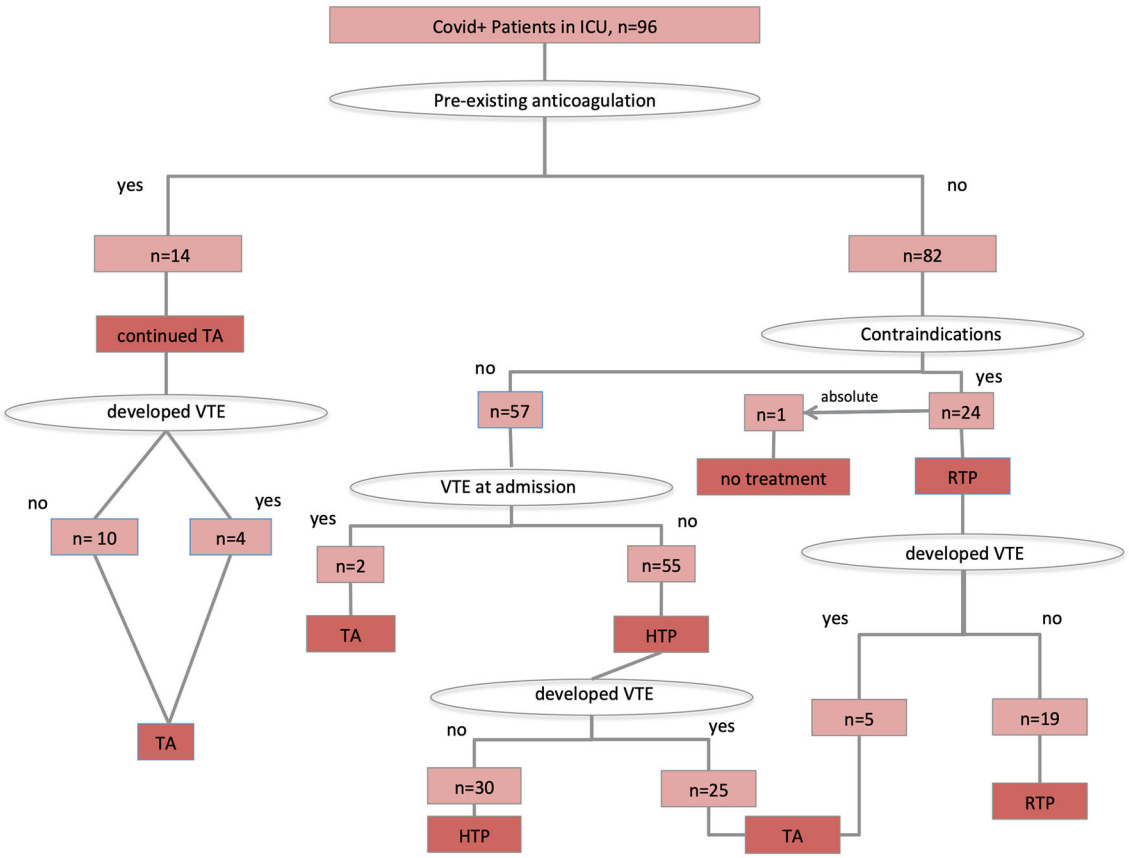

FIGURE 1 | Antithrombotic treatment protocol application. TA, therapeutic anticoagulation; HTP, higher-intensity thromboprophylaxis; RTP, regular-intensity thromboprophylaxis.

found in post mortem examination (10, 21). We decided to prospectively gather data from daily ultrasound screenings using a dedicated team of radiologists and angiologists. Performing a daily duplex ultrasound on all the patients is an advantage of our study. This allowed us to detect almost all patients with DVT, revealing the actual incidence of this complication. After discharge from the ICU the daily screening was continued only in those patients who were transferred to intermediate care for mechanical ventilation through tracheostomy. Although it is possible that some patients developed DVT at a later time, our study focused only on those events triggered by the critical stage during organ function support.

The team that carried out the examinations took all necessary precautions. One month after the last patient was discharged, all members of the team where tested serologically. One staff member of six tested positive, and none had presented any symptoms. Venous thrombosis was detected in a very high number (37%) of these patients with several among them remaining asymptomatic for VTE. This is consistent with reports of the high prevalence of thrombosis at all levels, including central lines, dialysis catheters, and extracorporeal membrane oxygenation (2, 5).

The second question regarding the anticoagulation treatment has been addressed by many study groups and is still widely debated. Most studies that reported data from the early stages of the pandemic included series of patients who had undergone different prophylactic and anticoagulation strategies, making results poorly comparable (5, 8, 22). Early in the pandemic one relevant study showed a benefit of anticoagulation treatment in terms of 28-day survival in patients with a six-fold D-dimer elevation, regardless of existing VTE. The results though were biased by a high percentage of patients who were not treated with thromboprophylaxis (8). A review of randomized trials comparing full anticoagulation to standard-dose and higher-intensity thromboprophylaxis treatments in Covid-19 patients identified 20 ongoing trials. The review showed trials to be of low quality and heterogeneous (23) with a mix of different outcomes and lack of differentiation regarding disease severity. A subsequent systematic review found slight evidence that therapeutic anticoagulation may improve survival amongst mechanically ventilated Covid-19 patients (24). More recently, two large randomized controlled trials compared prophylaxis to therapeutic anticoagulation in non-critical (25) and in critical (26) Sars-Cov-2 patients. The first one found an advantage in terms of survival amongst non-critical patients treated with therapeutic anticoagulation whereas the latter did not show an increase in survival and in number of days free of cardiovascular or respiratory organ

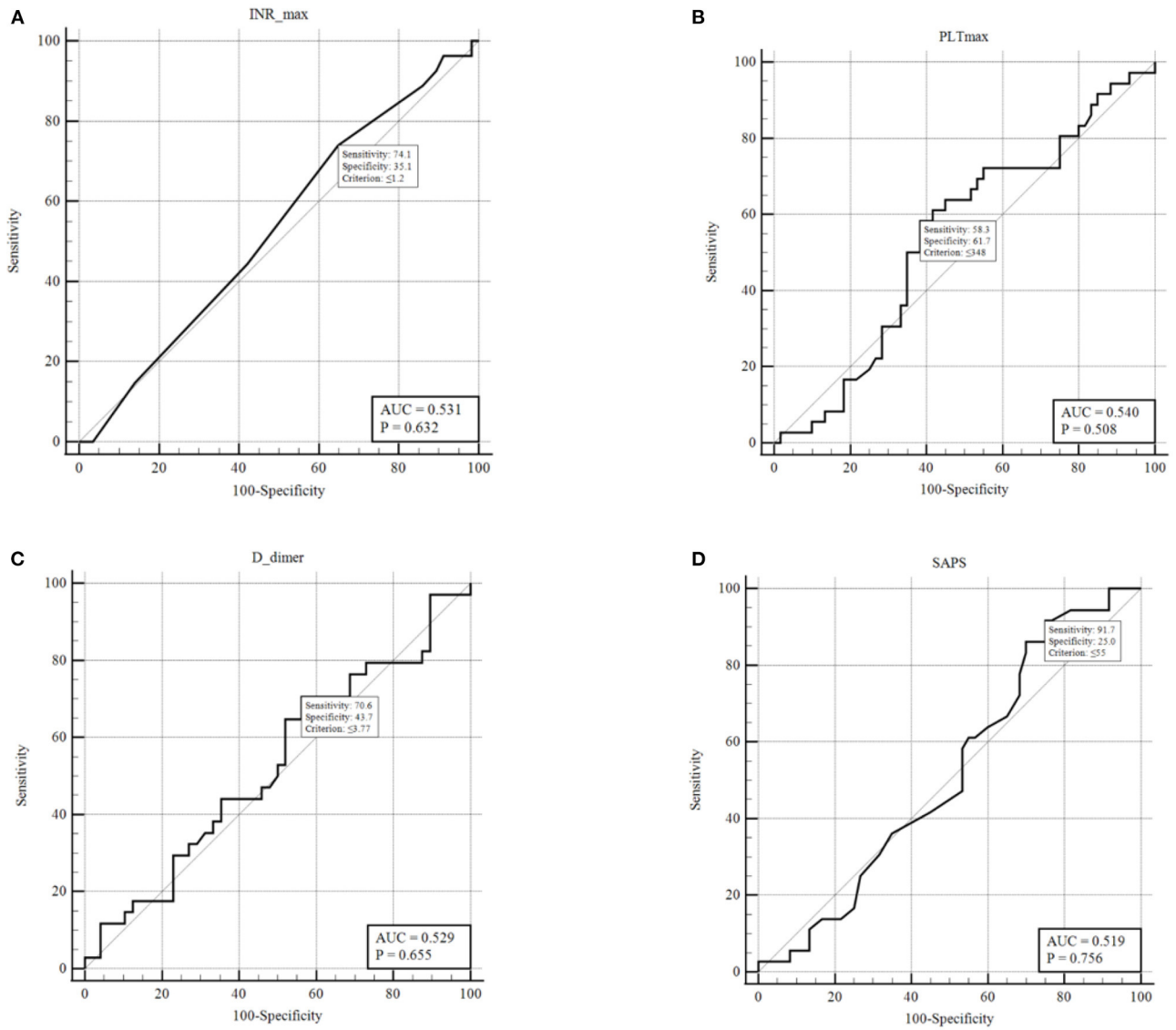

FIGURE 2 | ROC curves for: **(A)** INR last value pre-DVT or highest value if no DVT; **(B)** PLT last value pre-DVT or highest value if no DVT; **(C)** D-dimers last value pre-DVT or highest value if no DVT; **(D)** SAPS II score within 24 h from ICU admission.

support with therapeutic anticoagulation. Additionally, some recent studies suggest a platelet hyperactivation as contributing to the pro-thrombotic state occurring in Covid-19 infection (27, 28).

In our center, an aggressive treatment strategy with higher-intensity prophylaxis, when feasible and therapeutic anticoagulation as soon as DVT was detected was applied throughout. This approach has been recommended by several study groups (6), although it is currently still not validated by clear evidence (23).

Despite this more aggressive approach, there was a 37% prevalence of DVT, indicating that a subgroup of patients might benefit from therapeutic anticoagulation. This finding is confirmed by several recently published series that included patients admitted to the ICU (3, 29, 30).

The third question is generated by the necessity to detect those critical patients who may benefit from therapeutic anticoagulation, ideally before the onset of life-threatening VTE events, while avoiding overtreatment in all other critical patients. In fact, some studies have shown an increased risk of major bleedings in COVID-19 patients treated with therapeutic anticoagulation (31). Furthermore, the randomized controlled trial on critical patients by the REMAP-CAP, ACTIV-4a study group (26) was interrupted for futility of therapeutic anticoagulation over regular thromboprophylaxis, confirming that therapeutic anticoagulation should not be routinely administered to all critical patients. The contradicting results of other previous studies (24) suggest there may be a subgroup of critical patients that still might benefit from therapeutic anticoagulation.

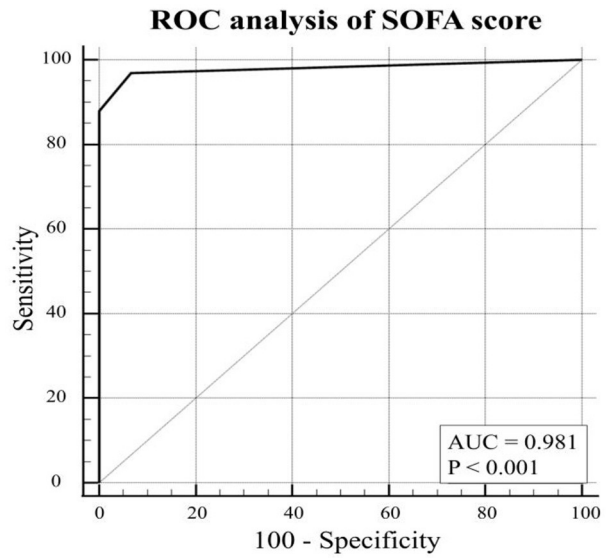

FIGURE 3 | ROC curve for SOFA score last value pre-DVT or highest value if no DVT.

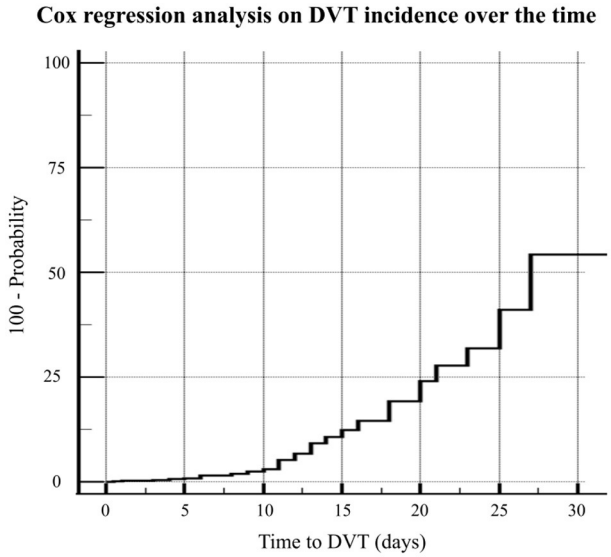

FIGURE 4 | The Cox proportional-hazard regression analysis including eight different factors potentially associated to time-to-DVT event (i.e., age, sex, BMI, SOFA score, comorbidities, anticoagulation intensity, d-dimer level, length of ICU stay).

Although several hematological alterations have been described in critical SARS-CoV-2 patients, only a few of them have been suggested to be useful predictors for survival and a reliable indicator with an accepted threshold for increased risk of VTE events in patients with severe SARS-CoV-2 has not yet been established.

In this study, we analyzed D-dimers, platelet count, aPTT, SIC, and SOFA scores. The SOFA score is a valid predictor of in-hospital mortality (32), identifying high-risk patients using basic clinical criteria (33). The SIC score also takes platelet count and INR values into account. It is a validated score to determine a high risk of disseminated intravascular coagulation among septic patients and may identify those who could benefit from anticoagulant therapy (34–36).

Regarding the D-dimer analysis, the Youden index determined a threshold of 3.77 mg/ml with associated sensitivity and specificity of 73.5 and 44.7%, respectively. Not treating patients with a D-dimer below this threshold will leave a significant number of patients untreated who are at high risk of developing DVT. Conversely, lowering this threshold will cause most critical patients to be treated with anticoagulation, given the prevalence of elevated D-dimers observed. It has been extensively shown that D-dimer levels are correlated to mortality in all hospitalized COVID-19 patients (37, 38), yet it has not proven in our study to be a useful indicator for the risk of DVT or to determine patients who should undergo full anticoagulation. Tang et al. (8) showed a benefit of anticoagulation treatment in terms of 28-day survival in patients with a six-fold D-dimer elevation (>3 mg/L), regardless of existing VTE. These results are not comparable with results reported in several other series, including ours, because of a high percentage of patients who were not treated with any thromboprophylaxis (78%).

The ROC curves for platelet count and aPTT exhibited an AUC of 0.54 and 0.57, respectively, indicating they must not be used as markers to detect high-risk or low-risk patients. The analysis of SIC scores showed a significant correlation with DVT with $P = 0.0002$. Although, when analyzing by grouping to determine a useful threshold, we found that SIC scores 1 + 2 vs. 3 + 4 had a low sensitivity (20%) and a specificity of 77.7% for DVT. A more significant grouping was found with SIC score 1 vs. ≥2, which had a high sensitivity (90%) but a specificity of only 48.1%, potentially exposing several patients to unnecessary therapeutic-intensity anticoagulation.

A significant correlation of SOFA score with DVT ($P < 0.0001$) was also found. By pooling patients with a SOFA score 1 vs. scores ≥2, we found the test to have a sensitivity of 96% and a specificity of 93%. Conversely, by grouping scores 1 + 2 vs. ≥3, the sensitivity is reduced to 87.9%, but the test displayed a specificity of 100%. This finding allows us to determine that patients with SOFA scores 1 and 2 are unlikely (93.8%) to develop DVT and may therefore be treated with thromboprophylaxis only. Conversely, patients with a SOFA score ≥3 are at high risk of developing thrombosis-related complications and may represent a subgroup that could benefit from therapeutic anticoagulation. We find this threshold to be the most useful from a clinical point of view because 69% of our patients were included in the SOFA 1 + 2 pool. This allows to withhold full anticoagulation treatment from a relevant number of critical patients, while determining a group of patients who might benefit from therapeutic anticoagulation treatment and for whom the increased risk of hemorrhage is justified. Since a relatively high number of patients (14) were already on therapeutic anticoagulation prior to admission, a subgroup analysis was performed. It showed no relevant difference to

the main analysis and confirms validity of our findings in patients who were not previously on anticoagulation. The role of higher-intensity thromboprophylaxis, conversely, remains uncertain. Although a strict protocol was applied, excluding only patients at increased risk for bleeding from this treatment regimen, the prevalence of thrombosis was comparable to that described in several other studies that applied lower regimen prophylaxis. Several prospective studies are being conducted to determine the effectiveness and safety of higher-intensity prophylactic regimens.

This study has some limitations. The first one is the retrospective analysis on prospectively collected data. Furthermore, the relatively small number of patients does not allow to perform finer subgroup analyses and may limit the overall quality of evidence provided. A potential bias could be represented by the relatively large number of patients on full anticoagulation treatment prior to admission, though statistical analysis in patients without previous anticoagulation showed no relevant difference. A further source of potential bias is the operator-dependent variability of the ultrasound screening. The exams were all performed by a relatively small team (six) of trained radiologists and angiologists to limit the variability. A few exams were carried out in very difficult conditions, potentially leaving some events undetected. Finally, PE events were not included in the analysis because there is not a reliable method to detect all events of PE and of *in situ* pulmonary artery thrombosis in mechanically ventilated patients. This potentially leaves some patients without DVT but who developed PE unrecognized in our study.

CONCLUSIONS

Both SIC score and SOFA score are significantly correlated with DVT in critical stages of SARS-CoV-2. Patients with SOFA scores 1 and 2 are at low risk of developing DVT and could avoid therapeutic-intensity anticoagulation. Conversely, patients with scores $\geq$3 are at high risk of DVT.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico Cantonale del Ticino, Switzerland, BASEC 2020-01354 CE 3659. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

LE, MB, FR, and DD did the literature search. GP, LG, LE, FM, and DD were responsible for study design. LS, MB, FR, CU, and CC collected the data. GP, FM, LG, LE, JB, and LS accomplished data analysis and interpretation. Drafting by LE, FM, CU, FR, CC, and MB. Critical revisions under responsibility of GP, LE, FM, LG, and JB. All authors contributed in correcting and approving the final manuscript.

FUNDING

The study was funded by the Scientific Fund of the Centro Vascolare Ticino, Switzerland. The funder had no role in the study design, in the collection, analysis, interpretation of data, in the writing of the report, and in the decision to submit the paper for publication. The funder enabled open access publication.

ACKNOWLEDGMENTS

We thank Paolo Merlani (Chief of Department of Critical Care, Ente Ospedaliero Cantonale, Lugano) for his precious review of this manuscript.

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frontiers in Cardiovascular Medicine

SYSTEMATIC REVIEW
published: 05 November 2021
doi: 10.3389/fcvm.2021.766377

Effectiveness and Safety of DOACs vs. VKAs in AF Patients With Cancer: Evidence From Randomized Clinical Trials and Observational Studies

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OPEN ACCESS

Edited by:
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University of Palermo, Italy

Reviewed by:
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Karolinska Institutet (KI), Sweden
Job Harenberg,
Heidelberg University, Germany

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Specialty section:
This article was submitted to Thrombosis, a section of the journal Frontiers in Cardiovascular Medicine

Received: 29 August 2021
Accepted: 13 October 2021
Published: 05 November 2021

Citation:
Liu F, Xu Z, Luo J, Yu P, Ma J, Yuan P and Zhu W (2021) Effectiveness and Safety of DOACs vs. VKAs in AF Patients With Cancer: Evidence From Randomized Clinical Trials and Observational Studies. Front. Cardiovasc. Med. 8:766377. doi: 10.3389/fcvm.2021.766377

Background: The use of direct oral anticoagulants (DOACs) is recommended as the preferred treatment drug in patients with nonvalvular atrial fibrillation (AF). However, the effectiveness and safety of DOACs compared with vitamin K antagonists (VKAs) in patients with cancer and AF are still controversial. Therefore, we performed a meta-analysis regarding the effectiveness and safety of DOACs vs. VKAs in AF patients with cancer.

Methods: A search of the Pubmed and EMBASE databases until August 2021 was performed. Adjusted risk ratios (RRs) and 95% confidence intervals (CIs) were pooled using a random-effects model with an inverse variance method.

Results: Thirteen studies were deemed to meet the criteria. For the effectiveness outcomes, the use of DOACs compared with VKAs use was significantly associated with decreased risks of stroke or systemic embolism (RR = 0.66, 95% CI: 0.54–0.80) and venous thromboembolism (RR = 0.40, 95% CI: 0.26–0.61), but not ischemic stroke (RR = 0.79, 95% CI: 0.56–1.11), myocardial infarction (RR = 0.78, 95% CI: 0.56–1.11), cardiovascular death (RR = 0.76, 95% CI: 0.53–1.09), and all-cause death (RR = 0.82, 95% CI: 0.43–1.56). For the safety outcomes, compared with VKAs use, the use of DOACs was associated with reduced risks of intracranial bleeding (RR = 0.60, 95% CI: 0.50–0.71) and gastrointestinal bleeding (RR = 0.87, 95% CI: 0.80–0.95). There were no significant differences in major bleeding (RR = 0.87, 95% CI: 0.74–1.04), major or nonmajor clinically relevant bleeding (RR = 0.87, 95% CI: 0.74–1.01), and any bleeding (RR = 0.88, 95% CI: 0.76–1.03).

Conclusion: Compared with VKAs, DOACs appeared to have significant reductions in stroke or systemic embolism, venous thromboembolism, intracranial bleeding, and gastrointestinal bleeding, but comparable risks of ischemic stroke, myocardial infarction, cardiovascular death, all-cause death, major bleeding, major or nonmajor clinically relevant bleeding, and any bleeding in patients with AF and cancer.

Keywords: atrial fibrillation, cancer, direct oral anticoagulants, vitamin K antagonists, meta-analysis

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in adults. The currently estimated prevalence of AF in adults is between 2 and 4%, and a 2.3-fold rise is expected, due to the longevity in the general population and the increased screenings of patients with undiagnosed AF (1). Increasing age is a foremost risk factor, but the increasing burdens of other comorbidities (e.g., hypertension, diabetes mellitus, heart failure, coronary artery disease, chronic kidney disease) are also important. Several other modifiable risk factors are potential contributors to AF development and progression (1). AF increases the risks of cardiovascular and cerebrovascular complications including a 5-fold risk of stroke (2). AF-related thromboembolic events are the main reasons for the increased rates of morbidity and mortality (3, 4).

A published research report involving more than 24,000 patients diagnosed with cancer showed that the prevalence of AF combined at the time of cancer diagnosis was about 2.4%, and the incidence of AF after cancer diagnosis was 1.8% (5). AF and cancer may interact with each other on pathophysiological grounds. AF in cancer patients may be caused by inflammation, age, comorbidities, surgery or medical cancer treatment, or direct tumor effects. However, cancer patients are at higher risks of thromboembolism and bleeding complications, because cancer interacts with the coagulation system, which is related to a hypercoagulable state (2). AF and cancer have independently increased risks of arterial and venous thrombosis compared with a single disease. Anticoagulation therapy for patients with AF and cancer is challenging because of the increased risk of thromboembolism and bleeding in this special population.

The current international guidelines recommend the use of direct oral anticoagulants (DOACs) as replacement therapy for vitamin K antagonists (VKAs) in patients with nonvalvular AF. DOACs also have advantages in the elderly, or AF patients with specific diseases such as acute coronary syndrome and chronic kidney disease (6). However, whether these recommendations apply to patients with cancer and AF needs further evidence. So far, most of the data on anticoagulant therapy for cancer patients is mainly for the treatment and prevention of venous thromboembolism (VTE). International guidelines recommend low molecular weight heparin (LMWH) (rather than VKAs or DOACs) for the prevention and treatment of VTE in cancer patients (7). Although DOACs have non-inferiority compared with VKAs in patients with AF, these drugs are not recommended in the guidelines for cancer patients. The effectiveness and safety of anticoagulation therapy in patients with AF and cancer are unclear.

Previous DOAC-related randomized controlled trials (RCTs) in the AF population only include a small number of cancer patients or even exclude some cancer patients (8–11). Current data of *post-hoc* analyses of RCTs (12–15) and observational cohort studies (3, 16–19) regarding the effectiveness and safety of DOACs compared with VKAs in patients with AF and cancer have been published. Therefore, this meta-analysis aimed to evaluate the effect of DOACs vs. VKAs in AF and cancer patients.

METHODS

Literature Retrieval

The two common databases of PubMed and Embase were systematically searched until August 2021 for available studies using the following search terms: (1) atrial fibrillation, (2) cancer OR tumor OR malignancy, (3) non-vitamin K antagonist oral anticoagulants OR direct oral anticoagulants OR dabigatran OR rivaroxaban OR apixaban OR edoxaban, and (4) vitamin K antagonists OR warfarin. The detailed searching strategies are shown in **Supplementary Table 1**. In this meta-analysis, we included publications in English.

Inclusion and Exclusion Criteria

We included the *post-hoc* analyses of RCTs or observational cohort studies focusing on the effectiveness and/or safety of DOACs (dabigatran, rivaroxaban, apixaban, or edoxaban) compared with VKAs in AF patients with cancer. The effectiveness outcomes included stroke or systemic embolism (SSE), ischemic stroke, myocardial infarction (MI), VTE, all-cause death, cardiovascular death; whereas the safety outcomes included major bleeding, major or nonmajor clinically relevant (NMCR) bleeding, intracranial bleeding, gastrointestinal bleeding, and any bleeding. The follow-up time was not restricted. We excluded certain publication types such as reviews, case reports, case series, editorials, and meeting abstracts because they had no sufficient data. Studies with overlapping data were also excluded.

Study Screenings and Data Extraction

Two authors (FW-L and ZX-X) independently did the process of data extraction. We first screened the titles and abstracts of the searched records to select potential studies, and the full text of which was screened in the subsequent phase. Disagreements were resolved through discussion, or consultation

with the third researcher (WG-Z). If two or more studies were from the same data source, the study that was more designed to meet the predefined criteria was included. If two studies met the inclusion criteria, we would include the newly published study, or the study with the longest follow-up or highest sample size.

Two authors independently collected the following characteristics from each included study, mainly included the first author and publication year, location, data source, study design, inclusion period, patient age and sex, types of DOACs, follow-up time, effectiveness and safety outcomes, type of cancers, the sample size and number of events in the VKA- or DOAC- groups, and adjusted risk ratios (RRs) and 95% confidence intervals (CIs).

Study Quality Assessment

Two authors (FW-L and ZX-X) used the Newcastle-Ottawa Scale (NOS) to perform the quality assessment for the included studies independently. The NOS tool had three domains with a total of nine points including the selection of cohorts (0–4 points), the comparability of cohorts (0–2 points), and the assessment of the outcomes (0–3 points). In this study, we defined studies with the NOS of <6 points as low quality (20).

Statistical Analysis

We assessed the consistency across the included studies using the Cochrane *Q*-test and I^2 statistic. A $P < 0.1$ for the Q statistic, or $I^2 \geq 50\%$ indicated substantial heterogeneity. We first collected the sample size and number of events in the VKA- or DOAC-groups and calculated their corresponding crude rates of effectiveness and safety outcomes. The comparison results between the VKA- or DOAC-groups were expressed as odds ratios (ORs) and 95% CIs. Second, we assessed the effectiveness and safety of DOACs vs. VKAs in AF patients with cancer using the adjusted RRs. The adjusted RRs and 95% CIs were converted to the natural logarithms and standard errors, which were pooled by a random-effects model using an inverse variance method. The publication bias for the reported effect estimates was assessed using the funnel plots.

All the statistical analyses were conducted using the Review Manager Version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, 2014, Copenhagen, Denmark; https://community.cochrane.org/). The statistical significance threshold was set at a $P < 0.05$.

RESULTS

The process of the literature retrieval is presented in **Supplementary Figure 1**. A total of 1,116 studies were identified through the electronic searches in the PubMed and Embase databases. According to the predefined criteria, we finally included 13 studies (four *post-hoc* analyses of RCTs and nine observational cohorts) in this meta-analysis (3, 4, 12–17, 19, 21–24). **Table 1** shows the baseline patient characteristics of the included studies. All of these included studies had a moderate-to-high quality with the NOS score of ≥6 points.

Crude Event Rates Between DOACs vs. VKAs

A total of nine included studies reported the crude rates of effectiveness or safety outcomes between DOACs vs. VKAs (3, 4, 12–17, 19). For the effectiveness outcomes shown in **Figure 1**, compared with VKA-users, DOAC-users had lower event rates of SSE (3.10 vs. 5.36%, OR = 0.55, 95% CI: 0.30–0.99), ischemic stroke (9.83 vs. 12.2%, OR = 0.60, 95% CI: 0.41–0.90), VTE (2.26 vs. 7.63%, OR = 0.40, 95% CI: 0.18–0.88), and MI (1.46 vs. 1.67%, OR = 0.64, 95% CI: 0.44–0.91), but there were comparable rates of cardiovascular death (4.79 vs. 6.63%, OR = 0.74, 95% CI: 0.49–1.12) and all-cause death (25.7 vs. 44.6%, OR = 0.69, 95% CI: 0.41–1.14).

The safety outcomes of DOACs vs. VKA are presented in **Figure 2**. The pooled results showed that DOAC-users had lower event rates of major bleeding (7.15 vs. 9.17%, OR = 0.61, 95% CI: 0.39–0.94) and intracranial bleeding (0.14 vs. 1.67%, OR = 0.13, 95% CI: 0.04–0.44) than VKA-users. However, there were no significant differences in major or NMCR bleeding (26.5 vs. 25.0%, OR = 0.88, 95% CI: 0.72–1.09), gastrointestinal bleeding (3.79 vs. 2.34%, OR = 0.75, 95% CI: 0.49–1.13), and any bleeding (11.9 vs. 15.3%, OR = 0.68, 95% CI: 0.37–1.22) between the two studied groups.

Adjusted Data of Outcomes Between DOACs vs. VKAs

A total of nine included studies reported the adjusted data of effectiveness or safety outcomes between DOACs vs. VKAs (3, 12–14, 17, 21–24). Adjusted confounders of the included studies are presented in **Supplementary Table 2**. As shown in **Figure 3**, for the effectiveness outcomes, the use of DOACs compared with VKA use was significantly associated with decreased risks of SSE (RR = 0.66, 95% CI: 0.54–0.80) and VTE (RR = 0.40, 95% CI: 0.26–0.61), but not ischemic stroke (RR = 0.79, 95% CI: 0.56–1.11), MI (RR = 0.78, 95% CI: 0.56–1.11), cardiovascular death (RR = 0.76, 95% CI: 0.53–1.09), and all-cause death (RR = 0.82, 95% CI: 0.43–1.56).

For the safety outcomes shown in **Figure 4**, compared with VKA use, the use of DOACs was significantly associated with reduced risks of intracranial bleeding (RR = 0.60, 95% CI: 0.50–0.71) and gastrointestinal bleeding (RR = 0.87, 95% CI: 0.80–0.95). There were no significant differences in major bleeding (RR = 0.87, 95% CI: 0.74–1.04), major or NMCR bleeding (RR = 0.87, 95% CI: 0.74–1.01), and any bleeding (RR = 0.88, 95% CI: 0.76–1.03).

Publication Bias

As shown in **Supplementary Figures 2**, **3**, no obvious publication biases were observed when assessed by using the funnel plots. Also, it was noted that the publication bias should not be evaluated for some reported outcomes when fewer than 10 included studies were included.

TABLE 1 | Baseline characteristics of the included studies.

Included studies	Study design	Data source	Sample size	Age (mean, y)/Sex	DOACs	VKAs	Efficacy outcomes	Safety outcomes	Follow-up (years)	Types of cancers
Chen et al. (12)	*Post-hoc* analysis of RCT	ROCKET AF; multicenter	640	77/both	Rivaroxaban	Warfarin	SSE, ischemic stroke, VTE, MI, cardiovascular death, and all-cause death	Major bleeding, major or NMCR bleeding, intracranial bleeding, and any bleeding	1.9	Prostate (28.6%), breast (14.7%), gastrointestinal (3.0%), lung (3.1%), head and neck (3.9%), colorectal (16.1%), melanoma (5.9%), leukemia or lymphoma (5.2%), gynecologic (6.6%), genitourinary (12.2%), thyroid (2.5%), brain (0.3%), unspecified (3.9%), and others (3.0%)
Fanola et al. (13)	*Post-hoc* analysis of RCT	ENGAGE AF-TIMI 48; multicenter	1,153	75/both	Edoxaban	Warfarin	SSE, ischemic stroke, MI, cardiovascular death, and all-cause death	Major bleeding, major or NMCR bleeding, and any bleeding	2.8	Prostate (13.7%), breast (6.5%), bladder (7.5%), gastrointestinal (20.5%), lung or pleura (11.0%), skin (5.9%), liver, gallbladder, or bile ducts (3.8%), pancreatic (3.8%), esophageal (2.5%), renal (2.5%), uterine (2.1%), oropharyngeal (2.6%), brain (2.1%), genital (1.3%), thyroid (1.1%), leukemia (2.8%), lymphoma (2.2%), others (1.3%), and unspecified (1.5%)
Melloni et al. (14)	*Post-hoc* analysis of RCT	ARISTOTLE; multicenter	1,236	–/both	Apixaban	Warfarin	SSE, ischemic stroke, VTE, MI, and all-cause death	Major bleeding, major or NMCR bleeding, intracranial bleeding, and any bleeding	1.8	Prostate (29%), breast (16%), bladder (7%), colon (11%), gastric (2%), ovarian/uterus (6%), lung (3%), melanoma (6%), rectal (3%), renal cell carcinoma (4%), Hodgkin's lymphoma (1%), non-Hodgkin's lymphoma (1%), leukemia (<1%), lymphoma (1%), and others (10%)
Flack et al. (15)	Observational cohort	RE-LY; multicenter	546	–/both	dabigatran	Warfarin	–	Gastrointestinal bleeding	2.2	Gastrointestinal
Ording et al. (16)	Observational cohort	Danish population-based medical databases	11,855	77/both	Not available	Unspecified	Ischemic stroke, VTE, and MI	Gastrointestinal bleeding	1.0	Urological (15%), breast cancer (12%), gastrointestinal (12%), lung (4%), hematological (3%), intracranial (0.1%), and others (54%)
Ording et al. (22)	Observational cohort	Danish nationwide cohort study	1,476	78/both	Dabigatran, rivaroxaban, apixaban, and edoxaban	Unspecified	–	Intracranial bleeding, gastrointestinal bleeding, and any bleeding	1.0	Gastrointestinal
Shah et al. (3)	Observational cohort	Market Scan databases, the United States	16,096	74/both	Dabigatran, rivaroxaban, and apixaban	Warfarin	Ischemic stroke, VTE	Any bleeding	1.0	Breast (19.2%), gastrointestinal (12.7%), lung (12.3%), Genitourinary (29.2%), gyneco-oncological (2.4%), hematological (9.8%), and others (14.4%)

(Continued)

TABLE 1 | Continued

Included studies	Study design	Data source	Sample size	Age (mean, y)/Sex	DOACs	VKAs	Efficacy outcomes	Safety outcomes	Follow-up (years)	Types of cancers
Kim et al. (4)	Observational cohort	Severance Cardiovascular Hospital, Seoul, Korea	1,651	70/both	Dabigatran, rivaroxaban, and apixaban	Warfarin	SSE, all-cause death	Major bleeding, intracranial bleeding, and gastrointestinal bleeding	1.8	Prostate (9.3%), gastrointestinal (20.6%), breast (2.4%), colorectal (14.9%), thyroid (10.8%), lung (12.2%), melanoma (5.9%), biliary tract (5.4%), urinary tract (6.1%), genitourinary (12.2%), head and neck (4.1%), hepatocellular carcinoma (3.0%), ovary and endometrial (2.6%), renal cell carcinoma (3.1%), hematologic malignancy (2.2%), and others (3.2%)
Pardo Sanz et al. (23)	Observational cohort	AMBER-AF registry, Oncology and Cardiology Departments, Spain	637	75.4/Female	Not available	Unspecified	SSE	Major bleeding	2.8	Breast
Sawant et al. (17)	Observational cohort	The national VA Healthcare data	196,521	76/both	dabigatran, rivaroxaban, apixaban	Warfarin	Ischemic stroke, all-cause death	NA	1.0	Not available
Yasui et al. (19)	Observational cohort	Osaka International Cancer Institute, Japan	224	72.7/both	Dabigatran, rivaroxaban, apixaban, and edoxaban	Warfarin	SSE, ischemic stroke	Major bleeding, intracranial bleeding, gastrointestinal bleeding	1.0	Gastrointestinal (44.2%), Lung (24.1%), genitourinary (11.2%), head and neck (9.8%), breast (4.0%), hematological (3.1%), and others (3.6%)
Atterman et al. (24)	Observational cohort	Swedish Patient register	8228	75.1/both	NA	Warfarin	-	Major or NMCR bleeding, intracranial bleeding, and gastrointestinal bleeding	1.0	Prostate (27.2%), gastrointestinal (19.1%), pancreatic (1.0%), lung (6.8%), breast (9.1%), gynecological (4.9%), urological (35.6%), intracranial (1.3%), hematological (10.7%), metastasized (9.2%), and others (14.4%)
Chan et al. (21)	Observational cohort	Taiwan National Health Insurance Research Database	7955	77/both	dabigatran, rivaroxaban, apixaban, and edoxaban	Warfarin	SSE, VTE, and MI	Major bleeding, intracranial bleeding, and gastrointestinal bleeding	1.45	Not available

AF, atrial fibrillation; DOACs, direct oral anticoagulants; VKAs, vitamin K antagonists; RCT, randomized controlled trial; SSE, stroke or systemic embolism; MI, myocardial infarction; VTE, venous thromboembolism; NMCR, non-major clinically relevant bleeding.

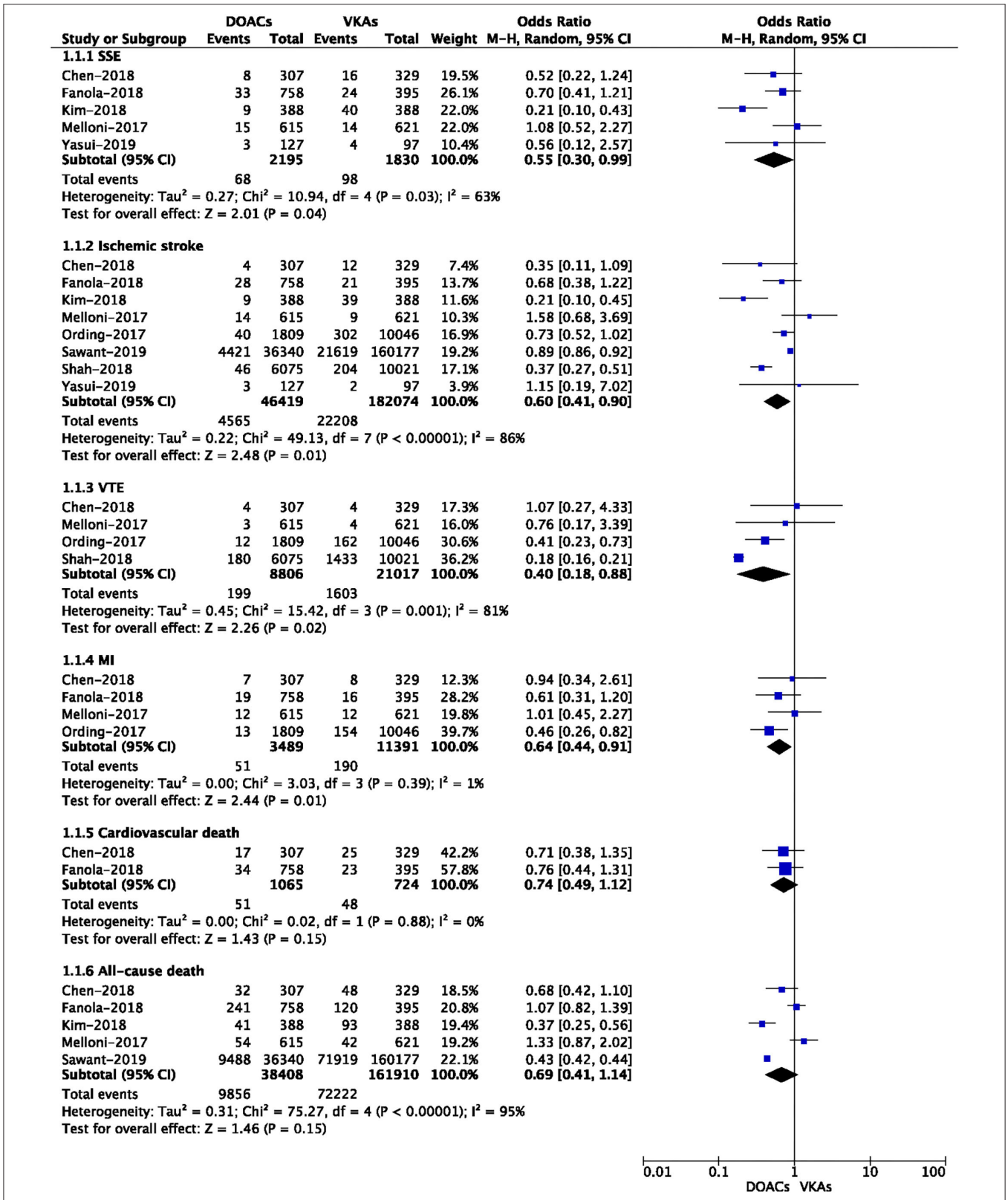

FIGURE 1 | Crude effectiveness event rates of direct oral anticoagulants compared with vitamin K antagonists among atrial fibrillation patients with cancer.

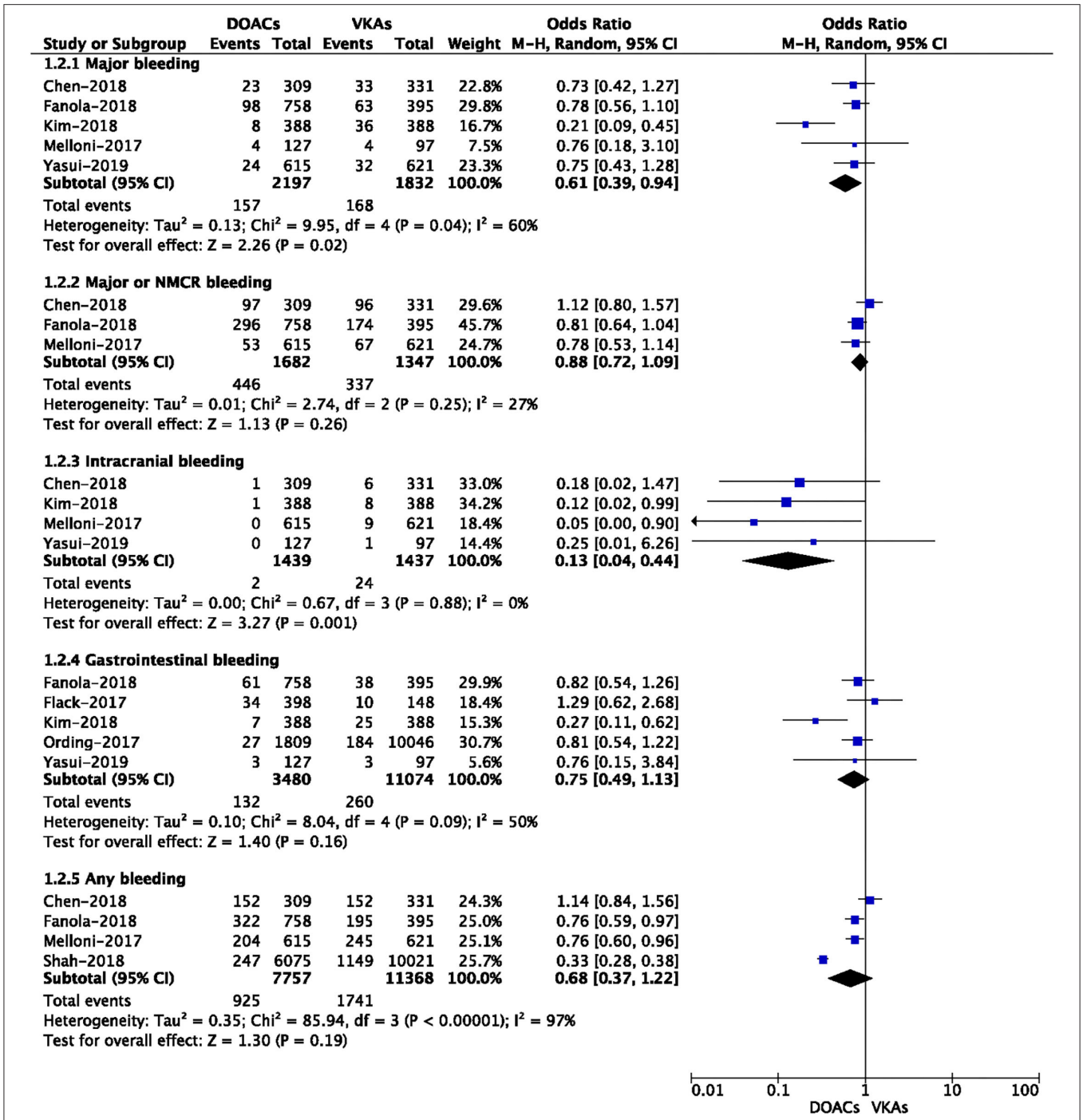

FIGURE 2 | Crude safety event rates of direct oral anticoagulants compared with vitamin K antagonists among atrial fibrillation patients with cancer.

DISCUSSION

The main findings of our current study were as follows: (1) DOACs use resulted in lower rates of SSE and VTE as compared to VKAs use; (2) DOACs were associated with safer profiles (lower intracranial or gastrointestinal bleeding) than VKAs; (3) In comparison to VKAs, DOACs were non-inferior regarding the outcomes of ischemic stroke, MI, cardiovascular death, all-cause death, major bleeding, major or NMCR bleeding, and any bleeding.

Considering that malignant tumors have unique clinical risk characteristics, the optimal anticoagulant treatment for patients with AF and cancer is still controversial. On the one hand, cancer is a pro-thrombotic state, and further increases the

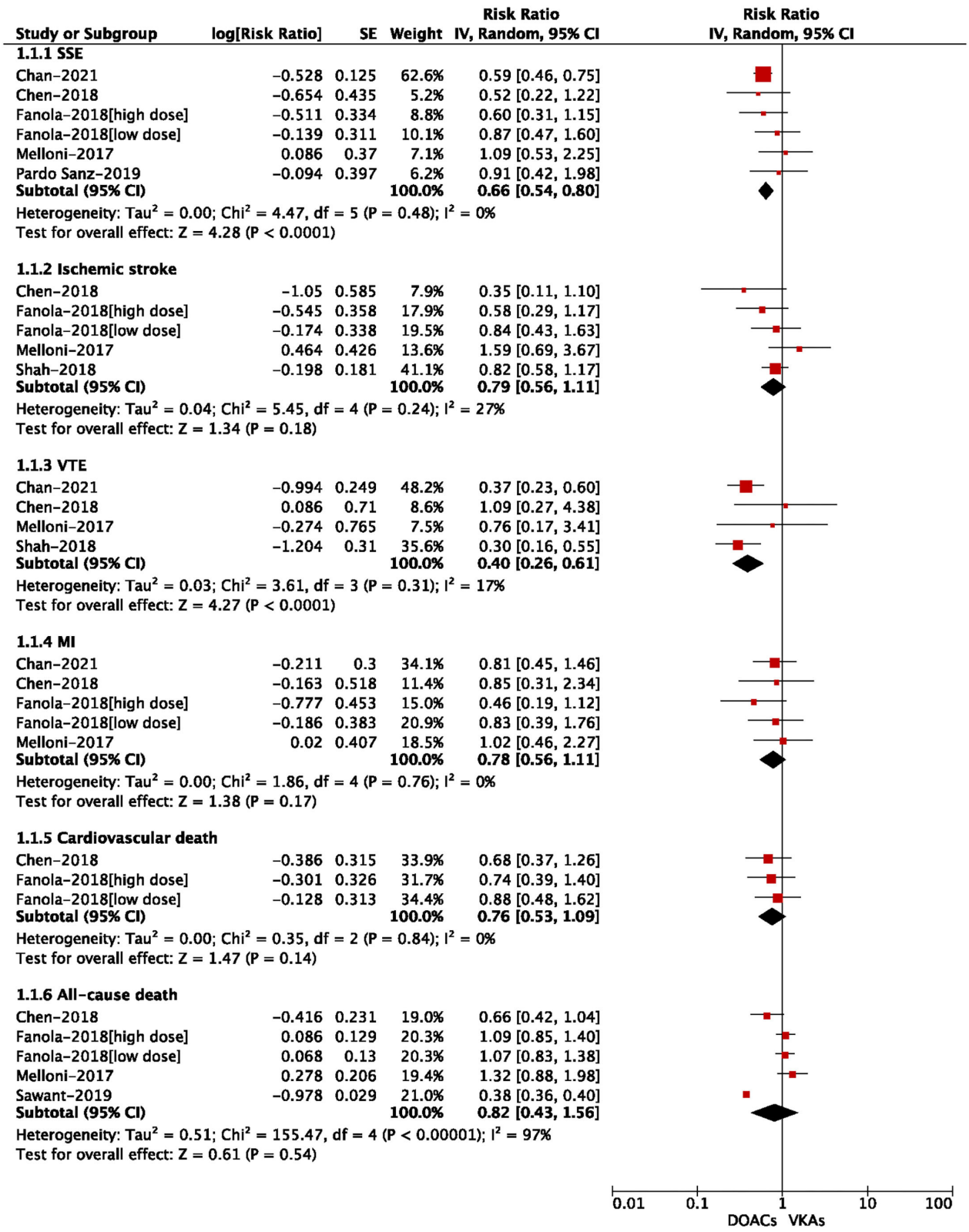

FIGURE 3 | Adjusted effectiveness data of direct oral anticoagulants compared with vitamin K antagonists among atrial fibrillation patients with cancer.

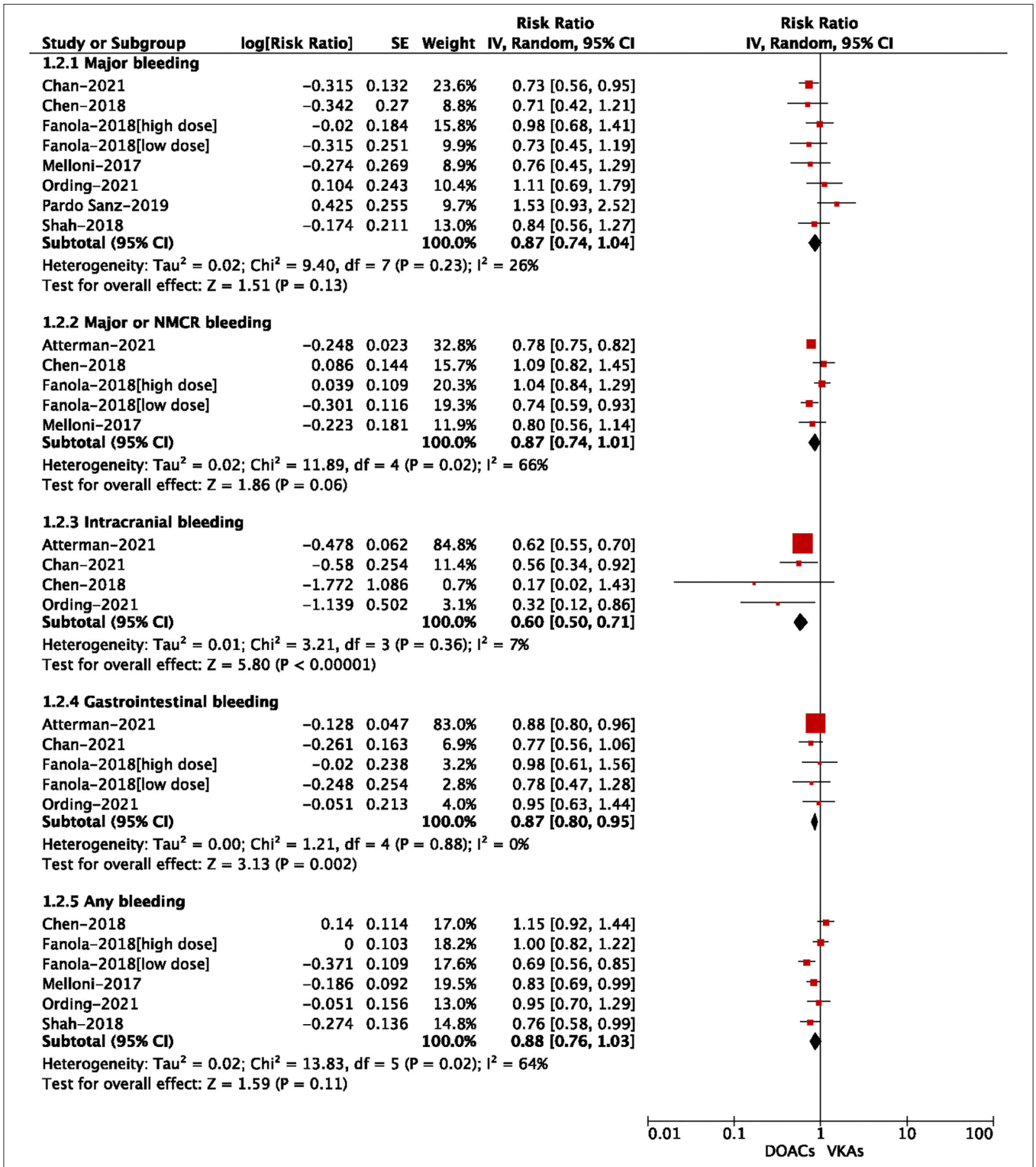

FIGURE 4 | Adjusted safety data of direct oral anticoagulants compared with vitamin K antagonists among atrial fibrillation patients with cancer.

risk of thromboembolism in patients with AF and cancer (25). On the other hand, cancer patients have a higher incidence of VTE and arterial thrombosis due to inflammatory cytokines, tumor vascular invasion, and vascular toxicity cancer treatments, while cancer-related thrombocytopenia and chemotherapy-related bone marrow suppression can increase bleeding

complications (26–28). Not only that, some malignancies (e.g. primary or metastatic intracranial tumors and hematological malignancies) itself increase the risk of hemorrhage, potentially constituting contraindications to anticoagulation therapy or requiring thorough clinical surveillance even in patients at high thromboembolic risk. Therefore, concerns about bleeding complications and paucity of evidence-based data may result in the underuse of DOACs in cancer patients with AF.

Due to the extremely limited data, there are still no specific recommendations on the use of DOACs for cancer patients in the AF guidelines. Current RCTs involving antithrombotic therapy for cancer patients to prevent VTE have been published, the guidelines prefer LMWH over VKAs or DOACs in the prevention and treatment of VTE (5). Mounting evidence is demonstrating that DOACs could represent a valid choice in patients with cancer. Prior trials have shown that rivaroxaban and edoxaban are not inferior to LMWH in the treatment of cancer-related VTE (29, 30). Therefore, DOACs (rivaroxaban and edoxaban) are currently recommended for the treatment of VTE as an alternative treatment for LMWH in cancer patients (16, 31, 32). However, due to the different pathophysiology and risk characteristics between cancer and AF, these recommendations cannot be generalized to patients with cancer and AF.

Compared with DOACs, VKAs have several limitations, such as frequent international normalized ratio (INR) control, frequent dose adjustments, and diet or drug interactions. These deficiencies may be amplified in cancer and AF patients. In particular, chemotherapy drugs and warfarin have a strong pharmacological interaction, and cancer patients often have liver dysfunction, mucositis, or diarrhea, which lead to fluctuations in vitamin K absorption and increase the risk of anticoagulation therapy (33). Only about 12% of cancer patients receiving warfarin can obtain a stable INR therapeutic range (34). In addition, the anticoagulant activity of VKAs depends on TTR (time in therapeutic range). As such, it is difficult for cancer patients to receive cancer treatment to obtain the best INR range, and the prevalence of active cancer patients with TTR $>$ 60% during the follow-up is only 10% (35). Moreover, DOACs are still more effective and safer than VKAs in AF patients with the best TTR (4).

The effectiveness and safety of DOACs compared with VKAs in AF and cancer patients have been explored in several recent studies. A prior systematic review by Russo et al. (36) supported that the effectiveness and safety profiles of NOACs in AF patients with malignancy appeared to be similar to those of VKA treatment. Unfortunately, they could not conduct a meta-analysis with the quantitative method to draw further conclusions due to the small number of included studies (36). Although the effectiveness and safety of DOACs and VKAs in AF patients with cancer are controversial, the conclusions seem to be more clear due to the emergence of several *post-hoc* analyses of RCTs and observational studies. Casula et al. (37) performed a meta-analysis by including three *post-hoc* analyses of RCTs (12–14), suggesting that direct oral Xa inhibitors (rivaroxaban, apixaban, edoxaban) had similar effects but were safer compared with warfarin in patients with cancer and AF. In addition to *post-hoc* analyses of RCTs, the meta-analyses by Chen et al. (38) and Mariani et al. (39) also included the different number of observational studies. By comparison, the largest number of studies (four *post-hoc* analyses of RCTs and nine observational cohorts) were included in our current meta-analysis. In addition, we assessed both crude event rates and adjusted data of outcomes between DOACs vs. VKAs in AF patients with cancer. Overall, in comparison to VKAs, DOACs appeared to have significant reductions in SSE, venous thromboembolism, intracranial bleeding, and gastrointestinal bleeding, but showed comparable rates of ischemic stroke, MI, cardiovascular death, all-cause death, major bleeding, major or NMCR bleeding, and any bleeding. Our meta-analysis was the largest and latest study comparing the effectiveness and safety outcomes of DOACs vs. VKAs in patients with non-valvular AF and cancer, potentially suggesting that DOACs might be considered suitable anticoagulant agents in this special population. Further prospective trials evaluating the effectiveness and safety of DOACs vs. VKAs in patients with AF combined with cancer could confirm our findings.

Limitations

Our research still had some limitations. First, the clinical characteristics of patients in different included studies were heterogeneous, such as cancer type, cancer stage, cancer diagnosis time, anti-tumor drug use, or chemotherapy response. The incidence of thrombotic events varied with cancer types, stages, and patient-related or treatment-related factors. Second, all types of DOACs were analyzed together as one group despite their different pharmacological properties and differences in clinical effectiveness and safety in the different indications. Due to limited data, we did not conduct a subgroup analysis based on the specific types of DOACs. Third, we did not conduct a subgroup analysis of DOACs and VKAs between patients with active cancer and those with a history of cancer. Finally, data of RCTs and observational studies should be assessed separately in future studies.

CONCLUSION

Current pooled data from the published studies suggested that in comparison to VKAs, DOACs appeared to have significant reductions in SSE, venous thromboembolism, intracranial bleeding, and gastrointestinal bleeding, but showed comparable rates of ischemic stroke, MI, cardiovascular death, all-cause death, major bleeding, major or NMCR bleeding, and any bleeding in patients with AF and cancer.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

This study was funded by National Natural Science Foundation of China (82100273), China National Postdoctoral Program for Innovative Talents (BX20200400), and China Postdoctoral Science Foundation (2020M673016).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.766377/full#supplementary-material

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frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 06 December 2021
doi: 10.3389/fcvm.2021.775564

Differential Presentations of Arterial Thromboembolic Events Between Venous Thromboembolism and Atrial Fibrillation Patients

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Edited by:
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Specialty section:
This article was submitted to Thrombosis, a section of the journal Frontiers in Cardiovascular Medicine

Received: 14 September 2021
Accepted: 15 November 2021
Published: 06 December 2021

Citation:
Lin Y-S, Lin M-S, Wu VC-C, Chen Y-L, Chang J-J, Chu P-H, Lip GYH and Chen M-C (2021) Differential Presentations of Arterial Thromboembolic Events Between Venous Thromboembolism and Atrial Fibrillation Patients. Front. Cardiovasc. Med. 8:775564. doi: 10.3389/fcvm.2021.775564

Objective: Atrial fibrillation (AF) and venous thromboembolism (VTE) share several risk factors related to arterial thromboembolism. No study has reported the differential contribution to arterial thromboembolic events and mortality between these two conditions in the same population. We therefore assessed the differential arterial thromboembolic events between AF and VTE.

Methods: We included AF and VTE national cohorts derived from Taiwan National Health Insurance Research Database between 2001 and 2013. The eligible population was 314,861 patients in the AF cohort and 41,102 patients in the VTE cohort. The primary outcome was arterial thromboembolic events, including ischemic stroke, extracranial arterial thromboembolism (ECATE) and myocardial infarction (MI). Secondary outcomes were all-cause mortality and cardiovascular death.

Results: After a 1:1 propensity matching, 32,688 patients in either group were analyzed. The risk of arterial thromboembolic events was lower in the VTE cohort than that in the AF cohort (subdistribution hazard ratio [SHR], 0.60; 95% confidence interval [CI], 0.57–0.62). The risk of ischemic stroke (SHR, 0.44; 95% CI, 0.42–0.46) and MI (SHR, 0.80; 95% CI, 0.72–0.89) were lower in the VTE cohort, while the risk of ECATE (SHR, 1.23; 95% CI, 1.14–1.33; particularly lower extremities) was higher in the VTE cohort. All-cause mortality rate was higher in the VTE cohort (HR, 1.18; 95% CI, 1.15–1.21) while the risk of cardiovascular death was lower in the VTE cohort (HR, 0.96; 95% CI, 0.93–0.995).

Conclusions: Patients with AF had higher risks of arterial thromboembolic events compared to patients with VTE, despite having risk factors in common. The VTE cohort had higher risks of all-cause mortality and ECATE, particularly lower extremity events,

compared to AF patients. The differential manifestations of thromboembolism sequelae and mortality between AF and VTE patients merit further investigation.

Keywords: atrial fibrillation, arterial thromboembolic event (ATE), venous thromboembolism (VTE), mortality, stroke, myocardial infarction (MI)

INTRODUCTION

Atrial fibrillation (AF) is associated with an increased risk of stroke, systemic thromboembolic events, and mortality (1). Long-term anticoagulation therapy, particularly with direct oral anticoagulants (DOACs), significantly reduces the risk of stroke and mortality (2). In terms of venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), the duration of anticoagulation therapy to prevent recurrences takes into consideration the risk of recurrent VTE and the risk of bleeding (3).

AF and VTE have many pathophysiological and clinical risk factors in common. In terms of pathophysiology, the pathogenesis of arterial thromboembolism in AF has been associated with a prothrombotic state by fulfilling Virchow's triad for thrombogenesis, i.e., with abnormal blood flow (stasis) in the atria, vessel wall abnormalities and abnormal blood constituents (coagulation factors) as well as inflammation (4). Likewise, the pathogenesis of arterial thromboembolism in VTE has been associated with a prothrombotic state, i.e., with abnormal blood flow (stasis) in the vessels, vessel wall abnormalities and abnormal blood constituents (coagulation factors) as well as inflammation (5, 6). Several studies showed that VTE increases risk of atherothrombotic cardiovascular events, including myocardial infarction (MI) (7). In terms of contributing factors, AF and VTE also share similar comorbidities (3, 6), such as age, hypertension, smoking, diabetes, and obesity (8–10), peripheral artery disease (11) and malignancy (12). Moreover, one community registry study reported that AF and VTE independently contributed to each other (13). However, the duration of prescribing anticoagulation is quite different between AF and VTE in current practice. Long-term anticoagulation should be prescribed for AF patients (2, 14) whereas more limited-duration of anticoagulation is sometimes prescribed for VTE patients unless there are high risk features for recurrence (3, 15).

We hypothesized that AF and VTE, despite sharing many pathophysiological and clinical risk factors, have different duration of prescribing anticoagulation and should have differential contribution to arterial thromboembolic events and mortality in the same population. Accordingly, we tested this hypothesis in a nationwide cohort study of VTE and AF patients from the Taiwan National Health Insurance Database.

METHODS

The data of this national retrospective cohort study was retrieved from the Taiwan National Health Insurance Research Database (NHIRD) released by the Taiwan National Health Research Institutes. The National Health Insurance system is a mandatory universal health insurance program that offers comprehensive medical care coverage to nearly all Taiwan residents since the inception of the program in March 1995. In the NHIRD, the patients' original identification numbers are encrypted and the encrypting procedure is consistent, so that linking claims belonging to the same enrollee is feasible and can be followed longitudinally. The available health care information included complete outpatient visits, hospitalization, and diseases, which were registered using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (16). In addition, medication prescriptions are also recorded. Patients with newly diagnosis of AF and VTE were included in this study. The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (201900915B1).

Identification of Patients With VTE and AF

This study included national AF and VTE cohorts. Patients with AF were identified with $\geq$2 times outpatient visits or in a discharge diagnosis using the ICD-9 CM diagnostic code of 427.31 between 2001 and 2013. Patients with VTE were identified using the discharge diagnosis (ICD-9-CM: 453 for DVT and 415.1 for PE) with use of anticoagulation during admission between 2001 and December 31, 2013. In the AF cohort, we excluded patients who were under age of 20 years old and were diagnosed as VTE historically (the diagnosis could be tracked up to year 1997) or in follow-up period. In the VTE cohort, we excluded patients who were under age of 20 years old and were diagnosed as AF historically (the diagnosis could be tracked up to year 1997) or in the follow-up period. In order to compare the differences in the clinical outcomes after developing AF and VTE, we excluded those who died at the index admission in both cohorts. Finally, 314,861 AF patients without VTE and 41,102 VTE patients without AF were included in this study (**Figure 1**).

Covariates

Covariates were age, sex, eighteen comorbidities, Charlson Comorbidity Index score, four historical events, and fourteen kinds of medications (**Table 1**). Comorbidities were recognized with at least two clinic visits or any inpatient record in the previous year before the index date. Historical events were detected using any inpatient diagnosis before the index date which could be tracked up to year 1997. The use of medication was extracted within 3 months after index date. All the information about medications were extracted from the claims data of outpatient visits or the refill for chronic illness in the pharmacy by using the Anatomical Therapeutic Chemical codes or the Taiwan NHI reimbursement code.

Outcomes

The primary outcome was arterial thromboembolic events, including ischemic stroke, myocardial infarction (MI) and

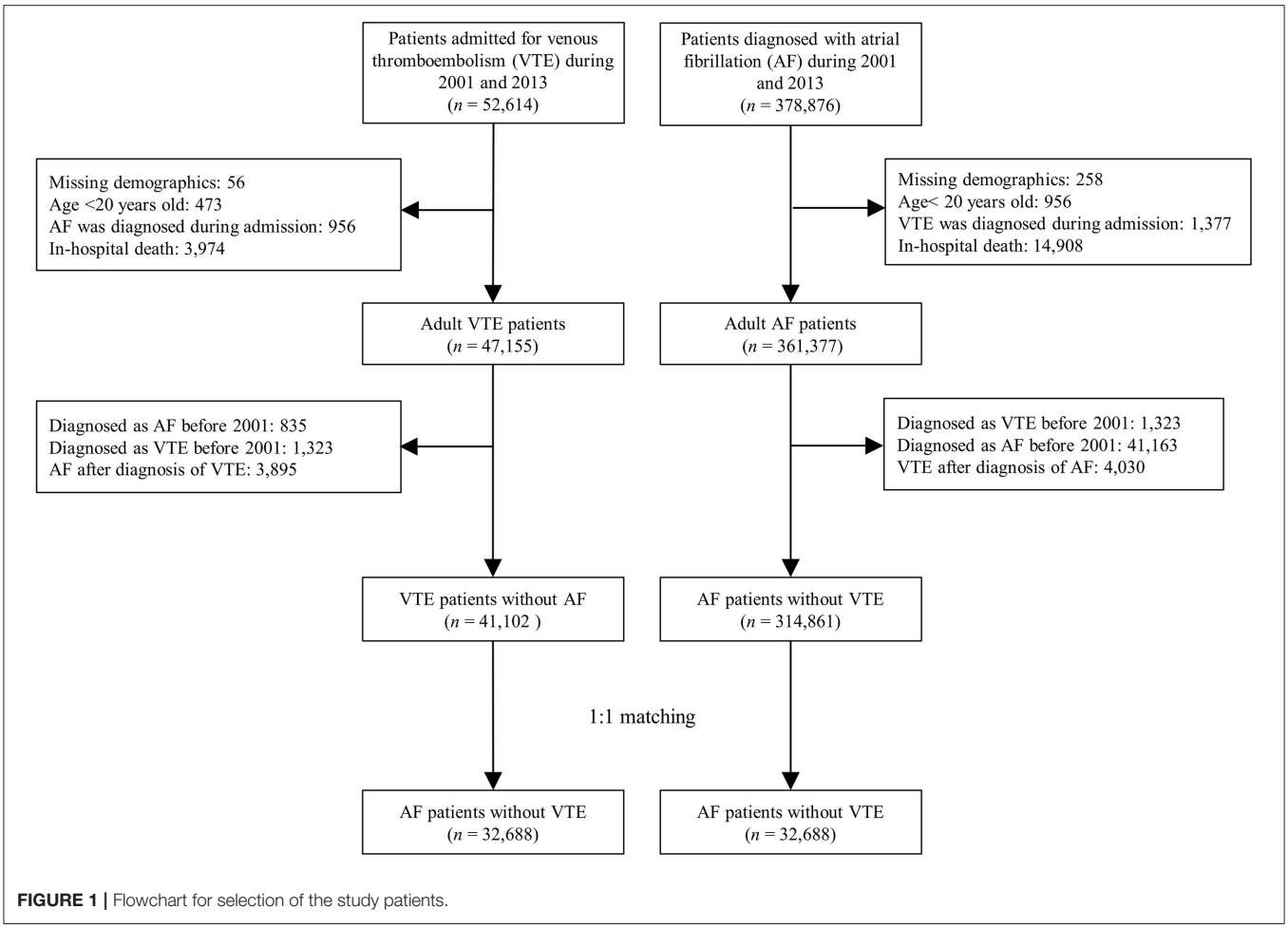

FIGURE 1 | Flowchart for selection of the study patients.

extracranial arterial thromboembolism (ECATE). Extracranial arterial thromboembolism included arterial thromboembolic occlusion of an extremity or extracranial vital organ, including kidney, intestine, and spleen. The occurrence of ischemic stroke and MI was defined as the principal discharge diagnosis of hospitalization. The occurrence of ECATE was defined as the principal or secondary diagnoses of hospitalization. Secondary outcomes were all-cause mortality and cardiovascular death. All-cause mortality was defined as withdrawal from the NHI program (17). The definition of cardiovascular (CV) death was the criteria of the Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials by the FDA in the United States. Each patient was followed from the discharge date of index admission to the date of event occurrence, date of death, or December 31, 2013.

Ascertainment of VTE, AF, Ischemic Stroke, MI, and ECATE

The validation of AF has been assessed and presented in our previous reports, with a high positive predictive value (PPV) of 89% (18). The accuracy of VTE was reliable in the Taiwan insurance claim system and some published studies also used the same diagnosis method (11, 19). Ischemic stroke and MI were also validated with high PPVs (20, 21). In terms of ECATE, a validation study was conducted at our medical center, randomly sampling 100 hospitalizations for systemic thromboembolism who were selected using the same criteria as mentioned in this study. After experienced physicians (YSL and VCCW) reviewed the medical records and all imaging results, including vascular duplex, computed tomography angiography and intervention reports, the PPV of systemic thromboembolism was 88% (data not shown).

Statistics

There would be substantial difference in the baseline characteristics between study groups (i.e., VTE and AF cohorts). Therefore, we performed 1:1 ratio propensity score matching to make the covariates balanced between groups. The propensity score was the predicted probability to be in the one group (i.e., VTE) given the values of covariates using the multivariable logistic regression without considering interaction effects. The variables selected to calculate propensity score were listed in **Table 1** where the follow-up year was replaced with the index date (**Table 1**). The matching was processed using a greedy nearest neighbor algorithm with a caliper of 0.2 times of the standard deviation of the logit of propensity score, with

TABLE 1 | Baseline characteristics of the patients diagnosed with AF or VTE.

	Before propensity matching			After propensity matching		
	VTE (*n* = 41,102)	**AF (*n* = 314,861)**	**STD**	**VTE (*n* = 32,688)**	**AF (*n* = 32,688)**	**STD**
Age (years)	64.3 ± 16.4	71.2 ± 13.5	−0.46	66.7 ± 15.4	67.4 ± 14.6	−0.04
Age group	18,837 (45.8)	89,486 (28.4)	0.37	13,087 (40.0)	12,464 (38.1)	0.04
< 65 years						
65-74 years	9,526 (23.2)	82,459 (26.2)	−0.07	8,082 (24.7)	8,422 (25.8)	−0.02
≥ 75 years	12,739 (31.0)	142,916 (45.4)	−0.30	11,519 (35.2)	11,802 (36.1)	−0.02
Male sex	19,152 (46.6)	174,954 (55.6)	−0.18	16,123 (49.3)	16,752 (51.2)	−0.04
Types of VTE	9,143 (22.2)	-		7,702 (23.6)	-	
Pulmonary embolism (PE)						
Deep vein thrombosis (DVT)	29,512 (71.8)	-		23,081 (70.6)	-	
DVT + PE	2,447 (6.0)	-		1,905 (5.8)	-	
Comorbid conditions	21,262 (51.7)	191,993 (61.0)	−0.19	18,355 (56.2)	18,942 (57.9)	−0.04
Hypertension						
Diabetes mellitus	10,800 (26.3)	75,303 (23.9)	0.05	8,877 (27.2)	8,880 (27.2)	<0.01
Ischemic heart disease	8,845 (21.5)	110,828 (35.2)	−0.31	8,023 (24.5)	8,695 (26.6)	−0.05
Dyslipidemia	7,382 (18.0)	52,525 (16.7)	0.03	6,133 (18.8)	6,423 (19.6)	−0.02
Gout	4,104 (10.0)	31,540 (10.0)	<0.01	3,463 (10.6)	3,526 (10.8)	−0.01
COPD	5,630 (13.7)	58,210 (18.5)	−0.13	4,843 (14.8)	4,793 (14.7)	<0.01
Peripheral artery disease	2,802 (6.8)	11,400 (3.6)	0.14	2,052 (6.3)	2,041 (6.2)	<0.01
Chronic kidney disease	7,190 (17.5)	45,300 (14.4)	0.08	5,803 (17.8)	5,758 (17.6)	<0.01
Dialysis	1,209 (2.9)	8,190 (2.6)	0.02	1,034 (3.2)	1,065 (3.3)	−0.01
Cancer	8,847 (21.5)	19,901 (6.3)	0.45	5,030 (15.4)	4,727 (14.5)	0.03
Auto-immune disease	811 (2.0)	1,891 (0.6)	0.12	424 (1.3)	393 (1.2)	0.01
Hepatitis C virus infection	835 (2.0)	4,841 (1.5)	0.04	626 (1.9)	593 (1.8)	0.01
Paralysis	3,245 (7.9)	22,491 (7.1)	0.03	2,705 (8.3)	2,810 (8.6)	−0.01
Osteoporosis	3,578 (8.7)	19,662 (6.2)	0.09	2,702 (8.3)	2,503 (7.7)	0.02
Charlson comorbidity index score	3.0 ± 3.0	2.0 ± 2.0	0.40	2.7 ± 2.7	2.7 ± 2.7	<0.01
History of disease	5,600 (13.6)	46,969 (14.9)	−0.04	4,933 (15.1)	5,230 (16.0)	−0.03
Prior any stroke						
Prior ischemic stroke or systemic thromboembolism	5,506 (13.4)	45,757 (14.5)	−0.03	4,832 (14.8)	5,228 (16.0)	−0.03
Old MI	1,249 (3.0)	13,564 (4.3)	−0.07	1,140 (3.5)	1,240 (3.8)	−0.02
Heart failure admission	3,654 (8.9)	40,121 (12.7)	−0.12	3,331 (10.2)	3,608 (11.0)	−0.03
Antithrombotic therapy within 3 months after index date	9,640 (23.5)	119,550 (38.0)	−0.32	9,475 (29.0)	9,012 (27.6)	0.03
None						

(Continued)

TABLE 1 | Continued

	Before propensity matching			After propensity matching		
	VTE (*n* = 41,102)	**AF (*n* = 314,861)**	**STD**	**VTE (*n* = 32,688)**	**AF (*n* = 32,688)**	**STD**
Antiplatelet	3,192 (7.8)	148,174 (47.1)	−0.98	3,189 (9.8)	3,364 (10.3)	−0.02
Anticoagulant	28,270 (68.8)	47,137 (15.0)	1.30	20,024 (61.3)	20,312 (62.1)	−0.02
Medication ACEi or ARB	10,771 (26.2)	137,957 (43.8)	−0.38	9,956 (30.5)	11,094 (33.9)	−0.07
Beta blocker	8,044 (19.6)	115,262 (36.6)	−0.39	7,496 (22.9)	8,337 (25.5)	−0.06
DCCB	9,594 (23.3)	85,295 (27.1)	−0.09	8,193 (25.1)	8,447 (25.8)	−0.02
Diuretic	9,849 (24.0)	80,723 (25.6)	−0.04	7,870 (24.1)	8,237 (25.2)	−0.03
Metformin	4,078 (9.9)	35,237 (11.2)	−0.04	3,428 (10.5)	3,540 (10.8)	−0.01
TZD	656 (1.6)	4,942 (1.6)	<0.01	520 (1.6)	506 (1.5)	<0.01
DPP4i	774 (1.9)	5,783 (1.8)	<0.01	681 (2.1)	742 (2.3)	−0.01
Insulin	1,900 (4.6)	10,125 (3.2)	0.07	1,476 (4.5)	1,458 (4.5)	<0.01
Estrogen	946 (2.3)	4,105 (1.3)	0.08	577 (1.8)	504 (1.5)	0.02
Antidepressants	3,728 (9.1)	20,564 (6.5)	0.09	2,754 (8.4)	2,747 (8.4)	<0.01
Statin	4,289 (10.4)	39,303 (12.5)	−0.06	3,846 (11.8)	4,264 (13.0)	−0.04
Digoxin	1,068 (2.6)	73,147 (23.2)	−0.65	1,067 (3.3)	1,257 (3.8)	−0.03
Follow up year	3.8 ± 3.5	4.2 ± 3.4	−0.12	3.7 ± 3.4	3.8 ± 3.4	−0.03

VTE, venous thromboembolism; AF, atrial fibrillation; STD, standardized difference; COPD, chronic obstructive pulmonary disease; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; DCCB, dihydropyrinde calcium channel blocker; TZD, thiazolidinedione; DDP4i, dipeptidyl peptidase 4 inhibitor.

Data were presented as frequency (percentage) or mean ± standard deviation.

random matching order and without replacement. The quality of matching was checked using the absolute value of standardized difference (STD) between the groups, where a value <0.1 was considered negligible difference. We additionally performed three propensity score matchings to compare the PE-only cohort with the DVT-only cohort, the DVT-only cohort with the AF cohort and the PE-only cohort with the AF cohort, respectively.

As to the time to fatal outcomes (i.e., all-cause mortality and cardiovascular death), the risks between the groups were compared by the Cox proportional hazard model. The incidences of time to non-fatal outcomes (e.g., ischemic stroke or MI) between groups were compared by the Fine and Gray subdistribution hazard model which considered all-cause mortality a competing risk. The within-pair clustering of outcomes after propensity score matching was accounted for by using a robust standard error (22). Finally, we performed a subgroup analysis stratified by the use of oral anticoagulant within 3 months after the index date. A two-sided P-value < 0.05 was considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics

This study enrolled 314,861 AF patients (mean age of 71.2 ± 13.5 years) and 41,102 VTE patients (mean age of 64.3 ± 16.4 years). These two cohorts were different in age distribution, whereby the VTE cohort was predominantly age < 65 years while the AF cohort was predominantly age ≥ 75 years (**Table 1**). The AF cohort had significantly greater prevalence of hypertension, ischemic heart disease, chronic obstructive pulmonary disease (COPD), hyperthyroidism and heart failure, while VTE cohort had higher prevalence of peripheral artery disease, cancer and auto-immune disease. In terms of medications, angiotensin converting enzyme inhibitors/angiotensin receptor blockers, beta blockers and digoxin were more frequently prescribed in the AF population. In this study, anticoagulant use was continuous in the AF cohorts while the duration of anticoagulant was at least for 3∼6 months in the VTE cohort and 38.6% of VTE patients had the duration of anticoagulant use for more than 6 months. In addition, the available follow-up period in AF cohort were longer than that in VTE cohort (AF cohort vs. VTE cohort: 4.2 ± 3.4 vs. 3.8 ± 3.5 years, standardized difference: −0.12).

After matching, 32,688 patients in either cohort were well-balanced in baseline characteristics, including follow-up period (**Table 1**). In patients with DVT-only vs. AF, the AF cohorts had higher incidence of ischemic heart disease, heart failure and COPD while DVT-only cohort had higher incidence of cancer, auto-immune disease and peripheral artery disease (**Supplementary Table 1**). In patients with PE-only vs. AF, the PE-only cohort had a higher incidence of cancer (**Supplementary Table 2**). In terms of the PE-only vs. DVT-only cohorts, the PE-only cohort had higher incidence of ischemic heart disease, heart failure and COPD while DVT-only cohort had higher prevalence of cancer and peripheral artery disease (**Supplementary Table 3**).

TABLE 2 | Follow-up outcomes in patients with VTE versus those with AF.

Outcome	Before propensity matching		After propensity matching			
	VTE (n = 41,102)	AF (n = 314,861)	VTE (n = 32,688)	AF (n = 32,688)	HR or SHR of VTE (95% CI)	P
Arterial thromboembolic events	4,864 (11.8)	61,684 (19.6)	4,143 (12.7)	6,383 (19.5)	0.60 (0.57–0.62)	<0.001
Ischemic stroke	2,881 (7.0)	47,867 (15.2)	2,481 (7.6)	5,141 (15.7)	0.44 (0.42–0.46)	<0.001
Extracranial arterial thromboembolism	1,725 (4.2)	10,026 (3.2)	1,410 (4.3)	1,122 (3.4)	1.23 (1.14–1.33)	<0.001
Lower extremity thromboembolism	1,435 (3.5)	8,361 (2.7)	1,184 (3.6)	917 (2.8)	1.26 (1.16–1.37)	<0.001
Non-lower extremity thromboembolism	365 (0.9)	2,329 (0.7)	288 (0.88)	284 (0.87)	0.99 (0.84–1.16)	0.867
Myocardial infarction	690 (1.7)	9,718 (3.1)	619 (1.9)	741 (2.3)	0.80 (0.72–0.89)	<0.001
Secondary outcomes						
All-cause mortality	18,098 (44.0)	135,551 (43.1)	14,188 (43.4)	12,345 (37.8)	1.18 (1.15–1.21)	<0.001
Cardiovascular death	7,321 (17.8)	73,344(23.3)	5,958 (18.2)	6,376 (19.5)	0.96 (0.93–0.995)	0.025
Non-cardiovascular death	10,777 (26.2)	62,207 (19.8)	8,230 (25.2)	5,969 (18.3)	1.42 (1.37–1.47)	<0.001

VTE, venous thromboembolism; AF, atrial fibrillation; HR, hazard ratio; SHR, subdistribution hazard ratio; CI, confidence interval.
Data were presented as frequency (percentage).

Outcomes Between VTE and AF Cohorts

The outcomes between VTE and AF cohort obtained after propensity matching are shown in **Table 2**; **Figure 2**. The risk of the arterial thromboembolic events was lower in the VTE cohort [subdistribution hazard ratio (SHR), 0.60; 95% confidence interval (CI), 0.57–0.62] (**Figure 2A**), as were the risks of ischemic stroke (SHR, 0.44; 95% CI, 0.42–0.46) (**Figure 2B**) and MI (SHR, 0.80; 95% CI, 0.72–0.89). The risks of ECATE (SHR, 1.23; 95% CI, 1.14–1.33) (**Figure 2C**) and all-cause mortality rate (HR, 1.18; 95% CI, 1.15–1.21) were higher in VTE cohort (**Figure 2E**), although the latter had lower CV death (HR, 0.96; 95% CI, 0.93–0.995) (**Figure 2D**).

In subgroup analysis of the cause of death after propensity matching, the percentage of CV death was significant higher in AF cohort than in VTE cohort (VTE cohort vs. AF cohort: 56.4 vs. 66.6%, $P < 0.001$) (**Supplementary Table 4**). The percentages of death related to cancer and infection other than pneumonia among the causes of non-CV death were significantly higher in the VTE cohort than in the AF cohort.

Furthermore, the outcomes between the subgroups stratified according to the use of anticoagulation therapy within 3 months after index date were analyzed. The impact of anticoagulant use on the association between AF/VTE and the risk of arterial thromboembolic events was very significant (non-anticoagulant user: SHR, 0.89; 95% CI, 0.83–0.96; anticoagulant user: SHR, 0.49; 95% CI, 0.47–0.52; P interaction < 0.001). In terms of individual arterial thromboembolic events and mortality, anticoagulant use also had a significant impact on the association between AF/VTE and these events, except for MI (**Table 3**).

Outcomes Between DVT-Only and AF Cohorts

After propensity matching, there was no substantial difference in the baseline characteristics between the DVT-only and AF cohorts (**Supplementary Table 1**). Clinical outcomes between DVT-only and AF cohorts are shown in **Supplementary Table 5**.

The incidence of arterial thromboembolic event was lower in the DVT-only cohort than that in the AF cohort (SHR, 0.62; 95% CI, 0.59–0.65) (**Supplementary Figure 1A**). The risks of ischemic stroke (SHR, 0.45; 95% CI, 0.43–0.48) (**Supplementary Figure 1B**) and MI (SHR, 0.76; 95% CI, 0.67–0.86) were lower, while the risk of ECATE was higher, in the DVT-only cohort (SHR, 1.31; 95% CI, 1.20–1.43) (**Supplementary Figure 1C**). All-cause mortality rates were higher in the DVT-only cohort (HR, 1.14; 95% CI, 1.11–1.17), while the rate of CV death was lower (HR, 0.89; 95% CI, 0.85–0.92) (**Supplementary Figures 1D,E**).

Outcomes Between PE-Only and AF Cohorts

After propensity matching, there was no substantial difference in the baseline characteristics between the PE alone and AF cohorts (**Supplementary Table 2**). Clinical outcomes between PE-only and AF cohorts were shown in **Supplementary Table 6**. The incidence of the arterial thromboembolic event was lower in the PE-only cohort than that in AF cohort (SHR, 0.52; 95% CI, 0.48–0.56) (**Supplementary Figure 2A**). The risk of ischemic stroke was lower in the PE-only cohort (SHR, 0.41; 95% CI, 0.37–0.45) (**Supplementary Figure 2B**) with no differences in ECATE (**Supplementary Figure 2C**) and MI event rates (**Supplementary Table 6**). The PE-only cohort had higher all-cause mortality (HR, 1.26; 95% CI, 1.20–1.32) and CV death (HR, 1.14; 95% CI, 1.07–1.22) than the AF cohort (**Supplementary Figures 2D,E**).

Outcomes Between PE-Only and DVT-Only Cohorts

After propensity matching, there was no substantial difference in the baseline characteristics between the PE-only and DVT-only cohorts (**Supplementary Table 3**). Clinical outcomes between PE-only and DVT-only cohorts were shown in **Supplementary Table 7**. The arterial thromboembolic event was lower in the PE-only cohort than in the DVT-only cohort (SHR, 0.80; 95% CI, 0.73–0.88) (**Figure 3A**). The risks of ischemic stroke (SHR, 0.82; 95% CI, 0.74–0.92) and ECATE, including lower extremity events, (SHR, 0.69; 95% CI, 0.58–0.82) were lower in the PE-only cohort than in the DVT-only cohort (**Figures 3B,C**). The risks of all-cause mortality (HR, 1.08; 95% CI, 1.03–1.13) and CV death (HR, 1.28; 95% CI, 1.19–1.37) were higher in the PE-only cohort compared to the DVT-only cohort (**Figures 3D,E**).

DISCUSSION

This retrospective 10-year nationwide cohort study enrolled two national cohorts shows that the arterial thromboembolic events, ischemic stroke and MI, were higher in matched patients with AF cohort than those with VTE cohort. Second, the VTE cohort had higher incidence of ECATE than AF cohort, particularly lower extremity thromboembolism. Third, the AF cohort had higher incidence of CV death, but lower incidence of all-cause mortality compared to the VTE cohort (**Figure 4**; **Supplementary Table 8**). In subgroup analyses comparing the DVT-only, PE-only and AF cohorts, the AF patients had highest incidence of ischemic stroke among the three cohorts and had similar incidence of MI compared to patients with PE-only. Patients with DVT-only had highest incidence of ECATE among the three cohorts, particularly lower extremity thromboembolic event. In terms of mortality, patients with PE-only had highest incidence of CV death and all-cause mortality (**Supplementary Table 8**).

A national 20-year observational study demonstrated that patients with VTE had a 1.26-1.31-fold increased risk of subsequent arterial thromboembolic events, including MI and stroke (23). Schulman et al. also showed that VTE was associated with a 1.28-fold increased risk of MI or stroke over a 10-year follow-up period (24). Epidemiological studies and meta-analysis have also recognized that AF is independently associated with a five-fold increased risk of stroke (1), 1.47-fold increased risk of MI (25), and a two-fold increased risk of mortality (26).

Although VTE and AF contribute to similar arterial thromboembolic events, we are unaware of any study that has compared the different presentations of arterial

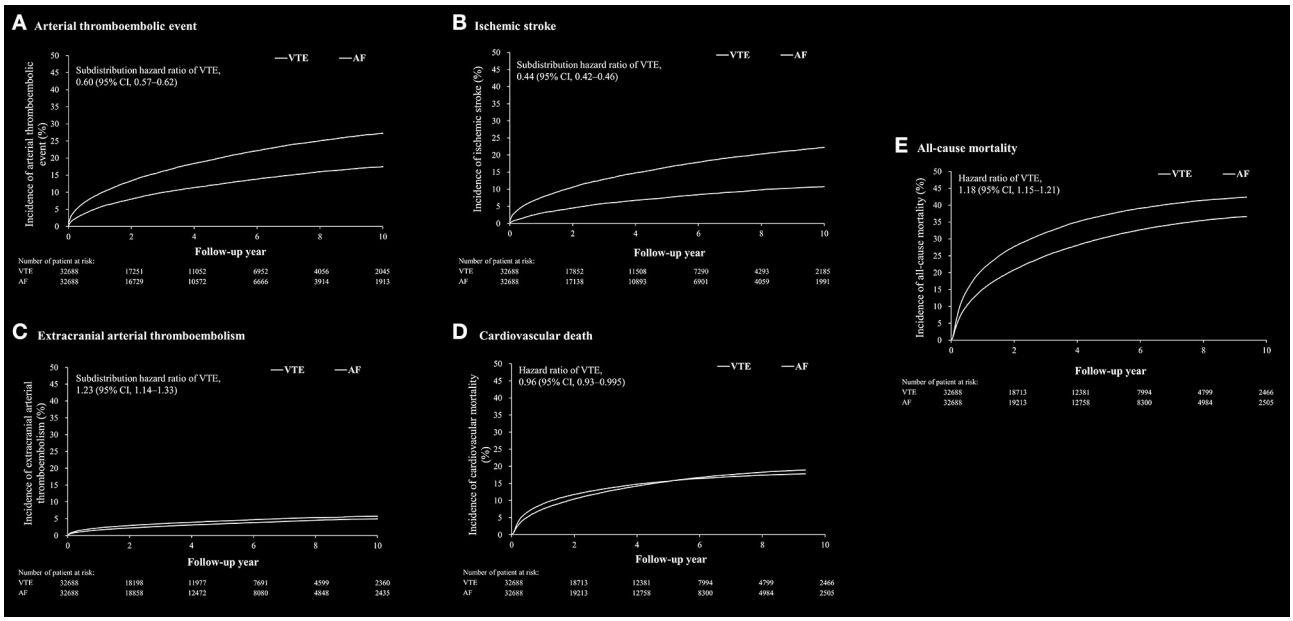

FIGURE 2 | The cumulative incidence rate of arterial thromboembolic event **(A)**, ischemic stroke **(B)**, extracranial arterial thromboembolic events **(C)**, cardiovascular death **(D)** and all-cause mortality **(E)** after propensity score matching between patients with venous thromboembolism (VTE) and patients with atrial fibrillation.

thromboembolic events between VTE and AF patients, from the same population cohort. Based on our study, AF contributed to more arterial thromboembolic events while VTE contributed to greater all-cause mortality. In terms of the causes of mortality, more AF patients (66.6%) died from cardiovascular death than VTE patients (56.4%) while more VTE patients (13.7%) died from cancer than AF patients (8.6%) (**Supplementary Table 4**). Our results were generally consistent with other studies in terms of causes of death in VTE and AF patients (27).

As mentioned above there are many parallels between the epidemiology of risk factors and associated pathogenesis of thrombosis in AF and VTE (4, 6, 8, 10, 28). Nonetheless, our study showed some differential distributions of baseline characteristics between VTE and AF cohorts. Of note, the prevalence of peripheral artery disease and cancer was higher in VTE cohort than AF cohort. In contrast, the prevalence of ischemic heart disease and heart failure was higher in AF cohort than VTE cohort. Importantly, even after propensity matching, AF cohort had higher risks of arterial thromboembolic event, ischemic stroke and MI compared to the VTE cohort. VTE cohort had higher all-cause mortality while AF cohort had higher CV mortality. Therefore, VTE and AF patients have different risks in presentations related to arterial thromboembolic events.

Long-term anticoagulation therapy to prevent arterial thromboembolism is a well-established strategy in AF population (2) and a net clinical benefit more than 5 years with DOACs is still evident (14). On the other hand, long-term anticoagulation was not recommended in VTE population due to uncertain net clinical benefit in the era of vitamin K antagonists (VKA, e.g., warfarin) (15). However, some studies have shown that extended treatment with DOAC for 6-15 months resulted in less recurrent VTE events than no treatment, and had less bleeding events compared to VKA (29–32). Of note, extended low-dose aspirin in VTE patients for up to 4 years results in a significant reduction in the rate of major vascular events, with improved net clinical benefit in the ASPIRE study (33). Moreover, our study showed that anticoagulant use had a significant impact on the association between AF/VTE and individual arterial thromboembolic events and all-cause and cardiovascular mortality (**Table 3**). Lifelong anticoagulation is indicated in AF patients with high CHA_2DS_2-VASc score ($\geq$2). The differential manifestations of thromboembolism sequelae and mortality between AF and VTE cohorts merit further investigation of an extended period or lifelong anticoagulation in VTE patients and validation in other ethnic population.

Our study has several limitations. First, we could not clearly identify the prevalence of provoked and unprovoked VTE in our VTE cohort. Several observational studies have reported that unprovoked VTE does not contribute to the same risk as provoked VTE in terms of clinical outcomes, including arterial thromboembolic events. However, a 20-year national observational cohort study reported no significant differences in arterial CV events between provoked and unprovoked VTE (23). In addition, the distinction between provoked/unprovoked PE is no longer supported by the 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism (34). Furthermore, clinical presentations/manifestations and laboratory data were not

TABLE 3 | Subgroup analysis of long-term outcomes of the VTE versus AF patients stratified by use of anticoagulation therapy within 3 months after index date in the propensity score matched cohort.

Outcome/ Subgroup	VTE (n = 32,688)	AF (n = 32,688)	HR or SHR of VTE (95% CI)	P for interaction
Arterial thromboembolic events				<0.001
Non-anticoagulant user	1,422 (11.2)	1,583 (12.8)	0.89 (0.83–0.96)	
Anticoagulant user	2,721 (13.6)	4,800 (23.6)	0.49 (0.47–0.52)	
Ischemic stroke				<0.001
Non-anticoagulant user	822 (6.5)	1,141 (9.2)	0.82 (0.75–0.89)	
Anticoagulant user	1,659 (8.3)	4,000 (19.7)	0.37 (0.35–0.39)	
Extracranial arterial thromboembolism				<0.001
Non-anticoagulant user	497 (3.9)	328 (2.7)	1.53 (1.33–1.75)	
Anticoagulant user	913 (4.6)	794 (3.9)	1.10 (1.001–1.21)	
Lower extremity thromboembolism				<0.001
Non-anticoagulant user	422 (3.3)	272 (2.2)	1.56 (1.34–1.82)	
Anticoagulant user	762 (3.8)	645 (3.2)	1.13 (1.02–1.26)	
Non-lower extremity thromboembolism				0.016
Non-anticoagulant user	96 (0.8)	71 (0.6)	1.35 (0.99–1.84)	
Anticoagulant user	192 (1.0)	213 (1.0)	0.86 (0.71–1.05)	
Myocardial infarction				0.349
Non-anticoagulant user	231 (1.8)	269 (2.2)	0.86 (0.72–1.02)	
Anticoagulant user	388 (1.9)	472 (2.3)	0.77 (0.68–0.88)	
All-cause mortality				<0.001
Non-anticoagulant user	7,519 (59.4)	6,324 (51.1)	1.37 (1.32–1.42)	
Anticoagulant user	6,669 (33.3)	6,021 (29.6)	1.07 (1.04–1.11)	
Cardiovascular death				<0.001
Non-anticoagulant user	2,676 (21.1)	2,619 (21.2)	1.19 (1.12–1.25)	
Anticoagulant user	2,769 (13.8)	3,301 (16.3)	0.81 (0.77–0.85)	
Non-cardiovascular death				0.020
Non-anticoagulant user	4,843 (38.2)	3,705 (29.9)	1.50 (1.44–1.57)	
Anticoagulant user	3,900 (19.5)	2,720 (13.4)	1.39 (1.33–1.46)	

VTE, venous thromboembolism; AF, atrial fibrillation; HR, hazard ratio; SHR, subdistribution hazard ratio; CI, confidence interval.

available in NHIRD and such information might affect the outcomes of VTE, especially those with PE (34). In order to reduce the bias, we excluded those died during hospitalization and within 3 months after discharge. Second, differentiating subtypes of AF (paroxysmal, sustained) cannot be performed because this information was not available in our national database. Although the incidence of ischemic stroke is considered to be generally lower in paroxysmal AF patients than in patients with sustained AF (35), it should not affect the outcomes between AF and VTE in such a large volume study. Third, the duration of anticoagulation therapy was different between AF vs. VTE cohorts (2, 34). We also did not compare the outcomes between AF and VTE cohorts in individual different scenarios with different durations of anticoagulation therapy. Furthermore, although there were different frequencies of anticoagulants and antiplatelets between AF and VTE cohorts before propensity matching (**Table 1**), our conclusion was based on the results derived from the study population after propensity matching (**Tables 1**, **2**). Therefore, the unbalanced prescription of anticoagulants and antiplatelets between AF and VTE cohorts before propensity matching should not influence our main results derived from the study population after propensity matching. Fourth, VTE cohort had a higher incidence of lower extremity thromboembolic events than AF cohort. We could not completely exclude the possibility of more image studies performed in the VTE cohort to reveal a higher incidence rate of lower extremity thromboembolic events. Finally, propensity score matching was used to reduce the potential confounding variables in this study. However, there were potential unknown variables in the study population for matching and comparison.

CONCLUSION

Patients with AF had higher risks of arterial thromboembolic events (ischemic stroke and MI) compared to patients with

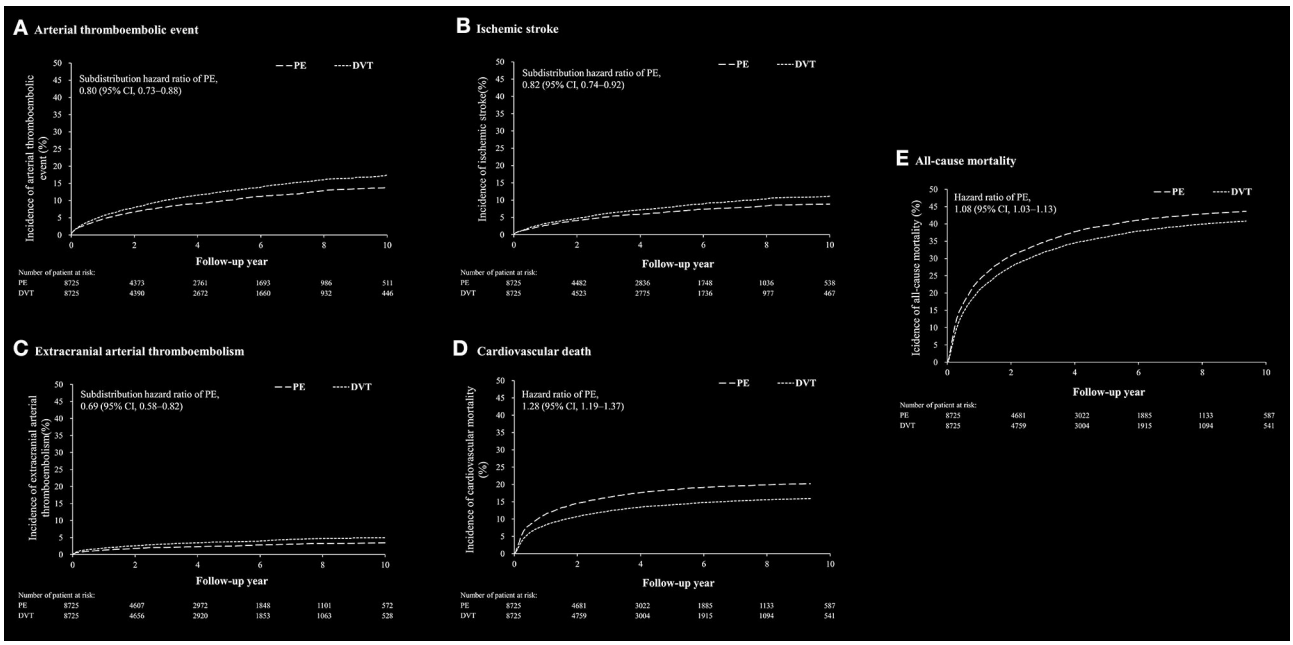

FIGURE 3 | The cumulative incidence rate of arterial thromboembolic event **(A)**, ischemic stroke **(B)**, extracranial arterial thromboembolic events **(C)**, cardiovascular death **(D)** and all-cause mortality **(E)** after propensity score matching between patients with pulmonary embolism (PE) alone and patients with deep vein thrombosis (DVT) alone.

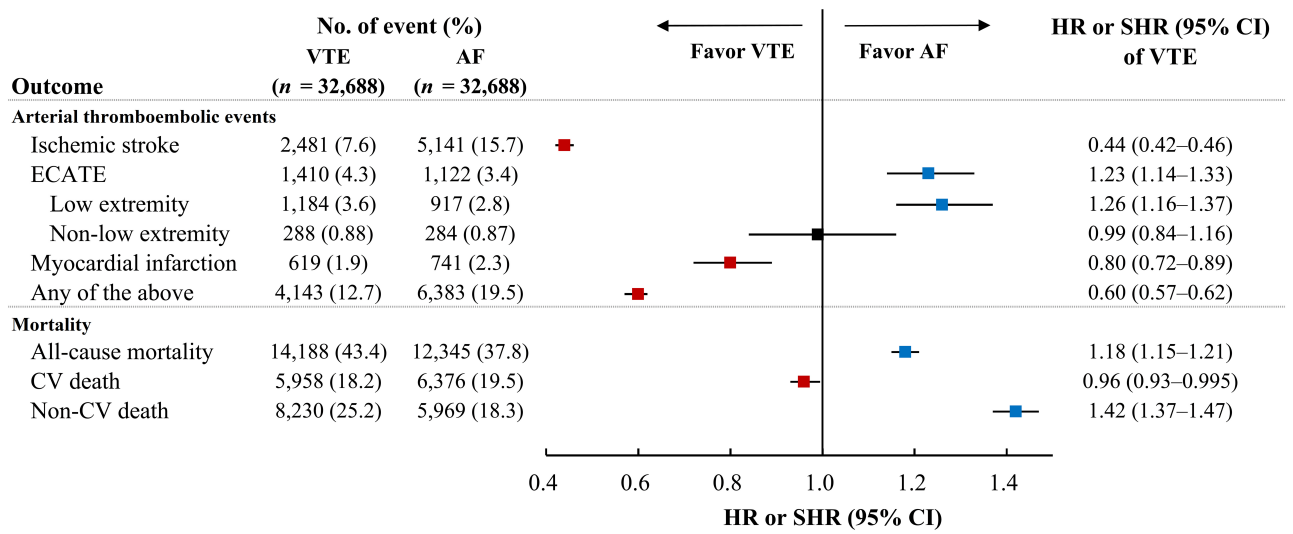

FIGURE 4 | The incidence of arterial thromboembolic events and mortality between VTE and AF cohorts. The incidence of ischemic stroke and myocardial infarction were lower in VTE cohort than AF cohort but ECATE, particularly in low extremity, was lower in AF cohort than VTE cohort. In terms of mortality, CV death was lower in VTE cohorts than AF cohort while all-cause mortality and non-CV death were lower in AF cohort than VTE cohort. AF, atrial fibrillation; CV, cardiovascular; ECATE, extracranial arterial thromboembolic event; VTE, venous thromboembolism.

VTE, despite having risk factors in common. The VTE cohort had higher risks of all-cause mortality and ECATE, particularly lower extremity events, compared to AF patients. The differential manifestations of thromboembolism sequelae and mortality between AF and VTE patients merit further investigation of an extended period or lifelong anticoagulation in VTE patients.

DATA AVAILABILITY STATEMENT

The data underlying this study is from the Taiwan's National Health Insurance Research Database (NHIRD), which has been transferred to the Health and Welfare Data Science Center (HWDC). Interested researchers can obtain the data through formal application to the HWDC, Department of Statistics,

Ministry of Health and Welfare, Taiwan (http://dep.mohw.gov.tw/DOS/np-2497-113.html). Requests to access these datasets should be directed to (http://dep.mohw.gov.tw/DOS/np-2497-113.html).

ETHICS STATEMENT

The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital: IRB number: 201900915B1. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Y-SL, M-SL, GL, and M-CC: study concept and design. VW, Y-LC, and J-JC: acquisition of data. Y-SL, M-SL, and P-HC: analysis and interpretation of data. Y-SL, GL, and M-CC: manuscript draft. GL and M-CC: critical revision of the manuscript for important intellectual content. All authors reviewed the manuscript and completed final approval.

ACKNOWLEDGMENTS

We would like to thank Alfred Hsing-Fen Lin and Ben Yu-Lin Chou for the statistical assistance during the completion of this manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.775564/full#supplementary-material

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Conflict of Interest: GL is a Consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Cardiovascular Medicine

MINI REVIEW
published: 23 December 2021
doi: 10.3389/fcvm.2021.773214

Antithrombotic Treatment in Lower Extremity Peripheral Arterial Disease

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Lower extremity arteries might be affected by atherosclerotic peripheral arterial disease (PAD), or by embolization causing ischaemic symptoms. Patients with PAD often have widespread atherosclerosis, and progression of PAD is associated with increased risk for both other cardiovascular events and cardiovascular mortality. Peripheral arterial disease patients should therefore be offered both non-pharmacological and pharmacological secondary prevention to reduce the risk for future ischemic arterial complications. This review is focussed on the rationale for recommendations on antiplatelet and anticoagulant treatment in PAD. Asymptomatic PAD does not warrant either anticoagulant or antiplatelet treatment, whereas patients with ischaemic lower extremity symptoms such as intermittent claudication or critical limb ischemia caused by atherosclerosis should be offered platelet antiaggregation with either low dose aspirin or clopidogrel. Combined treatment with aspirin and low-dose of the direct oral anticoagulant (DOAC) rivaroxaban should be considered and weighed against bleeding risk in symptomatic PAD patients considered at high risk for recurrent ischaemic events and in patients having undergone endovascular or open surgical intervention for PAD. Patiens with cardiogenic embolization to lower extremity arteries should be recommended anticoagulant treatment with either one of the DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) or warfarin.

Keywords: atherosclerosis, antiplatelet treatment, anticoagulation, peripheral atherosclerosis, PAD

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Thrombosis, a section of the journal Frontiers in Cardiovascular Medicine

Received: *09 September 2021*
Accepted: *07 December 2021*
Published: *23 December 2021*

Citation:
Gottsäter A (2021) Antithrombotic Treatment in Lower Extremity Peripheral Arterial Disease. Front. Cardiovasc. Med. 8:773214. doi: 10.3389/fcvm.2021.773214

INTRODUCTION, BACKGROUND

Peripheral arterial disease (PAD) is a common atherosclerotic manifestation (1, 2) most often occurring in lower extremity arteries. The condition might be asymptomatic, but both focal atherosclerotic lesions in the peripheral arteries and cardiogenic embolization to the lower extremities might cause ischaemic symptoms such as intermittent claudication defined as pain induced by walking (3, 4), or acute or chronic limb threatening ischemia (CLTI) defined as rest pain or ulceration (3, 4).

Patients with atherosclerotic PAD have widespread atherosclerosis and higher rates of cardiovascular events than patients with cardio- or cerebrovascular diseae (5). As both a low ankle-brachial index (ABI) (6) and progression of PAD (7) are related to increased risk for cardiovascular events and mortality, efficient treatment of atherosclerotic risk factors is recommended in PAD patients (3, 4).

Thrombolytic, endovascular, and open surgical treatment in the acute or chronic stages of PAD caused by peripheral atherosclerosis or embolization are covered in current guidelines (3, 4) together with recommendations on smoking cessation (8), lipid (9), and blood pressure (10)

lowering. This review is focussed upon antithrombotic treatment as secondary prevention of cardiovascular mortality and morbidity in patients with lower extremity ischemia caused by either peripheral atherosclerosis or cardiac embolization (**Tables 1**, **2**).

ANTITHROMBOTIC TREATMENT IN ASYMPTOMATIC PERIPHERAL ATHEROSCLEROTIC DISEASE

No beneficial effects of antithrombotic treatment have been established in patients with asymptomatic PAD, i.e., a low ABI without symptoms from the lower extremities or other concomitant vascular disease. In 3,350 asymptomatic subjects from the general population with ABI $\leq$ 0.95 detected at screening, aspirin did not confer any significant reduction in vascular events compared with placebo (11). Neither could any benefits with regard to cardiovascular events or major amputation be shown when effects of aspirin 100 mg daily were compared to placebo in patients with asymptomatic PAD (ABI $\leq$ 0.99) and concomitant diabetes (12). Current guidelines (3, 4) do therefore not recommend antiplatelet treatment in PAD patients without other symptomatic manifestations of atherosclerotic disease (**Table 1**).

ANTITHROMBOTIC TREATMENT IN SYMPTOMATIC STABLE PERIPHERAL ATHEROSCLEROTIC DISEASE

The antiplatelet trialists'meta-analysis (13) published already in 2002 established that different types of antiplatelet therapy reduce the risk of vascular death, myocardial infarction, and stroke by approximately 25% among patients with mainly symptomatic coronary and cerebrovascular disease. Patients with different manifestations of PAD were included as a subgroup in the meta-analysis, and a 23% odds reduction for vascular events could be demonstrated in this group (13). Randomized placebo-controlled studies performed exclusively in patients with stable PAD showing benefits of low dose aspirin for reduction of symptoms or cardiovascular events are lacking, however, whereas the ADP-receptor blocker thienopyridine ticlopidine was shown to be beneficial in this regard already in 1990 in a small study of 687 patients (40). The use of ticlopidine is limited by its gastroenterological and hematological side effects, however. Another thienopyridine, clopidogrel, was therefore compared with aspirin in patients with either myocardial infarction, ischemic stroke, or PAD in the CAPRIE trial (14). In the CAPRIE subgroup of 6,452 patients with PAD, clopidogrel reduced both cardiovascular mortality [hazard ratio (HR) 0.76, 95% confidence interval (CI) 0.64–0.91] and major cardiovascular adverse events (HR 0.78, 95% CI 0.65–0.93) compared to aspirin (14). When clopidogrel was later compared with ticagrelor in the EUCLID trial (15) conducted exclusively among symptomatic PAD patients, no significant differences between these two compounds could be demonstrated either regarding cardiovascular events or bleeding complications (15).

The protease-activated receptor 1 antagonist vorapaxar was found to reduce the risk of acute limb ischemia in the PAD subgroup in the TRA2°P-TIMI 50 study (41), but is also associated with increased risk for intracranial hemorrhage in patients with prior ischaemic cerebrovascular disease (34). In a meta-analysis of 49 RCTs comprising 34,518 patients neither aspirin, ticlopidine, ticagrelor, cilostazol, picotamide, or vorapaxar in monotherapy was superior to clopidogrel regarding the combined endpoint of efficacy and safety in PAD patients (16).

As no placebo arm was included in CAPRIE (14) and as EUCLID (15) lacked an aspirin arm, however, the evidence for platelet antiaggregation in PAD can still be somewhat disputed. Current guidelines (3, 4) recommend long-term single antiplatelet treatment with either aspirin or clopidogrel in symptomatic stable PAD patients who are not candidates for anticoagulant treatment as outlined below, provided they have no contra-indications such as increased bleeding risk, prior side effects of pharmacologic treatment, cognitive dysfunction, or other disabilities.

TABLE 1 | Summary of recommendations and concerns on antithrombotic treatment in peripheral arterial disease (PAD).

	Asymptomatic PAD without other symptomatic atherosclerosis	Stable symptomatic PAD	After endovascular intervention for PAD	After open surgery for PAD	Peripheral ischemia caused by cardioembolic disease
First line	No antithrombotic therapy	ASA or clopidogrel	ASA and low dose rivaroxaban	ASA or clopidogrel	DOAC
Alternative		ASA and low dose rivaroxaban	ASA and clopidogrel	ASA and low dose rivaroxaban	VKA
Alternative			ASA or clopidogrel	VKA if venous bypass	
Concerns		Evaluate bleeding risk	Evaluate bleeding risk Uncertainty on duration of combination	Evaluate bleeding risk	
References	(3, 4, 11, 12)	(3, 4, 13–19)	(3, 4, 20–23)	(3, 4, 19, 23–25)	(3, 4, 26–33)

ASA, aspirin; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

TABLE 2 | Studies of antithrombotic therapy in peripheral arterial disease (PAD).

Study (first author or eponym, year)	References	Patient population	Comparison	Follow up (mean or median, months)	Number of patients	RR or HR primary outcome (95% CI)	RR or HR major bleeding (95% CI)
Fowkes et al., 2010	(11)	Asymptomatic PAD	Aspirin or placebo	98	28,980	1.03 (0.84–1.27)	1.71 (0.99–2.97)
Belch et al., 2008	(12)	Asymptomatic PAD with diabetes	Aspirin or placebo	80	1,276	0.98 (0.76–1.26)	
CAPRIE, 1996	(14)	Prior PAD, stroke, or MI	Aspirin or clopidogrel	23	19,185	Relative risk reduction (%) 8.7 (0.3–16.5)	NS for ICH, $p = 0.23$
Hiatt et al., 2017	(15)	Symptomatic PAD	Ticagrelor or clopidigrel	30	13,885	1.02 (0.92–1.13)	1.10 (0.84–1.43)
Bonaca et al., 2016	(34)	PAD and MI	Ticagrelor and aspirin or aspirin only	36	1,143	Absolute risk reduction (%) 4.1 (−1.07–9.29)	1.32 (0.41–4.29)
Bhatt et al., 2006	(35)	Cardiovascular disease or multiple risk factors	Clopidogrel and aspirin or aspirin only	28	15,603	0.93 (0.83–1.05)	1.25 (0.97–1.61)
Anand et al., 2007	(36)	PAD	Aspirin and warfarin or aspirin only	35	2,161	0.92 (0.73–1.16)	3.41 (1.84–6.35)
Anand et al., 2018	(18)	Stable lower exrtremity or carotid PAD	Low dose rivaroxaban and aspirin or aspirin only	21	7,470	0.72 (0.57–0.90)	1.61 (1.12–2.31)
Tepe et al. 2012, Strobel et al. 2013	(21, 22)	After endovascular PAD intervention	Clopidogrel and aspirin or aspirin only	12	80	NS for revascularization, $p = 0.35$	
Bonaca et al. 2020, Hiatt et al. 2020	(23, 37)	After PAD intervention	Low dose rivaroxaban and aspirin or aspirin only	36	6,564	0.85 (0.76–0.96)	1.43 (0.97–2.10)
Dutch BOA, 2000	(38)	After open surgical PAD intervention	Oral anticoagulant or aspirin	21	2,690	0.95 (0.82–1.11)	1.96 (1.42–2.71)
Belch et al., 2010	(25)	After open surgical PAD intervention	Aspirin and clopidogrel or aspirin only	12	851	0.98 (0.78–1.23)	NS, 2.1 vs. 1.2%
Johnson et al., 2002	(39)	After open surgical PAD intervention	Oral anticoagulant and aspirin or aspirin only	Up to 60	831	NS for patency in whole group	1.41 (1.09–1.84) for death

CI, confidence interval; HR, hazard ratio; ICH, intracranial hemorrhage; MI, myocardial infarction; NS, no significance; RR, risk ratio. As modes of reporting, primary endpoints, and definitions of major bleeding differ in the different studies, please see the original publications for details.

Dual Antiplatelet Therapy

Dual antiplatelet therapy (DAPT) with a combination of 75–162 mg of aspirin and 75 mg of clopidogrel was evaluated in the CHARISMA trial (35) performed in 15,603 patients with either established vascular disease or multiple risk factors for atherosclerosis. Dual antiplatelet therapy compared to aspirin alone conferred no significant risk reduction (RR) for the primary study endpoint of either cardiovascular death, myocardial infarction, or stroke (RR 0.93; 95% CI 0.83–1.05; $p = 0.22$), whereas a significant RR was demonstrated for the secondary endpoint; hospitalization for ischemia or revascularization (RR 0.92; 95% CI 0.86–0.995; $p = 0.04$). In the subgroup of 3,096 CHARISMA patients with PAD (17) of which the vast majority were symptomatic, however, both rates of myocardial infarction (2.3 vs. 3.7%; $p = 0.029$), and hospitalization for ischemic events (16.5 vs. 20.1%; $p = 0.011$) were lower with DAPT than with aspirin alone. Rates of severe, fatal, or moderate bleeding did not differ, but minor bleeding occurred more often with DAPT (34.4 vs. 20.8%; $p = 0.001$). As a subgroup analysis of a negative trial should not be used as a basis for treatment decisions, there is no guideline support for routine use of DAPT in patients with stable PAD (3, 4). This conclusion is also supported by results from the above mentioned meta-analysis of 49 RCTs comprising 34,518 patients (16).

Combined Antiplatelet and Anticoagulant Therapy

When the combination of antiplatelet treatment and full dose anticoagulation with warfarin was evaluated after myocardial infarction (42) it was found to be beneficial regarding risk for death, reinfarction or stroke, whereas no such benefits of combination therapy could be established when studying effects of the same combination in PAD patients in the WAVE trial (36). Furthermore, combination therapy also conferred unacceptable inceased bleeding rates in both study settings (36, 42).

When later evaluating the combination of aspirin with a direct oral anticoagulant (DOAC) in PAD patients, a lower dose of anticoagulation was therefore employed. The COMPASS study (18, 43) compared three different active treatments; a combination of low dose rivaroxaban 2.5 mg twice daily and aspirin 100 mg daily, rivaroxaban 5 mg twice daily, and aspirin 100 mg daily with corresponding placebos in 24,824 patients with

stable coronary artery disease or PAD. In a subgroup analysis (18) of the 7,470 COMPASS patients with either stable lower extremity PAD or carotid artery disease, the combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg daily reduced both the primary composite endpoint cardiovascular death, myocardial infarction, or stroke (5 vs. 7%; $p = 0.0047$), and the primary PAD-related endpoint "major adverse limb events" including amputation (1 vs. 2%; $p = 0.0037$) compared to aspirin alone, whereas rivaroxaban 5 mg twice daily did not confer any definitive benefits compared to aspirin (18). The combination of rivaroxaban and aspirin combination also increased major bleeding compared with aspirin alone (3 vs. 2%; HR 1.61, 95% CI 1.12–2.31; $p = 0.0089$), however, mainly due to an increased risk for gastrointestinal bleeding.

European PAD guidelines (4) issued after the publication of COMPASS (18, 43) therefore recommend that a combination of ASA 100 mg daily and rivaroxaban 2.5 mg twice daily should be considered in stable PAD patients without high bleeding risk or other relevant contraindications. The same consideration is also recommended in the global guidelines for treatment of patients with the most serious form of PAD, CTLI (19).

ANTITHROMBOTIC TREATMENT AFTER INTERVENTION FOR PERIPHERAL ATHEROSCLEROTIC DISEASE

Endovascular Intervention

Endovascular percutaneous transluminal angioplasty (PTA) with or without stent placement might increase the risk for thromboembolic events both by disrupting the endothelium or atherosclerotic plaques and by introduction of foreign material in the artery. This might activate platelets and coagulation factors, initiate atherothrombosis, and consequently increase the risk of arterial occlusion. In a systematic follow-up of nationwide Swedish registry data (44), the risk of non-fatal MI, ischemic stroke, or cardiovascular death 36 months after peripheral revascularization was 14% among patients with IC and and 34% among those with CLTI. Furthermore, the TRA2°P study (41, 45) confirmed that peripheral revascularization increased the risk of acute limb ischemia and the need for both urgent and elective reintervention. Particular interest has therfore been focussed on this patient group when assessing effects of antithrombotic treatment.

Antiplatelet therapy after endovascular revascularization of peripheral arteries has often been based on recommendations (46) based on studies of patients undergoing percutaneous coronary interventions (PCI), and many vascular units routinely recommend a combination of aspirin and clopidogrel for 1–3 months after peripheral revascularization. One month of DAPT is also recommended in the current version of the PAD guidelines issued by the European Society of Vascular Surgery and European Society of Cardiology (3). A thourough meta-analysis (20) of 5,464 publications in the field in 2016 revealed, however, that only one of the evaluated articles was relevant. In the MIRROR trial (21, 22) the combination of aspirin and clopidogrel was compared with monotherapy with aspirin after percutaneous angioplasty with or without stenting in the femoropopliteal segment. The 6-month results of MIRROR (21) were promising with lower need for target lesion revascularization with combination therapy, but after 12 months of follow-up (22), this difference was no longer detectable.

Authors of the meta-analysis concluded that the lacking evidence for DAPT after lower limb endovascular revascularization might partly be explained by the fact that interventionalists have already adopted the DAPT regime used after PCI (46), making it difficult to conduct new randomized trials of DAPT after endovascular revascularization in PAD (20).

Furthermore, in the recently published VOYAGER study (23) rivaroxaban 2.5 mg twice daily combined with aspirin 100 mg daily was compared to aspirin 100 mg and placebo in 6,564 patients revascularized due to symptomatic PAD. Revascularization had been performed with endovascular or hybrid methods in 65% of cases, and with open surgery in the remaining 35%. The majority of patients were treated because of intermitent claudication, but 23% had CLTI. The combined primary efficacy endpoint of cardiovascular death, myocardial infarction, stroke, acute limb ischemia, or amputation above ankle occurred in 17.3% and 19.9% of patients in the combination and aspirin only group, respectively (HR 0.85; 95% CI 0.76–0.96; $p = 0.009$) during 36 months, corresponding to an absolute RR of 2.6% and a number needed to treat (NNT) of 39. As the primary safety endpoint, major bleeding defined in accordance with the Thrombolysis In Myocardial Infarction (TIMI) classification (47), did not differ significantly between groups (2.7 and 1.9%, $p = 0.07$), and as the safety of rivaroxaban was later shown to be consistent regardless of concomitant clopidogrel use (37), it must be concluded that the evidence is far more solid for the use of the combination of low doses of aspirin and rivaroxaban after endovascular peripheral revascularization than for DAPT.

Open Vascular Surgery

Full dose vitamin K antagonists was compared to aspirin in 2,690 patients having undergone infrainguinal bypass surgery in the Dutch Bypass Oral Anticoagulants or Aspirin (BOA) trial (38). The study was neutral (HR 0.95; 95% CI 0.82–1.11), but subgroup analyses revealed that vitamin K antagonism conferred a reduction in graft occlusion (HR 0.69; 95% CI 0.54–0.88) in patients receiving vein grafts, but an increased risk in those receiving prosthetic grafts (HR 1.26; 95% CI 1.03–1.55). The evidence for vitamin K antagonist use after venous bypass has later been considered as insufficient in a Cochrane analysis (24), however.

The CASPAR study (25) showed no additive effect of combining aspirin with clopidogrel after open bypass surgery in lower limb arteries regarding the composite primary efficacy endpoint of index-graft occlusion, revascularization, above-ankle amputation of the affected limb, or death, except for in the subgroup of patients with prosthethic grafts. The combination of aspirin and full dose warfarin after lower extremity bypass was associated with both increased morbidity and mortality (39).

Guidelines (3, 4, 19) therefore recommend single antiplatelet therapy after open surgery for PAD, although the different European guidelines mentions vitamin-K antagonists after

venous bypass either as an alternative (4) or as an option for which evidence is weak and bleeding risk is higher compared to antiplatelet drugs (3) (**Table 1**).

As beneficial effects of combination therapy could be demonstrated also in the subgroup of VOYAGER patients having undergone revascularization with open surgical methods (23), however, the combination of low dose aspirin and rivaroxaban could well be considered also in this situation in patients without high bleeding risk or other contraindications.

ANTICOAGULATION IN PATIENTS WITH PERIPHERIAL ISCHEMIA CAUSED BY CARDIAC EMBOLIZATION

Cerebral embolism is by far the most common and feared embolic consequences of atrial fibrillation (AF), and 80% of deaths related to cardiogenic embolism are caused by ischemic stroke (48). Atrial fibrillation is also the most common cause of peripheral embolism, however, and estimated to be present in 60–95% of patients undergoing surgery for acute limb ischemia (49). The yearly incidence of aortoiliac and lower-extremity arterial thromboembolism in AF is about 0.4%, corresponding to an excess risk of 4.0 (95% CI 3.5–4.6) in men and 5.7 (95% CI 5.1–6.3) in women (50).

Current European guidelines for AF (26) recommend assessment of the risk for systemic cardiac embolisation by evaluation of the factors below summarized in the CHA_2DS_2-VASc score (50). As anticoagulant treatment is recommended already in patients with CHA_2DS_2-VASc score $\geq$1 in men and $\geq$2 in women (26), and as a previous episode of thromboembolism (S) confers two points, all patients with permanent or paroxysmal AF who have suffered an episode of lower extremity embolism have a score of 2 or higher. After endovascular, open surgical, or thrombolytic treatment of the acute event, they should therefore be offered secondary prevention by full dose anticoagulation in the abscence of important contraindications. This recommendation also applies to patients with peripheral embolization caused by prosthethic heart valves or other cardiac sources of embolism (3).

As the presence of atherosclerotic peripheral vascular disease in itself confers one CHA_2DS_2-VASc point (26), most PAD patients with concomitant AF will qualify for anticoagulation also in the abscence of documented thromboembolic episodes in the lower extremities.

In patients with an established indication for anticoagulation undergoing endovascular PAD recanalization, European guidelines recommend consideration of a 1–12 month course of aspirin or clopidogrel as addition to the anticoagulant in the abscence of high bleeding risk (3, 4). After open surgical procedures for PAD in this patient group, on the other hand, only continued anticoagulation is recommended (3, 4).

Direct oral anticoagulant, the thrombin inhibitor dabigatran (27) or one of the factor Xa-inhibitors rivaroxaban (28), edoxaban (29), and apixaban (30) are first hand alternatives for anticoagulation. Meta-analysis (31) has established that treatment with these agents in comparison to warfarin confers 19% RR for stroke or other systemic embolism and a 51% RR in haemorrhagic stroke. Direct oral anticoagulant treatment was also associated with a non-significant 14% reduction in major bleeding risk, a 52% reduction in intracranial hemorrhage, and a 25% increase in gastrointestinal bleeding compared to warfarin (31). Although focus in the above trials (27–30) and meta-analysis (31) has been on stroke prevention with DOAC, a systematic literature review (32) confirmed that DOAC are also at least as effective as warfarin to reduce the risk for limb ischemia in patients with AF. Furthermore, among patients with AF and concomitant CLTI, the superiority of DOAC in comparison to either warfarin or antiplatelet therapy has been established in a retrospective cohort analysis (33).

Warfarin can of course still be used as an alternative for prevention of systemic thromboembolic events in patients with AF or other sources of embolism to peripheral arteries (26), however, and is superior to dabigatran in patients with mechanical heart valves (51) and to rivaroxaban in those with antiphospholipid syndrome (52). The therapeutic target is an international normalized ratio (INR) of 2.0–3.0. There is no evidence for warfarin treatment with lower INR-targets, or for combination treatment with warfarin in combination with aspirin or other antiplatelet agents in PAD.

EMERGING ROLE, UNMET NEEDS, AND GRAY AREAS

The benefits of combined treatment with low doses of aspirin and rivaroxaban has been established in both stable PAD (18, 43) and after peripheral revascularization (23, 37), and this benefit increases with baseline risk in the patient (53). Bleeding risk with this treatment also has to be taken into account, however, and PAD patients with a perceived high risk for bleeding complications were excluded from the studies. We must therefore more clearly define the groups of PAD patients in which combination treatment with low doses of aspirin and rivaroxaban is safe and cost-effective in clinical practice.

Furthermore, we lack studies establishing the efficacy and safety of combined antitplatelet and full dose anticoagulant treatment after peripheral revascularization in patients with AF or other established indications for anticoagulation. To which patients in this group should platelet inhibition be added to the oral anticoagulation, and for how long after the intervention?

Neither do we know if PAD progression in itself, measured for example as a worsening ABI, is enough to warrant modification of antithrombotic therapy.

SUMMARY

Whereas asymptomatic PAD does not warrant either anticoagulant or antiplatelet treatment, patients with ischaemic symptoms such as intermittent claudication or CLTI caused

by atherosclerosis should be offered platelet antiaggregation with either low dose aspirin or clopidogrel, and those with cardioembolic disease should be recommended full dose anticoagulant treatment with either DOAC or warfarin. Combined treatment with aspirin and low dose rivaroxaban should be considered and weighed against bleeding risk in symptomatic PAD patients with high risk for recurrent ischaemic events and in those having undergone peripheral endovascular or open surgical intervention. These concerns and recommendations are summarized in **Table 1**.

AUTHOR'S NOTE

AG is the only author of this review submitted for the research topic—Anticoagulation in cardiovascular diseases: evolving role, unmet needs, and gray areas.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cardiovascular Medicine

REVIEW
published: 23 December 2021
doi: 10.3389/fcvm.2021.803169

Vascular Dementia and Crosstalk Between the Complement and Coagulation Systems

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Vascular Dementia (VaD) is a neurocognitive disorder caused by reduced blood flow to the brain tissue, resulting in infarction, and is the second most common type of dementia. The complement and coagulation systems are evolutionary host defence mechanisms activated by acute tissue injury to induce inflammation, clot formation and lysis; recent studies have revealed that these systems are closely interlinked. Overactivation of these systems has been recognised to play a key role in the pathogenesis of neurological disorders such as Alzheimer's disease and multiple sclerosis, however their role in VaD has not yet been extensively reviewed. This review aims to bridge the gap in knowledge by collating current understanding of VaD to enable identification of complement and coagulation components involved in the pathogenesis of this disorder that may have their effects amplified or supressed by crosstalk. Exploration of these mechanisms may unveil novel therapeutic targets or biomarkers that would improve current treatment strategies for VaD.

Keywords: vascular dementia (VaD), complement, coagulation, crosstalk, small vessel disease

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Thrombosis, a section of the journal Frontiers in Cardiovascular Medicine

Received: *27 October 2021*
Accepted: *29 November 2021*
Published: *23 December 2021*

Citation:
Mossanen Parsi M, Duval C and Ariëns RAS (2021) Vascular Dementia and Crosstalk Between the Complement and Coagulation Systems. Front. Cardiovasc. Med. 8:803169. doi: 10.3389/fcvm.2021.803169

INTRODUCTION

Vascular Dementia (VaD) is a progressive neurocognitive disorder with classic cerebrovascular and cardiovascular risk factors. Crosstalk between the coagulation and complement systems has gathered increasing scientific attention in recent years, however there is still much to uncover especially regarding the impact of these systems on different disease states such as VaD. The understanding of the interaction between coagulation and complement in VaD is lacking and there are currently no reviews available that discuss them side-by-side. This review aims to bridge the gap in knowledge by collating current understanding of VaD to enable identification of complement and coagulation components involved in the pathogenesis of this disorder, that may have their effects amplified or supressed by crosstalk. Improved understanding of underlying mechanisms may ultimately aid in improving treatment options available for VaD.

VaD is caused by reduced blood flow to the brain, and can present with behavioural symptoms, locomotor problems, and loss of executive function (1, 2) (**Figure 1**). VaD is the second most common type of dementia, accounting for roughly 15% to 20% of dementia cases in North America and Europe (3). Subtypes of this condition are defined by the cause and nature of vascular pathology, number of intracranial vessels involved, anatomical location of tissue changes, and the time after the initial vascular event (2). These subtypes include post-stroke dementia, multi-infarct dementia, subcortical dementia, mixed dementia, and CADASIL (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) (1). There are currently no specific medications approved for the treatment of VaD (4). Underdiagnosis of VaD, lack of treatment

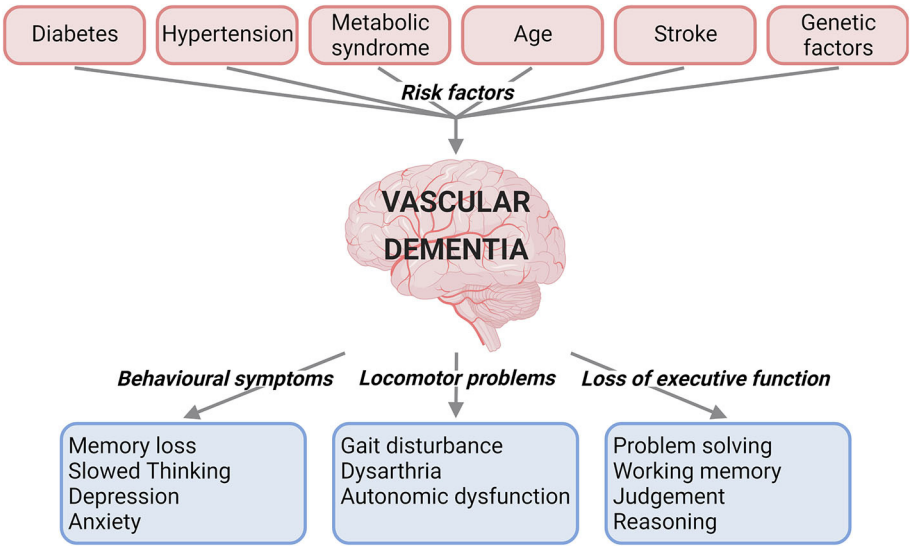

FIGURE 1 | Summary of the risk factors and clinical characteristics for vascular dementia. Risk factors such as diabetes, hypertension, metabolic syndrome, age, stroke, and genetic factors have been linked to vascular dementia. The clinical presentations of vascular dementia range from behavioural and locomotor symptoms to loss of executive function *(created with BioRender.com)*.

options and an increase in the population suffering from VaD risk factors emphasise the necessity for research and treatment development for this disease. Clinical trials of the acetylcholinesterase inhibitor Donepezil, currently indicated for Alzheimer's disease were not promising in VaD, with the drug found to be much less effective in VaD than in Alzheimer's disease (5), with patients attaining small improvements in cognitive function, but no improvement in global functioning that helps day-to-day life. Moreover, since definitive confirmation of VaD is only possible post-mortem, it has been difficult to ascertain the exact prevalence of VaD worldwide due to varying diagnostic criteria and very few population-based cohort studies available on the subject (6, 7).

For neuropathological diagnosis of VaD, key cerebrovascular lesions need to be present such as ischaemic infarcts (necrosis due to blood vessel blockage), haemorrhagic infarcts (bleeding in or around the brain), lacunar infarcts (small infarcts in the deep tissues of the brain from penetrating artery occlusion), and microinfarcts (microscopic lesions <1 mm in diameter) (8–10). Lacunar infarcts and microinfarcts are the most common type of infarct found in VaD (11). However, regardless of the type, accumulation of infarcts increases the likelihood of dementia (12). Other key neuropathological changes include atherosclerosis seen in medium to large sized arteries at the base of the brain with plaques containing lymphocytes and macrophages that have begun to destroy the vessel wall (later stage plaques may have necrotic cores, cholesterol clefts and calcification), arteriosclerosis seen in small arteries and arterioles (very common and early change), and other microangiopathies (2, 12–14). However, a robust internationally accepted set of neuropathological criteria for VaD is still needed.

Cerebral small vessel disease (SVD) is not only associated with an increased risk of stroke (15–17), but data from 13 different studies on 12,931 patients across Western Europe and the USA found SVD as the most common cerebrovascular pathology in clinically diagnosed VaD followed by large-vessel disease (2, 18–30). SVD is the most common and important vascular cause of VaD, also referred to as subcortical VaD (31, 32). SVD causes slow progressive changes to the brain due to diseased arterioles and micro-vessels but can also affect larger vessels and veins (33). SVD often coexists with atherosclerosis of the extracranial vessels and cardioembolic disease, which all associate with VaD (34). In SVD, vessels undergo progressive age-related changes such as fibrinoid necrosis (necrosis of vessel wall), hyalinization (thickening of vessel wall), intima thickening, arteriosclerosis, astrocytic gliosis, and expansion of perivascular spaces, which cumulatively all decrease perfusion and result in lacunar infarcts and microinfarcts (2, 33, 35, 36). These lesions arise from a loss of blood flow response, since the thickened and less elastic vessel walls cannot respond to fluctuations in blood pressure by dilating or constricting to maintain constant tissue perfusion (33, 37, 38). This leaves brain tissue vulnerable to infarction, especially the deep cerebral structures and white matter since these are supplied by end arteries with almost no anastomoses to compensate (2). It has been suggested that lacunar strokes are more often a result of vascular degeneration, rather than arteriole occlusion as originally assumed, however more research is needed to confirm this (39).

RISK FACTORS OF VASCULAR DEMENTIA

Many factors have to date been linked to increased risk of developing VaD (**Figure 1**).

Diabetes

Diabetes mellitus has been found to double the risk of dementia and has been established as a clear risk factor for VaD (40). Having diabetes in midlife (<65 years) is a stronger risk factor for dementia than in later life (41). In addition to duration of diabetes, the occurrence of peripheral vascular disease is also an independent risk factor for dementia (42). The link between diabetes and VaD is not surprising since diabetes increases the risk of stroke, lacunar infarcts and vascular damage, which inevitably increase the risk of VaD (1, 43, 44).

Hypertension

Hypertension is a risk factor for VaD, especially if untreated. It has been reported that the use of antihypertensives to control blood pressure in midlife reduces the incidence of dementia in later life (45–48). Uncontrolled hypertension precedes white matter lesion development and worsens VaD disease progression (49). Conversely, other studies have found an association between low blood pressure and dementia risk, with the Framingham Study finding no association between blood pressure and cognitive performance (50–52). Therefore, it is unclear whether decrease in blood pressure is a side effect of dementia or a decline in blood pressure in later life after having high blood pressure in midlife is a sign of dementia to come (1).

Metabolic Syndrome

Metabolic syndrome is characterised by a combination of several metabolic derangements that include hypertension, dyslipidaemia, central obesity, and insulin resistance (53). A cohort of 7,087 participants from the French Three-City study showed that baseline metabolic syndrome in patients >65 years increased the risk of incident VaD over four years (54). Triglycerides (45% increase) and diabetes (58% increase) in particular were significantly associated with an increase in all-cause dementia (54). Metabolic syndrome also doubles the risk of developing dementia in individuals with mild cognitive impairment (55). However, the exact role of metabolic syndrome in cognitive dysfunction is still unclear due to age having varying effects on the syndrome's impact on cognitive decline (1).

Age

The cerebrovascular endothelium becomes increasingly permeable with age, with blood-brain barrier endothelial integrity decreasing progressively after the age of 70, and such changes are commonly seen in VaD patients (31, 56). Even people without dementia in the general population have an increasing prevalence of cortical infarcts, lacunar infarcts, and microbleeds as they get older (57–59). Despite these infarcts and microhaemorrhages or microbleeds being common in elderly patients with normal cognition, these lesions are associated with reduced cognition and executive function (2, 60, 61). Microbleeds were present in 85% of patients with subcortical VaD, and are therefore likely to be a marker of SVD (62). Interestingly, age-related dementia risk has steadily decreased in Europe and North America over the past couple of decades with one possible explanation being better vascular risk factor control in mid-life, which reduces the cumulative effect experienced by the cerebrovascular system over time (63, 64).

Stroke

Post-stroke dementia is a subtype of VaD resulting from ischaemic and haemorrhagic stroke, where 10% of patients develop dementia after their first stroke and a third of patients after recurrent stroke (65). South Asians are at a particularly high risk of ischaemic stroke due to a greater burden of hypertension, diabetes, and dyslipidaemia (66, 67). Although not all stroke patients develop post-stroke dementia, recurrent stroke prevention and cardiovascular risk factor control remain the therapeutic cornerstone of preventing VaD (3) due to stroke doubling the risk of all-cause dementia (68).

Genetics

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is the most common genetic cause of stroke and VaD in adults (69, 70). CADASIL is the result of a mutation to the *NOTCH3* gene that encodes for a transmembrane receptor crucial to blood vessel integrity (71, 72), eventually leading to dementia due to systemic vascular degeneration (73), however the exact mechanism of disease remains to be uncovered (74). CARASIL is the very rare autosomal recessive (R) form of this hereditary microangiopathy, which is caused by a mutation to the *HTRA1* gene encoding a serine protease (71, 75). Onset of cognitive decline and ischaemic stroke resulting from these microangiopathies characteristically begins in early to mid-life (69), however further research is still required to establish the exact mechanism that leads to VaD.

PATHOLOGY OF VASCULAR DEMENTIA

Current understanding of the pathophysiology behind SVD and thromboembolic events that lead to cerebral damage and VaD is centred around mechanisms involving hypoxia, oxidative stress, and inflammation (**Figure 2**).

Hypoxia

Hypoperfusion and reduced cerebral blood flow is a characteristic feature of VaD (76). Chronic hypoperfusion and thromboembolic events result in reduced cerebral blood flow and hypoxia, which aggravates oxidative stress and triggers inflammatory responses (1, 77).

The brain demands a large cardiac output to fulfil its high oxygen and metabolic demand for normal functioning, which makes this organ extremely vulnerable to hypoxic damage. The periventricular white matter, basal ganglia, and hippocampus are all highly susceptible to hypoperfusion induced lesions; additionally, poor collateral blood supply in the deep structures of the brain leave cerebral white matter very susceptible to hypoxia induced damage (78). Frontal lobe white matter myelin loss is a hallmark of VaD, and this demyelination is a result of hypoxic injury to the oligodendrocytes (79). These ischaemic lesions result in neurocognitive decline as demonstrated in rats suffering a decline in cognitive performance when cerebral blood flow was reduced (80).

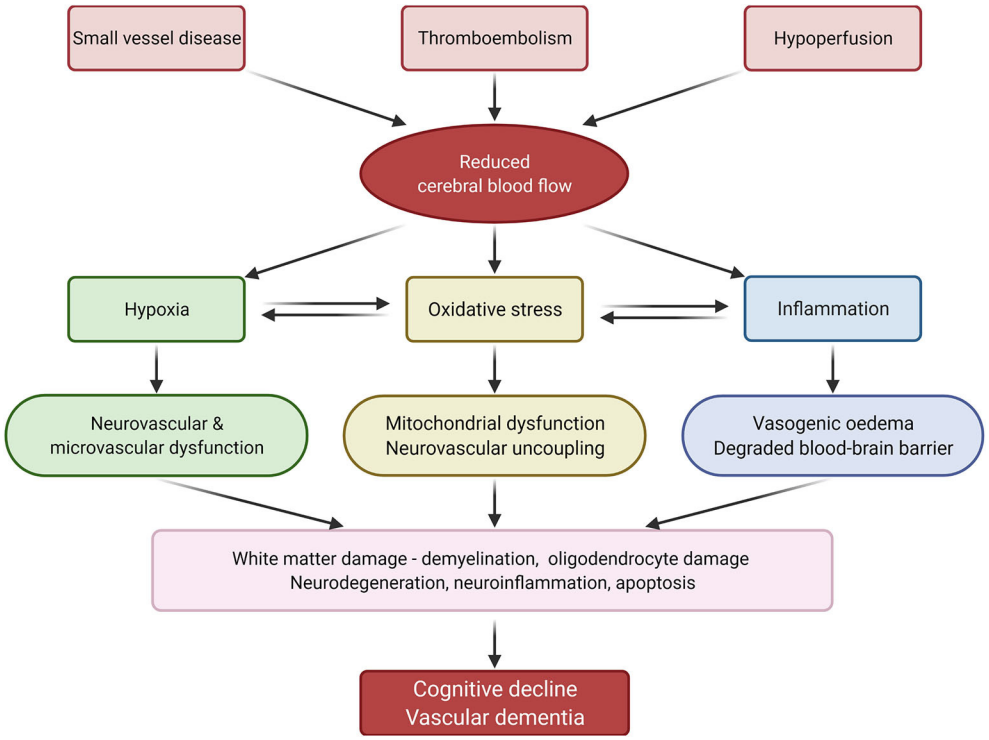

FIGURE 2 | Summary of vascular dementia pathology. Reduced cerebral blood flow, caused by small vessel disease, thromboembolism and hypoperfusion, induces inflammation, oxidative stress, and hypoxia, which in turn lead to cognitive decline and vascular dementia. Adapted from Venkat et al. (1) *(created with BioRender.com).*

Oxidative Stress

Oxidative stress refers to the excessive generation of reactive oxygen species and reactive nitrogen species that damage cellular proteins, lipids, and DNA (80). Studies indicate that oxidative stress is associated with the pathogenesis of VaD (81), which may be because the brain is relatively more susceptible to oxidative stress than other organs due to its high metabolic rate, high polyunsaturated lipid content, and lower levels of endogenous antioxidant activity and protective mechanisms (80).

Cerebral hypoperfusion-induced hypoxia can promote mitochondrial dysfunction, inhibit protein synthesis, and cause ATP depletion and ionic pump disorder (82). Mitochondrial dysfunction leads to increased reactive oxygen species production, which is problematic because of a simultaneous reduction in antioxidase production due to protein synthesis inhibition (80). This combination results in more severe oxidative damage due to the significant disruption in balance of reactive oxygen species to antioxidants, which damages vascular endothelial cells, glial cells, and neuronal cells therefore causing neurovascular uncoupling that results in a reduction in cerebral blood flow, further exacerbating this cycle (1, 80). Furthermore, reactive oxygen species react with nitric oxide to form peroxynitrite, eliminating circulating nitric oxide that is necessary for cerebrovascular functions such as vasodilation and enzymes oxidation, further disrupting cerebral blood flow (83).

Diabetes may partly increase the risk of VaD through build-up of reactive oxygen species as a result of hyperglycaemia which perpetuates this disease process (84). Similarly, hypercholesterolaemia is associated with an increase in free-radical formation and reduced antioxidant levels (81, 85). In mouse models, vascular oxidative stress disrupts the cerebral microvasculature's ability to clear amyloid-β peptide, leading to toxic accumulation of amyloid proteins that contribute to neurodegenerative mechanisms and cognitive impairment (86, 87).

Inflammation

Tissue hypoxia triggers a series of complex molecular mechanisms inducing vascular inflammation, neurovascular unit disruption, microvascular remodelling, and dysfunction in response to tissue injury (88–90). Hypoxia-inducible factor-1α and matrix metalloproteinase-9 are released which produce free radicals, induce vasogenic oedema, degrade the blood-brain barrier and increase inflammatory factors such as interleukin 1 and 6, matrix metalloproteinase 2 and 9, tumour necrosis factor α, toll-like receptor 4 and C-reactive protein (1, 33, 91–93). These inflammatory factors aggravate white matter damage in the brain, cause neurodegeneration, cell death and neuroglial inflammation which further progress VaD development (31).

COAGULATION AND COMPLEMENT SYSTEMS IN VASCULAR DEMENTIA

The coagulation and complement systems are separate complex evolutionary defence mechanisms underpinning inflammation, clot formation and degradation to protect the host. Extensive

literature reveals important crosstalk between these two systems (94–97) which uncovers exciting therapeutic potential for pathologies resulting from overactivation of these systems, such as thromboembolic disorders associated with stroke and VaD.

The coagulation system is a series of physiological events that ensure haemostasis (stopping of bleeding) by producing a fibrin meshwork that stabilises the preliminary platelet plug formed at the site of endothelial damage (98). Endothelial damage exposes collagen and tissue factor, which activate platelets and the extrinsic pathway of coagulation respectively. Thrombin generated through the coagulation system converts fibrinogen to fibrin, forming the fibrin fibres mesh that stabilises the initial platelet plug (98) (**Figure 3**).

The complement system is key to the body's defence mechanism against pathogens as part of innate and adaptive immunities (99). Contact with pathogenic surfaces triggers a series of reactions resulting in three main outcomes: production of proinflammatory mediators, opsonisation (marking of cells for phagocytosis) and destruction of pathogenic cells via the formation of a membrane attack complex that makes pores in the pathogen cell membrane (100). Complement activation occurs through three possible pathways: classical, lectin and alternative pathways, resulting in complement activation and membrane attack complex formation (99) (**Figure 3**).

Coagulation and VaD

Coagulation can be activated by vascular injury caused by hypoxia and inflammation (101). Follow-up studies of the Rotterdam study in the 1990's found that dementia risk increased with elevated levels of serum fibrinogen, thrombin-antithrombin complex, D-dimer, and tissue-type plasminogen activator (102, 103). Although the authors noted that some misclassification between Alzheimer's disease and VaD may have occurred due to difficulty differentiating between the two diseases, 31 out of the 192 dementia cases in the cohort were VaD patients (103), raising concerns about the statistical power of some of these associations. Gallacher *et al.* also found associations between dementia risk and fibrinogen in addition to factor (F)VIII, plasminogen activator inhibitor-1, and plasma viscosity (104). Although their study was smaller than the Dutch studies and only included men, the associations were made over a much longer 17-year prospective time frame (104). It was suggested that these components increased VaD risk by altering fibrin clot formation and lysis activity through the FVIII / von Willebrand factor complex and elevated plasminogen activator inhibitor-1 (impaired fibrinolytic activity), which lead to hypercoagulability and microinfarction (104). Further systematic reviews and meta-analyses support associations between fibrinogen, FVIII, D-dimer, FVIIa, and von Willebrand factor in VaD patients (105, 106).

FVIII levels increase in acute stroke (107) and generally with age (108), in addition to their association with increased VaD risk (104–106). However, a recent study found no strong association between FVIIIa clotting activity and cognitive function or burden of white matter hyperintensities on magnetic resonance images (109). Although this study did not specifically look at VaD, as previously discussed, white matter damage is one of the hallmarks of VaD and SVD (79). It is therefore possible that FVIII does not progress cognitive decline and VaD through its clotting activity, but rather through another mechanistic role that needs exploration, such as crosstalk with other systems. Thrombomodulin and tissue factor on the other hand, have been associated with the extent of leukoaraiosis (abnormal white matter) in cerebral SVD (110).

Some studies have found associations between vascular cellular adhesion molecule-1, C-reactive protein, and interleukin-6 with VaD and cognitive decline (111, 112), whilst other studies have not (103, 104). Although sample size was an issue in all of these studies, the Dutch studies had slightly more robust data due to repeats. Nonetheless, further research is necessary to establish the roles of these inflammatory markers in cognitive decline (113, 114).

Lower levels of endothelial progenitor cells are found in CADASIL patients (115), which is associated with more significant degeneration of cognitive and motor performances, possibly due to their role in maintaining normal homeostasis and structure of the endothelium (116). CADASIL patients also had significantly higher von Willebrand factor levels than controls (115), which is a marker of endothelial damage and dysfunction (117). Elevated levels of lipoprotein-associated phospholipase A2, an enzyme which influences platelet activation and inflammatory molecule production for low-density lipoproteins, have been identified as a risk factor for dementia development (118).

Finally, kinins from the kallikrein-kinin system are pro-inflammatory peptides that are important in regulating vascular permeability, oedema formation, trans-endothelial cell migration and inflammation in different organs following injury (119). Activation of FXII initiates both the intrinsic coagulation pathway and the kallikrein-kinin system when it meets negatively charged surfaces, triggering both clotting and inflammation seen in ischaemic stroke (120–123). Prekallikrein is a key component of the contact-kinin system and can activate FXII in the intrinsic pathway. Prekallikrein-deficient mice had significantly smaller brain infarctions and less severe neurological deficits due to reduced intracerebral thrombosis, with improved cerebral blood flow and blood-brain barrier function, suggesting that prekallikrein inhibition could be a potential strategy for stroke prevention (124). It is likely that these same mechanisms contribute to stroke induced VaD, suggesting that prekallikrein inhibition in humans could be a potential therapeutic target in VaD prevention.

Complement and VaD

The complement system component C3a (anaphylatoxin) has been reported to be involved in cerebral white matter injury in rats (125). Microglia are the resident macrophage cells of the central nervous system and are key to maintaining normal brain homeostasis, however chronic activation of these cells via the C3a-C3aR (receptor) pathway in hypoperfusion can aggravate white matter injury by engulfing myelin fibres, resulting in cognitive dysfunction (125). One study found that intracortical administration of a C3aR antagonist (SB 290157) resulted in reduced phagocytosis of neurones, since microglia

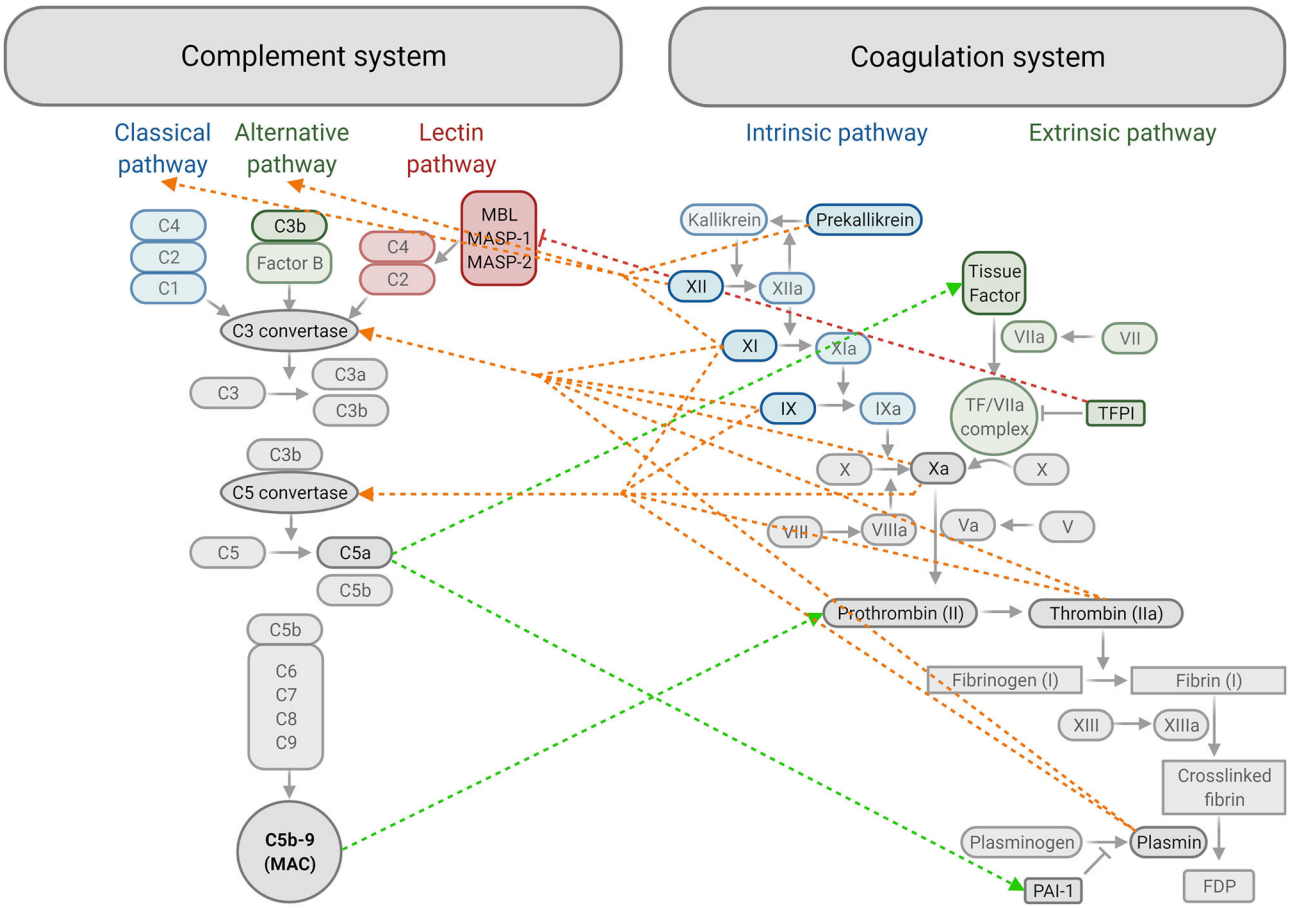

FIGURE 3 | Summary of crosstalk between components of the complement and coagulation systems. The classical, alternative and lectin activating pathways of complement produce C3 convertase, which allows for downstream activation of C3, C5 and formation of the membrane attack complex (*MAC*) or C5b-9. Activation of Factor IX in the intrinsic pathway and formation of the tissue factor/FVIIa complex in the extrinsic pathway converge at the common coagulation pathway by activating FX. This allows for the formation of a fibrin clot downstream, strengthening the initial platelet plug, which is later degraded into fibrin degradation products (*FDP*) by plasmin. Plasminogen activator inhibitor-1 (*PAI-1*) inhibits the formation of plasmin and tissue factor pathway inhibitor (*TFPI*) inhibits formation of the tissue factor / FVIIa complex. ←-- activation of the complement system by the coagulation system; --→ activation of the coagulation system by the complement system; |– – inhibition of the complement system by the coagulation system. *MBL*, Mannose-binding lectin; *MASP*, Mannose-binding lectin-associated serine protease *(created with BioRender.com)*.

expressing C3aR were inactivated (126). The CODAM study found a strong positive correlation between carotid artery intima-media thickness, ankle-arm blood pressure index, and plasma C3a levels in humans (127), suggesting that C3a promotes atherosclerosis, which could contribute to the pathogenesis of SVD. Interestingly, in hyaline arteriosclerosis, inactive C3b is a major component of the hyaline material deposited in the vessel wall of arterioles, suggesting another role for the complement system in SVD pathology (36). Inhibition of mannose-binding lectin pathway offers therapeutic benefit by attenuating C3 activity after oxidative stress (128). Finally, *in vitro* studies and mouse models have demonstrated that C5a (anaphylatoxin) can induce the release of histones and reactive oxygen species that leads to inflammation, endothelial damage, and thrombosis (129), fitting the oxidative stress model of VaD.

Crosstalk Between the Coagulation and Complement Systems

Studies looking at the effect of complement proteins on coagulation activity, and vice versa, have identified a number of communication avenues between the systems (**Figure 3**). Complement protein C5a was found to increase tissue factor expression in human umbilical vein endothelial cells (130), which was supported by another study reproducing this effect in monocytes (131). This is significant because it shows that the complement system may contribute to initiation of coagulation, since tissue factor is the primary physiological initiator of the coagulation system (94). Mouse models have also indicated that C5 activation amplifies tissue factor activation on myeloid cells, whilst C3 activation helps induce platelet activation, showing that both C3a and C5a have prothrombotic roles in promoting fibrin formation (132). Plasminogen activator

inhibitor-1 is a potent inhibitor of the conversion of plasminogen to plasmin, and therefore fibrinolysis (133). C5a has been found to increase plasminogen activator inhibitor-1 expression from mast cells (134), thus preventing clot breakdown. This could explain the association between dementia and elevated plasminogen activator inhibitor-1 levels reported by Gallacher et al. (104). Additionally, assembly of the C5b-9 (membrane attack complex) on endothelial plasma membranes triggers the exposing of FVa binding sites on the membrane, therefore promoting prothrombinase complex assembly to accelerate thrombin generation (135, 136).

Conversely, studies of the influence of coagulation system activity on complement has revealed that the coagulation factors FXII, FXI and prekallikrein not only initiate the intrinsic pathway, but can also initiate the classical (antigen-antibody complex) and alternative (Factor B mediated formation of C3 convertase) complement pathways (94, 137). C3 and C5 are typically converted to their active form by C3 and C5 convertase, however studies have shown that they can also be cleaved to C3a and C5a by FXa (most potent) followed by plasmin, thrombin, FIXa, and FXIa (138, 139).

Activity can be both stimulated and inhibited in either system by crosstalk, for example thrombomodulin in the coagulation system can downregulate complement by inactivating C3b into the inactive iC3b (140). Another example is tissue factor pathway inhibitor, which plays a role in impeding blood coagulation by preventing the activation of the tissue factor / FVIIa complex and FXa (141–144). Work by Keizer *et al.* has identified tissue factor pathway inhibitor as a selective inhibitor of mannose-binding lectin-associated serine protease-2, which therefore inhibited cleavage of C4 and C2 in the lectin pathway (94, 145). This may be a useful therapeutic target for VaD, as studies have suggested deficiencies of the lectin pathway have protective effects against stroke and ischaemic-reperfusion injury in mouse and human (145–148). For example, a prospective cohort study found mannose-binding lectin deficiency was associated with smaller cerebral infarcts and better outcomes following ischaemic stroke (147). Extrapolating from this, one could argue mannose-binding lectin deficiency could potentially reduce the risk of post-stroke VaD.

Finally, a positive complement-platelet activation loop exists, whereby activated platelets release complement components that promote vascular inflammation, atheroma formation and activate further platelets, which exacerbates complement activation (149–154). Future studies could investigate whether this activation loop has a role in the mechanism behind cerebrovascular inflammation and the disruption of the blood-brain barrier in VaD. Much remains to be uncovered about the crosstalk between the complement and coagulation systems in the pathogenesis, prevention, and treatment of VaD.

CONCLUSION AND FUTURE PERSPECTIVES

VaD is a complex neurocognitive disorder with major impact on quality of life. There is still much to learn about this disease, one of which being the role of complement and coagulation systems in the underlying mechanisms, along with crosstalk between these systems which could provide novel therapeutic targets to improve patient outcomes, fulfilling the urgent need for effective treatment strategies. Measuring serum markers of activated complement and coagulation components could also be useful for the identification of individuals at risk of cognitive decline and track dementia progression.

The link between complement, coagulation, crosstalk and VaD in this review highlights possible areas for future research that remain to be fully explored. i) What is the mechanistic link between coagulation components FVIII, FVIIa, fibrinogen, thrombin-antithrombin complex, D-dimer, tissue-type plasminogen activator, plasminogen activator inhibitor-1, von Willebrand factor and VaD? ii) What is the role of the inflammatory markers vascular cellular adhesion molecule-1, C-reactive protein, and interleukin-6 in cognitive decline? iii) Are C3a and C5a involved in white matter injury in humans? iv) Can prekallikrein inhibition reduce the risk of stroke and VaD in humans? v) What is the extent of crosstalk between all these components and how does this lead to VaD development?

Over and under activation of the complement and coagulation systems have been recognised to play a part in various diseases such as Alzheimer's disease, multiple sclerosis, atypical haemolytic uremic syndrome, and antiphospholipid syndrome (94, 101). Therefore, the potential role of these systems in VaD should be considered. Current studies have already suggested a link between blood hypercoagulability and cognitive decline in dementia, however the statistical power of these studies is still not great enough to confirm without a doubt that the haemostatic system is part of the pathological mechanisms that lead to VaD (113). The limited data on complement and VaD emphasise the need for further research into complement components and how these could potentially be involved in driving the process of hypoxia, oxidative stress and inflammation that result in cerebral infarction. Another problem that still needs addressing is the lack of an internationally recognised standard of VaD neuropathological criteria to enable direct comparison and analysis of research (2). It is currently difficult to compare the results of studies due to varying selection criteria for patients, which means that patients that are eligible in one study are not recognised as VaD patients in another study due to differing diagnostic criteria.

AUTHOR CONTRIBUTIONS

MMP sourced and analysed the literature and wrote the first draft of the review. CD and RA critically reviewed the literature analysis and helped developing the manuscript. All authors contributed to the writing of this manuscript and approved the final version.

FUNDING

The RA lab is funded by a British Heart Foundation (BHF) Programme Grant (Grant RG/13/3/30104, renewal RG/18/11/34036) and a Welcome Trust Investigator Award (204951/B/16/Z).

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frontiers in Cardiovascular Medicine

SYSTEMATIC REVIEW
published: 04 March 2022
doi: 10.3389/fcvm.2022.841341

Direct Oral Anticoagulants vs. Warfarin in Latin American Patients With Atrial Fibrillation: Evidence From Four *post-hoc* Analyses of Randomized Clinical Trials

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OPEN ACCESS

Edited by:
Antonino Tuttolomondo,
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Reviewed by:
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Specialty section:
This article was submitted to Thrombosis, a section of the journal Frontiers in Cardiovascular Medicine

Received: 22 December 2021
Accepted: 08 February 2022
Published: 04 March 2022

Citation:
Liu F, Wang Y, Luo J, Huang L, Zhu W, Yin K and Xue Z (2022) Direct Oral Anticoagulants vs. Warfarin in Latin American Patients With Atrial Fibrillation: Evidence From Four post-hoc Analyses of Randomized Clinical Trials. Front. Cardiovasc. Med. 9:841341. doi: 10.3389/fcvm.2022.841341

Background: Several studies have investigated the effect of direct oral anticoagulants (DOACs) in Latin American patients with atrial fibrillation (AF), but the results remain controversial. Therefore, we aimed to compare the efficacy and safety of DOACs vs. warfarin in Latin American patients with AF.

Methods: We systematically searched the PubMed and Embase databases until November 2021 for studies that compared the effect of DOACs vs. warfarin in Latin patients with AF. Adjusted hazard ratios (HRs) and 95% CIs were pooled by a random-effects model using an inverse variance method.

Results: Four *post-hoc* analyses of randomized clinical trials (RCTs) involving 42,411 DOACs and 29,270 warfarin users were included. In Latin American patients with AF, for the effectiveness outcomes, the use of DOACs compared with warfarin was significantly associated with decreased risks of stroke or systemic embolism (SSE) (HR = 0.78; 95%CI.64–0.96), stroke (HR = 0.75; 95%CI.57–0.99), hemorrhagic stroke (HR = 0.14; 95%CI.05–0.36), all-cause death (HR = 0.89; 95% CI.80–1.00), but not ischemic stroke and cardiovascular death. For the safety outcomes, compared with warfarin, the use of DOACs was associated with reduced risks of major or non-major clinically relevant (NMCR) bleeding (HR = 0.70; 95% CI.57–0.86), major bleeding (HR = 0.70; 95%CI.53–0.92), intracranial hemorrhage (ICH) (HR = 0.42; 95%CI.24–0.74), or any bleeding (HR = 0.70;95% CI.62–0.78), but not gastrointestinal bleeding. In non-Latin American patients with AF, for the effectiveness outcomes, the use of DOACs compared with warfarin was significantly associated with decreased risks of SSE (HR = 0.87; 95%CI.75–1.00), hemorrhagic stroke (HR = 0.41; 95%CI.28–0.60), cardiovascular death (HR = 0.87; 95% CI.81–0.94), all-cause death (HR = 0.90; 95% CI.85–0.94). Conversely, the risk of myocardial infarction increased (HR = 1.34; 95% CI 1.13–1.60), but not ischemic stroke. For the safety outcomes, compared with warfarin, the use of DOACs was associated with reduced risks of major or NMCR bleeding (HR = 0.75; 95%CI.61–0.92), major bleeding

(HR = 0.76; 95%CI.63–0.92), ICH (HR = 0.42; 95%CI.36–0.52), and any bleeding (HR = 0.81; 95% CI.71–0.92), but not gastrointestinal bleeding.

Conclusion: Current pooled data from the four *post-hoc* analyses of RCTs suggested that compared with warfarin, DOACs appeared to have significant reductions in SSE, stroke, hemorrhagic stroke, all-cause death, major or NMCR bleeding, major bleeding, ICH, and any bleeding, but comparable risks of ischemic stroke, cardiovascular death, and gastrointestinal bleeding in Latin American patients with AF. DOACs appeared to have significant reductions in SSE, hemorrhagic stroke, all-cause death, cardiovascular death, major or NMCR bleeding, major bleeding, ICH, and any bleeding, and increased the risk of myocardial infarction, but comparable risks of stroke, ischemic stroke, and gastrointestinal bleeding in non-Latin American patients with AF.

Keywords: atrial fibrillation, direct oral anticoagulants, warfarin, Latin American, meta-analysis

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in adults. The currently estimated prevalence of AF in adults ranges from 2 to 4%, and a 2.3-fold rise is expected due to the longevity in the general population and the increased screening of patients with previously undiagnosed AF (1). Advanced age is widely regarded as a foremost risk factor, but increasing burden of other comorbidities including hypertension, diabetes mellitus, heart failure, coronary artery disease, chronic kidney disease, obesity, and obstructive sleep apnea also contributes to the higher prevalence of AF. Not only that, many modifiable risk factors are potent contributors to AF development and progression (2). Many cardiovascular and cerebrovascular complications, such as 5-fold rise in stroke and 2 times the risk of mortality, are prevalently screened in patients with AF (3). AF-associated thromboembolic events are lead contributors for the poor prognosis in patients with AF, which involves higher morbidity and mortality (4, 5). Antithrombotic therapy effectively reduces the incidence of embolism in patients with AF. Direct oral anticoagulants (DOACs) have superior effectiveness and safety outcome for the prevention of stroke and thromboembolic events in patients with AF (6). DOACs are recommended as preferred alternatives to warfarin in the American College of Cardiology and/or American Heart Association/Heart Rhythm Society (7) and European Society of Cardiology guidelines (8) due to its superior characteristics in effectiveness, safety, and convenience, especially for elderly patients with acute coronary syndrome or chronic kidney disease (9, 10). Important differences in clinical characteristics, response to treatment, and outcomes of patients with AF distribute to the diverse regions of the world. In Latin America, AF is regarded as a considerable cause of high mortality and disability (11). Although prevalence data is limited, the incidence of AF-related stroke and associated morbidity is increasing in this region (12), and anticoagulation is underused (13). Therefore, patients with AF in Latin America undergo higher risk of death and thromboembolic events due to the aging population and poorly managed risk factors of AF, such as hypertension, diabetes, heart failure, etc. The anticoagulant treatment of patients with AF is particularly significant in Latin America.

Several previously published studies demonstrated that patients with AF in Latin America treated with warfarin had higher adjusted mortality rates and incidence of stroke and/or systemic embolism, intracranial hemorrhage, and life-threatening or fatal bleeding compared with patients with AF in the rest of the world (ROW) (14). Data regarding the effectiveness and safety outcome of anticoagulation regimens in this region is insufficient. Although several new *post-hoc* analyses of randomized clinical trials (RCTs) well-examined the association between regions (Latin America vs. non-Latin America) and effectiveness and safety outcomes, even explored the use of individual DOACs compared with warfarin in Latin American patients, the superiority of DOACs therapy is still controversial. Although, a previous meta-analysis included the *post-hoc* analyses and sub-analyses of DOACs, RCTs identified a non-inferiority of DOACs compared with warfarin in Latin American patients with AF (15). However, the RCTs included in this meta-analysis are outdated. New RCTs have been published in recent years and report more endpoint events and even find different results. Therefore, we aimed to reassess the effectiveness and safety outcomes of DOACs vs. warfarin in Latin American and non-Latin American patients with AF.

METHODS

Literature Retrieval

The two common databases of PubMed and Embase were systematically searched until November 2021 for the available studies using the following search terms: (1) atrial fibrillation (2) non-vitamin K antagonist oral anticoagulants OR direct oral anticoagulants OR dabigatran OR rivaroxaban OR apixaban OR edoxaban, and (3) vitamin K antagonists OR warfarin. The detailed search strategies are shown in **Supplementary Table 1**. In this meta-analysis, we included publications in English.

Inclusion and Exclusion Criteria

We included the *post-hoc* analyses of RCTs focusing on the effectiveness and/or safety of DOACs (dabigatran, rivaroxaban,

apixaban, or edoxaban) compared with warfarin in Latin American patients with non-valvular AF. The effectiveness outcomes included stroke or systemic embolism (SSE), stroke, ischemic stroke, hemorrhagic stroke, ischemic stroke, all-cause death, cardiovascular death, and myocardial infarction; whereas the safety outcomes included major bleeding, major or non-major clinically relevant (NMCR) bleeding, intracranial hemorrhage (ICH), gastrointestinal bleeding, and any bleeding. The follow-up time was not restricted. We excluded certain publication types such as reviews, case reports, case series, editorials, letters, and meeting abstracts because they had no sufficient data. Studies with overlapping data were also excluded.

Study Screenings and Data Extraction

Two authors (FW-L and YH-W) independently did the data extraction. We first screened the titles and abstracts of the searched records to select potential studies, and the full text of which was screened in the subsequent phase. Disagreements were resolved through discussion or consultation with the third researcher (WG-Z). Two authors independently collected the following characteristics: the first author and publication year, location, data source, study design, inclusion period, patient age and sex, type or dose of DOACs, follow-up time, effectiveness and safety outcomes, the sample size, and the number of events in the vitamin K antagonist (VKA) or DOAC groups, and adjusted hazard ratios (HRs) and 95% CIs.

Quality Assessment

We used the Newcastle-Ottawa Scale (NOS) to perform the quality assessment for the included studies. The NOS tool had three domains, scored a total of 9 points including the selection of cohorts (4 points), the comparability of cohorts (2 points), and the assessment of the outcome (3 points). In this study, we defined studies with the NOS of < 6 points as low quality (16).

Statistical Analysis

We assessed the consistency across the included studies using the Cochrane Q test and the I^2 statistic. A $P < 0.1$ for the Q statistic or $I^2 \geq 50\%$ indicated substantial heterogeneity. We first collected the sample size and the number of events in the warfarin or DOAC groups and calculated their corresponding crude rates of effectiveness and safety outcomes. The comparison results between the warfarin or DOAC groups were expressed as HRs and 95%CIs. Second, we assessed the effectiveness and safety of DOACs vs. warfarin in patients with AF using the adjusted HRs. The adjusted HRs and 95%CIs were converted to the natural logarithms (Ln[HR]) and standard errors, which were pooled by a random-effects model using an inverse variance method.

All statistical analyses were conducted using the Review Manager Version 5.4 (the Nordic Cochrane Center, Rigshospitalet, Denmark). The statistical significance threshold was set at a $P < 0.05$.

RESULTS

The process of the literature retrieval is presented in **Supplementary Figure 1**. A total of 170 studies were identified through the electronic searches in the PubMed and Embase databases. According to the predefined criteria, we finally included 4 studies in this meta-analysis (14, 17–19). **Table 1** shows the baseline patient characteristics of the included studies. All include studies are *hoc* RCT and the data sources are from effective anticoagulation with factor Xa next generation atrial fibrillation–thrombolysis in myocardial infarction 48 (ENGAGE AF-TIMI 48) (14), apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation trial (ARISTOTLE TRIAL) (17), rivaroxaban once daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF trial) (18), and randomized evaluation of long-term anticoagulant therapy (RE-LY) (19). Latin American includes Argentina Brazil, Chile, Colombia, Mexico, Peru, and Venezuela, and all the remaining countries included in the entire trial were considered to be non-LA countries. In total, 8,965 Latin American patients (5,096 taking DOACs and 3,869 taking warfarin) and 62,716 non-Latin American patients (37,315 taking DOACs and 25,401 taking warfarin) were included in this meta-analysis. All of these included studies had a moderate-to-high quality with the NOS score of $\geq$6 points.

Crude Event Rates Between DOACs vs. Warfarin

In Latin American patients with AF, for the effectiveness outcomes shown in **Supplementary Figure 2**, the use of DOACs compared with warfarin was significantly associated with decreased risks of SSE [odds ratio (OR) = 0.79; 95% CI.64–0.99] and hemorrhagic stroke (OR = 0.13; 95% CI.05–0.33), but not stroke (OR = 0.76; 95% CI.54–1.07), ischemic stroke (OR = 1.19; 95% CI.80–1.78), all-cause death (OR = 0.91; 95%CI.78–1.07), and cardiovascular death (OR = 1.00; 95%CI.61–1.67). For the safety outcomes in **Supplementary Figure 3**, compared with warfarin, the use of DOACs was associated with reduced risks of major or NMCR bleeding (OR = 0.72; 95%CI.56–0.94), major bleeding (OR = 0.72; 95% CI.53–0.98), ICH (OR = 0.43; 95% CI.21–0.88), and any bleeding (OR = 0.66; 95% CI.57–0.78), but not gastrointestinal bleeding (OR = 0.65; 95% CI.10–3.99).

For patients treated with anticoagulants in non-Latin American patients with AF, for the effectiveness outcomes in **Supplementary Figure 4**, the use of DOACs compared with warfarin use was significantly associated with decreased risks of SSE (OR = 0.87; 95% CI.76–1.00), hemorrhagic stroke (OR = 0.41; 95% CI.25–0.67), all-cause death (OR = 0.89; 95% CI.84–0.95), cardiovascular death (OR = 0.87; 95% CI.79–0.95), but not stroke (OR = 0.92; 95%CI.69–1.22), ischemic stroke (OR = 1.08; 95% CI.82–1.42). For the safety outcomes in **Supplementary Figure 5**, compared with warfarin use, the use of DOACs was associated with reduced risks of major bleeding (OR = 0.77; 95% CI.62–0.95), ICH (OR = 0.43; 95%CI.35–0.53), and any bleeding (OR = 0.62; 95% CI.43–0.88), but not major or NMCR bleeding (OR = 0.80; 95%CI.61–1.04) and gastrointestinal bleeding (OR = 0.90; 95%CI.78–1.04).

TABLE 1 | Clinical characteristics of the included studies.

	Avezum-2018		Corbalán-2018		Bahit-2020		Blumer-2021	
	Latin American	**Non-Latin American**	**Latin American**	**Non-Latin American**	**Latin American**	**Non-Latin American**	**Latin American**	**Non-Latin American**
Study design	*Post-hoc* analysis of RCT		*Post-hoc* analysis of RCT		*Post-hoc* analysis of RCT		*Post-hoc* analysis of RCT	
Date source	RE-LY		ENGAGE AF-TIMI 48		ARISTOTLE TRIAL		ROCKET AF trial	
DOACs	dabigatran		edoxaban		apixaban		rivaroxaban	
Efficacy outcomes	SSE Stroke Ischemic stroke Haemorrhagic stroke Myocardial infarction Death from any cause		SSE Stroke Ischemic stroke All cause death Cardiovascular death		SSE All cause death		SSE All cause death	
Safety outcomes	Life-threatening bleeding Total bleeding Major bleeding Intracranial hemorrhage Gastrointestinal bleeding Minor bleeding Any bleeding		Major bleeding Major or NMCR bleeding Intracranial hemorrhage Gastrointestinal bleeding, Any bleeding		Major bleeding Major or NMCR bleeding Intracranial hemorrhage		Major bleeding, Major or NMCR bleeding Intracranial hemorrhage	
Region	Argentina Brazil Colombia Mexico Peru	All remaining countries included in the entire trial were considered to be non-LA countries	Argentina Brazil Chile Colombia Guatemala Mexico Peru	NA	Argentina, Brazil Chile Colombia Puerto Rico Mexico	North America (USA, Canada) Europe (Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Netherlands, Norway, Poland, Romania, Spain, South Africa, Sweden, Turkey, United Kingdom, Ukraine) Asia Pacific (Australia, China, Hong Kong, India, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan	Argentina Brazil Chile Colombia Mexico Peru Venezuela	rest of the world
Age (years)	71.6	71.5	71.4	70.5	71	69.7	75	72
Sex (% female)	-	-	40.6	30.3	38.6	34.5	42	39
No. of AF patients	956	17,157	2,661	18,444	3,486	14,733	1,878	12,386
BMI	-	-	-	-	29	-	27.8	28.3
Pattern of atrial fibrillation (%)								
Persistent	70.7	33.2	85.2	73	91.5	83.1	91	79
Paroxysmal	-	-	14.8	27	8.5	16.9	8	19
New onset/newly diagnosed	-	-	-	-	-	-	1	2
CHADS2 score	2.2	2.1	2.9	2.8	2.1	2.1	3.6	3.5
CHA2DS2-VASc score	3.5	3.6	4.2	4.3	-	-	3.6	3.5

(Continued)

TABLE 1 | Continued

	Avezum-2018		Corbalán-2018		Bahit-2020		Blumer-2021	
	Latin American	**Non-Latin American**	**Latin American**	**Non-Latin American**	**Latin American**	**Non-Latin American**	**Latin American**	**Non-Latin American**
Comorbidities (%)								
Prior stroke, TIA, or non-CNS embolism	11.5	12.6	29.8	28.1	13.8	17.1	56	55
Carotid or peripheral artery disease	-	-	-	-	-	-	7	9
Hypertension	82.3	78.7	95.2	93.4	89.1	87.1	93	90
Diabetes	-	-	28.5	37.2	-	-	39	40
Prior MI	-	-	6.4	12.3	9.8	15.2	11	18
CHF	41.1	31.5	63.4	56.6	38.3	34.8	60	63
COPD	-	-	-	-	-		7	11
Medications (%)								
Prior VKA use	44.0	63.0	48.0	60.5	45.8	42.1	61	63
Prior chronic aspirin use	48.4	39.1	-	-	33.0	30.4	38	36
ACE inhibitor/ARB	55.9	44.2			-	-	75	74
Beta-blocker	-	-	59.9	67.2	56.2	64.9	56	66
Renin, angiotensin, or aldosterone inhibitor	-	-	72.7	64.9	-	-	-	-
Calcium-channel blockers	-	-	18.4	33.0	-	-	-	-
Lipid lowering	-	-	28.3	50.6	-	-		
Diuretic agents	-	-	36.7	29	-	-	6.1	59
Digitalis	-	-	36.7	29	-	-	42	38
Amiodarone			19.5	10.7	-		14	7
Follow-up (year)	2.0		2.8		1.8		1.9	
Quality assessment	NOS = 9 points		NOS = 9 points		NOS = 9 points		NOS = 8 points	

AF, atrial fibrillation; RCT, Randomized Controlled Trial; BMI, body mass index; EAST-AFNET 4, Early Treatment of Atrial Fibrillation for Stroke Prevention Trial; RE-LY, Randomized Evaluation of Long-Term Anticoagulant Therapy; ARISTOTLE TRIAL, Apixaban for reduction in stroke and other ThromboembоLic events in atrial fibrillation (ARISTOTLE) trial; ROCKET AF trial, (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; SSE, stroke or systemic embolism; major or NMCR bleeding, major or non-major clinically relevant (NMCR) bleeding; CNS, central nervous system; BMI, body mass index; CHF, congestive Heart failure; MI, myocardial infarction; TIA, transient ischemic attack; VKA, vitamin K antagonist; COPD, chronic obstructive pulmonary disease; CHA2DS2-VASc, congestive heart failure/left ventricular ejection fraction ≤40%, hypertension, age ≥ 75 years (2 points), diabetes mellitus, prior stroke/transient ischemic attack/thromboembolism (2 points), vascular disease, age 65–74 years, female sex; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; NOS, Newcastle-Ottawa Scale.

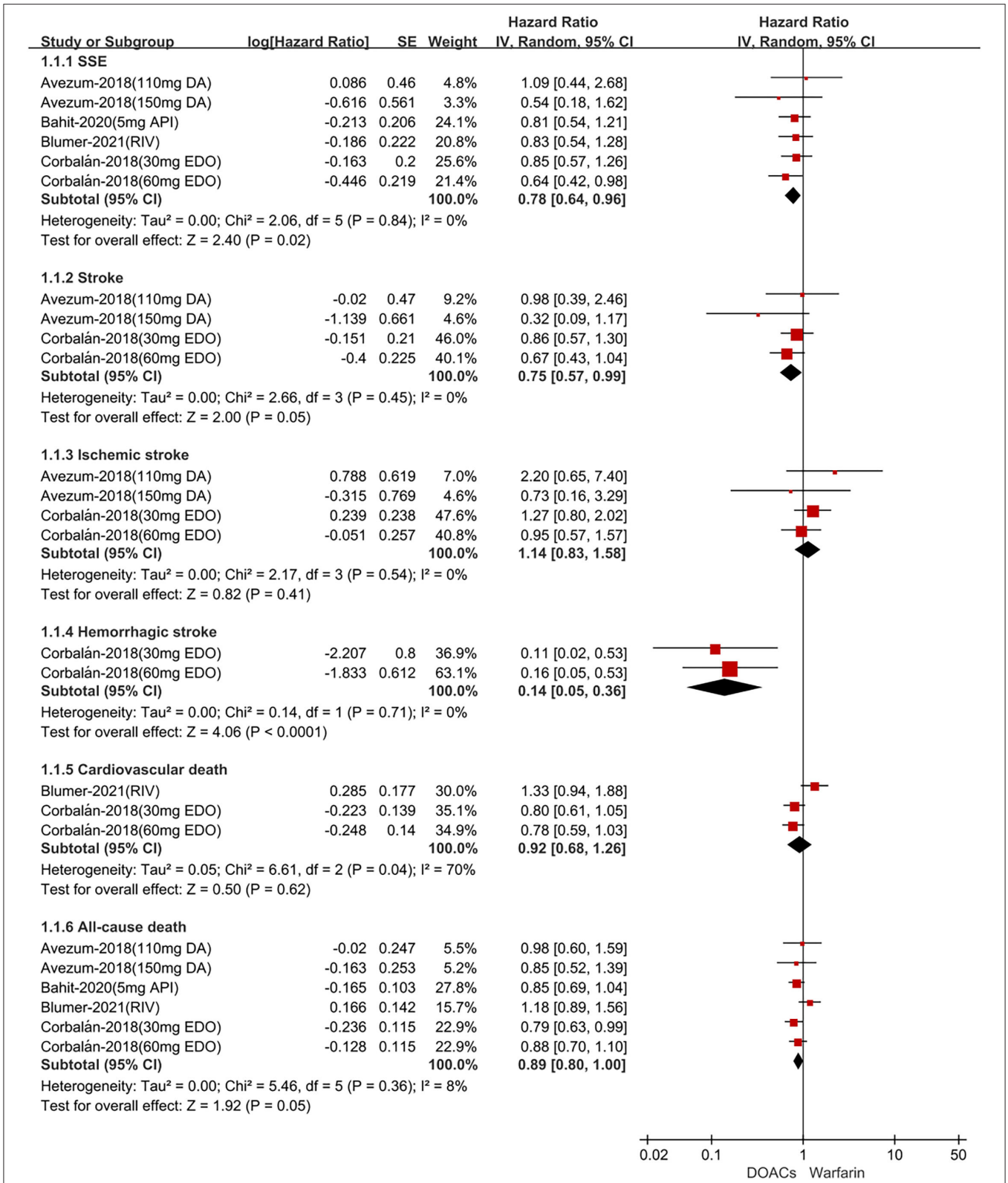

FIGURE 1 | Adjusted effectiveness date of direct oral anticoagulants compared with warfarin in Latin patients with atrial fibrillation. DOACs, direct oral anticoagulants; DA, dabigatran; API, apixaban; EDO, edoxaban; RIV, rivaroxaban; SSE, stroke or systemic embolism; CI, confidence interval.

Adjusted Data of Outcomes Between DOACs vs. Warfarin

In Latin American patients with AF, for the effectiveness outcomes shown in **Figure 1**, the use of DOACs compared with warfarin was significantly associated with decreased risks of SSE (HR = 0.78; 95% CI.64–0.96), stroke (HR = 0.75; 95%CI.57–0.99), hemorrhagic stroke (HR = 0.14;95%CI.05–0.36), all-cause death (HR = 0.89; 95%CI.80–1.00), but not ischemic stroke (HR = 1.14; 95%CI.83–1.58) and cardiovascular death (HR = 0.92; 95%CI.68–1.26). For the safety outcomes in **Figure 2**,

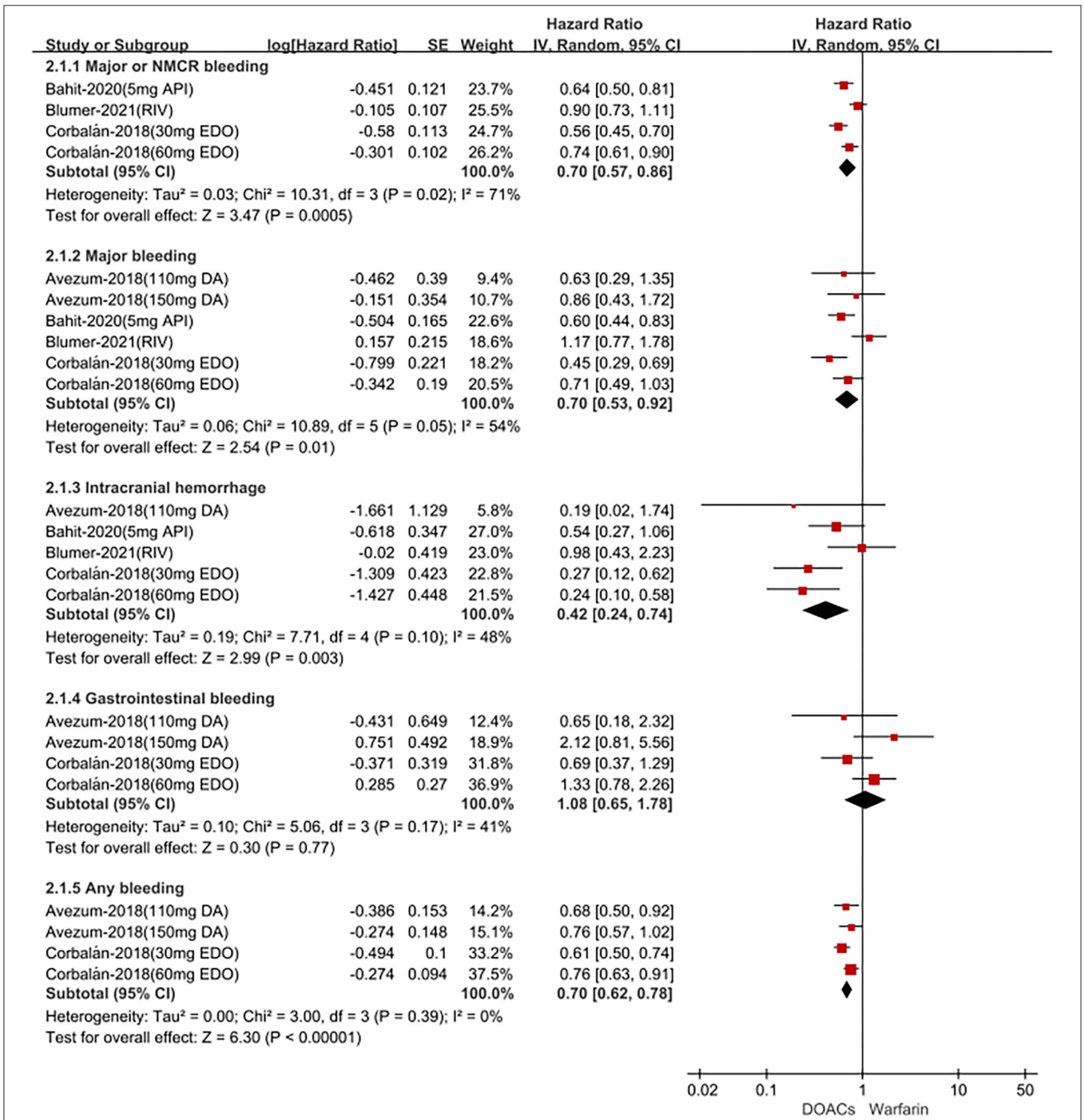

FIGURE 2 | Adjusted safety date of direct oral anticoagulants compared with warfarin in Latin patients with atrial fibrillation. DOACs, direct oral anticoagulants; DA, dabigatran; API, apixaban; EDO, edoxaban; RIV, rivaroxaban; CI, confidence interval.

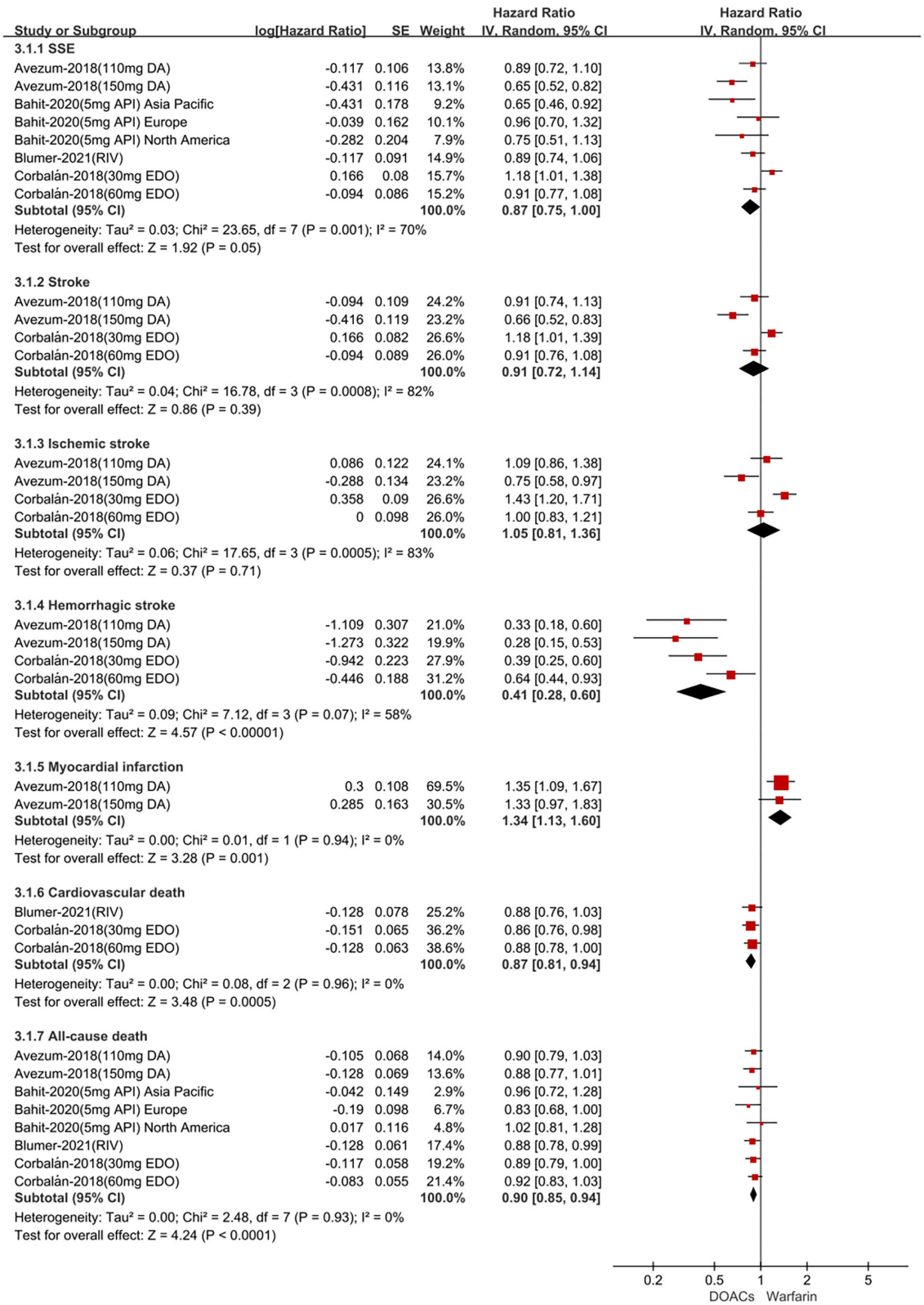

FIGURE 3 | Adjusted effectiveness date of direct oral anticoagulants compared with warfarin in non-Latin patients with atrial fibrillation. DOACs, direct oral anticoagulants; DA, dabigatran; API, apixaban; EDO, edoxaban; RIV, rivaroxaban; SSE, stroke or systemic embolism; CI, confidence interval.

compared with warfarin, the use of DOACs was associated with reduced risks of major or NMCR bleeding (HR = 0.70; 95%CI.57–0.86), major bleeding (HR = 0.70; 95%CI.53–0.92), ICH (HR = 0.42; 95% CI.24–0.74), and any bleeding (HR = 0.70; 95%CI.62–0.78), but not gastrointestinal bleeding (HR = 1.08; 95% CI.65–1.78).

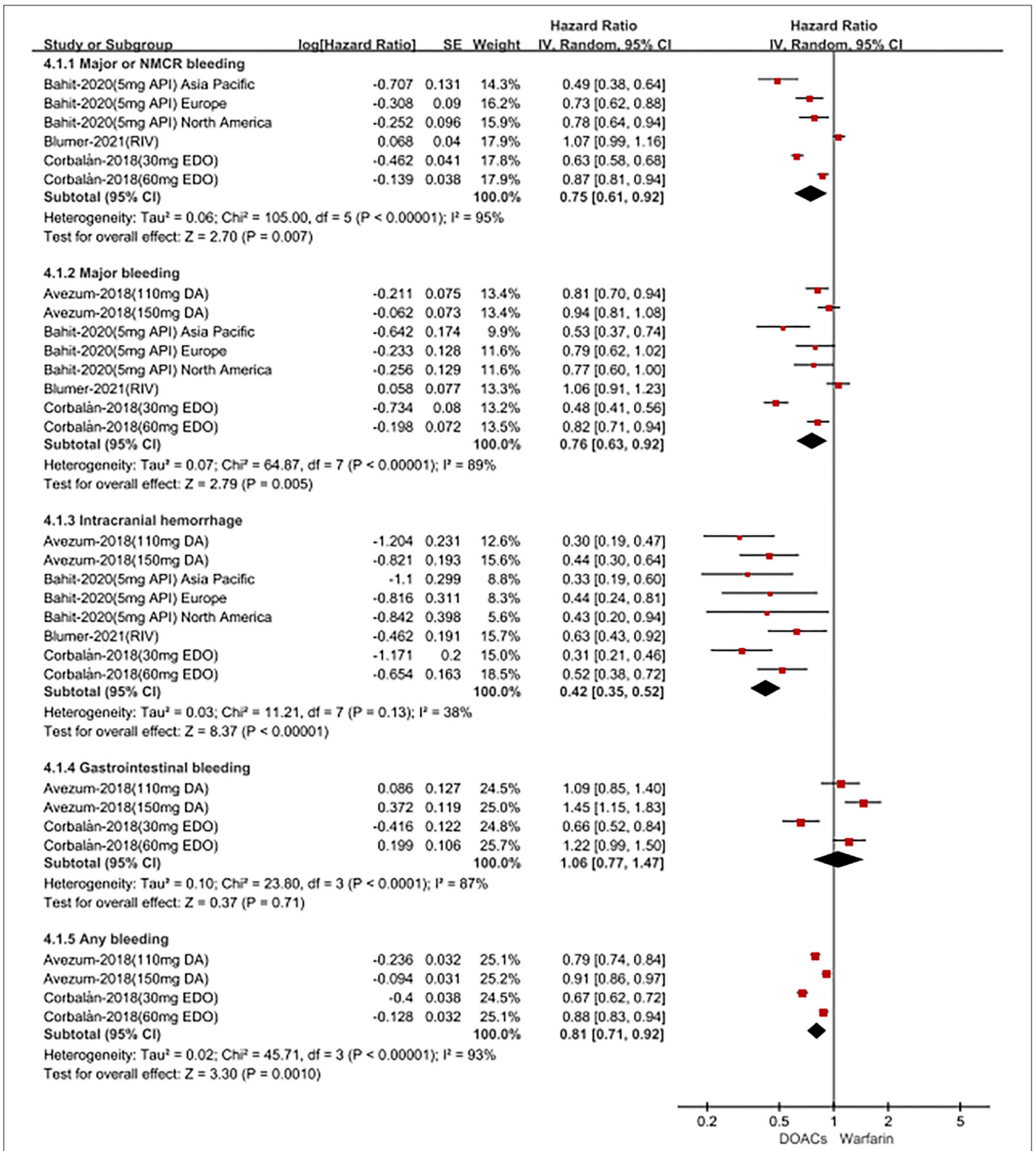

FIGURE 4 | Adjusted safety date of direct oral anticoagulants compared with warfarin in non-Latin patients with atrial fibrillation. DOACs, direct oral anticoagulants; DA, dabigatran; API, apixaban; EDO, edoxaban; RIV, rivaroxaban; CI, confidence interval.

For patients treated with anticoagulants in non-Latin American patients with AF, for the effectiveness outcomes in **Figure 3**, the use of DOACs compared with warfarin was significantly associated with decreased risks of SSE (HR = 0.87; 95%CI.75–1.00), hemorrhagic stroke (HR = 0.41; 95%CI.28–0.60), cardiovascular death (HR = 0.87; 95% CI.81–0.94), all-cause death (HR = 0.90; 95%CI.85–0.94), conversely, increasing the risk of myocardial infarction (HR = 1.34; 95%CI 1.13–1.60), but not stroke (HR = 0.91; 95%CI.72–1.14) and ischemic stroke (HR = 1.05; 95% CI.81–1.36). For the safety outcomes in **Figure 4**, compared with warfarin use, the use of DOACs was associated with reduced risks of major or NMCR bleeding (HR = 0.75; 95% CI.61–0.92), major bleeding (HR = 0.76; 95%CI.63–0.92), ICH (HR = 0.42; 95% CI.36–0.52) and any bleeding (HR = 0.81; 95%CI.71–0.92), but not gastrointestinal bleeding (HR = 1.06; 95%CI.77–1.47). Not only that, we also conducted a summary analysis of the adjusted data of outcomes between Latin American patients and non-Latin American patients in **Figure 5**. The *P*-interaction between Latin American patients and non-Latin American patients with AF was no significant difference.

Publication Bias

We have not performed an analysis of publication bias due to only 4 studies were included in our meta-analysis. It was noted that the publication bias should not be evaluated for some reported outcomes when fewer than 10 studies were included.

DISCUSSION

The main findings of our study were as follows: (1) DOAC use resulted in lower rates of SSE, stroke, hemorrhagic stroke, all-cause death, and associated with safer profiles (lower major or NMCR bleeding, major bleeding, ICH, and any bleeding) than warfarin in Latin American patients with AF; (2) DOAC use resulted in lower rates of SSE, hemorrhagic stroke, all-cause death, cardiovascular death, and associated with safer profiles (lower major or NMCR bleeding, major bleeding, ICH, and any bleeding) than warfarin in non-Latin American patients with AF; (3) DOAC use increased the risk of myocardial infarction than warfarin in non-Latin American patients with AF, but not in Latin American patients with AF; (4) in comparison to VKAs, DOACs were non-inferior regarding the outcomes of ischemic stroke, cardiovascular death, and gastrointestinal bleeding in Latin American patients with AF and the outcomes of stroke, ischemic stroke, and gastrointestinal bleeding in non- Latin American patients.

Important differences in clinical characteristics, response to treatment, and outcomes of patients with AF exist in the diverse regions of the world. Previous studies have shown that Latin American patients with AF are suffering from higher risks of death and embolism than non-Latin American patients with AF (20, 21). Actually, there are many reasons for the increased risk of death and embolism in Latin American patients with AF. Life expectancy differed substantially across cities within the same country. Cause-specific mortality also varied across cities, with some causes of death (unintentional and violent injuries and deaths) showing large variation within countries, whereas other causes of death (communicable, maternal, neonatal and nutritional, cancer, cardiovascular disease, and other non-communicable diseases) varied substantially between countries. These results highlight considerable heterogeneity in life expectancy and causes of death across cities of Latin America (22). Moreover, heterogeneity of risk factors (23–25) and socioeconomic conditions, public awareness, and availability of healthcare services that influence outcomes of diseases differ substantially between countries (26, 27) in Latin America and still need to be taken into account. Furthermore, inadequate prescription for medications associated with death reduction might also affect the prognosis of Latin American patients with AF (14). Therefore, antithrombotic therapy is particularly important to reduce the risk of embolism in Latin American patients with AF. Previous meta-analyses including the *post-hoc* analyses and sub-analyses of DOAC RCTs showed that there is a non-inferiority of DOACs compared with warfarin in Latin American patients with AF (15). Compared to the previous study, the RCTs included in this meta-analysis are outdated. More importantly, the number of available clinical studies are small and the results are controversial. In recent years, several new *post-hoc* analyses of RCTs not only examined the association between region and efficacy and safety outcomes but also explored the use of individual DOACs compared with warfarin in Latin American patients. The RCTs provide more endpoint events and arrive at different conclusions. Therefore, we aimed to reassess the effectiveness and safety outcomes of DOACs vs. warfarin in Latin American and non-Latin American patients with AF. Our meta-analysis shows that DOACs appeared to have significant reductions in SSE, stroke, hemorrhagic stroke, all-cause death, major or NMCR bleeding, major bleeding, ICH, and any bleeding, but showed comparable rates of ischemic stroke, cardiovascular death, and gastrointestinal bleeding in Latin American patients with AF. DOACs appeared to have significant reductions in SSE, hemorrhagic stroke, all-cause death, cardiovascular death, major or NMCR bleeding, major bleeding, ICH, and any bleeding and increased the risk of myocardial infarction, but comparable risks of stroke, ischemic stroke, and gastrointestinal bleeding in non-Latin American patients with AF. In addition, we assessed crude event rates of outcomes between DOACs vs. warfarin in Latin/non-Latin American patients with AF. Overall, in comparison to warfarin, DOACs had lower or similar rates of thromboembolic and bleeding risk, which was consistent with a previous study (15). Interestingly, we found that DOACs increased the risk of myocardial infarction compared with warfarin in non-Latin American patients with AF. The result was derived from the RE-LY study, which included patients using dabigatran. Previous studies have warned this risk (28, 29). Prospective data on dabigatran in this population undergoing PCI are still needed.

It is worth pointing out that DOACs have advantages over warfarin such as short onset time, short half-life, low inter- and intra-individual variability, and drug-drug interactions. The current international guidelines recommend the use of DOACs as replacement therapy for VKAs in patients with non-valvular AF because it has more effective, safer, and more convenient features. Different from DOACs, the anticoagulant activity of

Subgroup	NO.of patients	DOACs NO.of events (%)	Warfarin	Pooled HR (95% CI)	I^2 value	P-value	P-interaction
SSE							
LA	8965	117(3.47)	159(4.11)	0.78 (0.64-0.96)	0%	0.02	0.43
NLA	62716	1282(3.43)	951(3.74)	0.87 (0.75-1.00)	70%	0.43	
Stroke							
LA	3617	888(3.65)	57(4.73)	0.75 (0.57-0.99)	0%	0.05	0.31
NLA	35601	846(3.56)	446(3.76)	0.91(0.72-1.14)	82%	0.39	
Ischemic stroke							
LA	3617	83(3.43)	35(2.90)	1.14 (0.83-1.58)	0%	0.41	0.69
NLA	35601	741(3.12)	334(2.81)	1.05(0.81-1.36)	83%	0.71	
Hemorrhagic stroke							
LA	3617	5(0.20)	21(1.74)	0.14(0.05-0.36)	0%	0.0001	0.04
NLA	35601	100(0.42)	114(0.96)	0.41(0.28-0.60)	58%	0.00001	
Myocardial infarction							
LA	636	2(0.62)	2(0.63)	0.97(0.14-6.90)			0.74
NLA	17157	174(1.52)	64(1.12)	1.34(1.13-1.60)	0%	0.001	
All-cause death							
LA	8965	621(12.18)	489(12.63)	0.89 (0.80-1.00)	8%	0.05	0.94
NLA	62716	2958(7.92)	2138(8.41)	0.90 (0.85-0.94)	0%	0.001	
Cardiovascular death							
LA	4541	267(9.84)	176(9.62)	0.92 (0.68-1.26)	70%	0.62	0.73
NLA	30826	1165(6.30)	836(6.77)	0.87(0.81-0.94)	0%	0.0005	
Major or NMCR bleeding							
LA	8943	579(12.99)	739(12.47)	0.70 (0.57-0.86)	71%	0.0005	0.64
NLA	45558	4198(16.23)	3515(17.84)	0.75 (0.61-0.92)	95%	0.007	
Major bleeding							
LA	8965	211(4.14)	219(5.44)	0.70(0.53-0.92)	0.54	0.01	0.62
NLA	62716	769(2.06)	905(3.56)	0.76(0.63-0.92)	89%	0.0005	
Intracranial hemorrhage							
LA	8965	38(0.74)	65(1.68)	0.42 (0.24-0.74)	48%	0.003	0.97
NLA	62716	236(0.63)	363(1.43)	0.42 (0.35-0.52)	38%	<0.00001	
Gastrointestinal bleeding							
LA	3617	30(1.24)	29(2.40)	1.08 (0.65-1.78)	41%	0.77	0.96
NLA	35601	516(2.17)	285(2.40)	1.06(0.77-1.47)	87%	0.71	
Any bleeding							
LA	3617	536(22.21)	362(30.06)	0.70 (0.62-0.78)	0%	0.00001	0.08
NLA	35601	5577(23.48)	3918(33.05)	0.81(0.71-0.92)	93%	0.001	

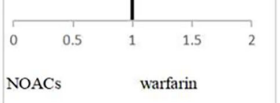

FIGURE 5 | Efficacy and safety outcomes in AF patients from Latin American and non-Latin American. SSE, stroke or systemic embolism; CI, confidence interval; HR, hazard ratio; LA, Latin American; NLA, non-Latin American; CI, confidence interval; major or NMCR bleeding, major or non-major clinically relevant bleeding.

VKAs depends on TTR (time in therapeutic range). Among the included studies, the mean TTR of VKAs users in Latin America ranged from 58 to 66%, which was not higher than that of non-Latin Americans overall and lower than what is recommended in the guidelines (1, 30). Therefore, DOACs may be regarded as a safer alternative to VKAs in Latin American patients with AF. Although no observational studies have been carried out to directly compare the use of DOACs and warfarin in Latin American patients with AF, several studies have validated the benefits of the use of DOACs in this population. Data from the GLORIA-AF (Global Registry on Long-Term Antithrombotic Treatment in Patients with Atrial Fibrillation, Phase II) study indicated the consistent safety and effectiveness of dabigatran in Latin American patients with AF during a 2-years follow-up (31). Moreover, the XANTUS-EL (Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation in Eastern Europe, the Middle East and Africa [EEMEA], and Latin America) study confirmed the benefits of rivaroxaban for stroke prevention in patients with non-valvular AF from Eastern Europe, the Middle East, Africa, and Latin America (32). However, the results concerning whether DOACs are more cost-effective than warfarin in Latin America remain a controversy (33). The evidence provided by our meta-analysis may offer some confidence to clinicians when selecting DOACs for Latin American patients who need anticoagulation therapy, especially for those at a high risk of bleeding. The present results support that the use of DOACs is at least non-inferior to warfarin in Latin American patients with AF and provides an effective anticoagulant choice without monitoring. Further studies should be performed to clarify this problem.

Limitations

Several limitations should be acknowledged. First, because of the small number of included studies, we did not perform subgroup analysis based on dosage or type of DOACs. Second, individual patient-level data from trials were not available, and some of the patients in Latin American countries enrolled might not be ethnically Latin American. Third, the results of the present analysis do not represent all countries in Latin America, as a limited number of countries in this region were included. Finally, we cannot exclude the possibility that there is potential confounding or interaction between enrollment in Latin America and anticoagulants.

CONCLUSION

The current pooled data from the four *post-hoc* analyses of RCTs suggested that compared with warfarin, DOACs appeared to have significant reductions in SSE, stroke, hemorrhagic stroke, all-cause death, major or NMCR bleeding, major bleeding, ICH, and any bleeding, but comparable risks of ischemic stroke, cardiovascular death, and gastrointestinal bleeding in Latin American patients with AF. DOACs appeared to have significant reductions in SSE, hemorrhagic stroke, all-cause death, cardiovascular death, major or NMCR bleeding, major bleeding, ICH, and any bleeding, and increased the risk of myocardial infarction, but comparable risks of stroke, ischemic stroke, and gastrointestinal bleeding in non-Latin American patients with AF.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.841341/full#supplementary-material

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frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 17 March 2022
doi: 10.3389/fcvm.2022.817826

Accuracy of a Single, Heparin-Calibrated Anti-Xa Assay for the Measurement of Rivaroxaban, Apixaban, and Edoxaban Drug Concentrations: A Prospective Cross-Sectional Study

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Background: Applying a single anti-Xa assay, calibrated to unfractionated heparin to measure rivaroxaban, apixaban, and edoxaban would simplify laboratory procedures and save healthcare costs.

Aim: We hypothesized that a heparin-calibrated anti-Xa assay would accurately measure rivaroxaban, apixaban, and edoxaban drug concentrations and correctly predict clinically relevant drug levels.

Methods: This analysis is part of the Simple-Xa study, a prospective multicenter cross-sectional study conducted in clinical practice. Patients treated with rivaroxaban, apixaban, or edoxaban were included. Anti-Xa activity was measured using the Siemens INNOVANCE® Heparin assay. Drug concentrations were determined using ultra-high performance liquid chromatography-tandem mass spectrometry (LC-MS/MS). Cut-off levels were determined in a derivation dataset (50% of patients) and sensitivities and specificities were calculated in a verification dataset (50% of patients).

Results: Overall, 845 patients were available for analysis. Correlation coefficients (r_S) between the heparin-calibrated anti-Xa assay and drug concentrations were 0.97 (95% CI 0.97, 0.98) for rivaroxaban, 0.96 (0.96, 0.97) for apixaban, and 0.96 (0.94, 0.99) for edoxaban. The area under the receiver operating characteristics curve (ROC) was 0.99

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Edited by:
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Specialty section:
This article was submitted to Thrombosis, a section of the journal Frontiers in Cardiovascular Medicine

Received: 18 November 2021
Accepted: 22 February 2022
Published: 17 March 2022

Citation:
Meihandoest T, Studt J-D, Mendez A, Alberio L, Fontana P, Wuillemin WA, Schmidt A, Graf L, Gerber B, Amstutz U, Bovet C, Sauter TC, Asmis LM and Nagler M (2022) Accuracy of a Single, Heparin-Calibrated Anti-Xa Assay for the Measurement of Rivaroxaban, Apixaban, and Edoxaban Drug Concentrations: A Prospective Cross-Sectional Study. Front. Cardiovasc. Med. 9:817826. doi: 10.3389/fcvm.2022.817826

for all clinically relevant drug concentrations. In the verification dataset, the sensitivity was 94.2% (95% CI 90.8–96.6) for 30 $\mu g\ L^{-1}$, 95.8% (92.4–98.0) for 50 $\mu g\ L^{-1}$, and 98.7% (95.5–99.9) for 100 $\mu g\ L^{-1}$. Specificities were 86.3% (79.2–91.7), 89.8% (84.5–93.7), and 88.7% (84.2–92.2), respectively.

Conclusion: In a large prospective study in clinical practice, a strong correlation of heparin-calibrated anti-Xa measurements with LC-MS/MS results was observed and clinically relevant drug concentrations were predicted correctly.

Keywords: diagnostic accuracy, anti-Xa assay, laboratory monitoring, direct oral anticoagulants, rivaroxaban

HIGHLIGHTS

What is known about this topic?

- Applying a single anti-Xa assay to measure rivaroxaban, apixaban, and edoxaban would simplify laboratory procedures and save healthcare costs.
- It remains unclear if this can be achieved using a single anti-Xa assay, calibrated to unfractionated heparin.

What does this paper add?

- We conducted a prospective multicenter cross-sectional study including 845 patients taking rivaroxaban, apixaban, or edoxaban in clinical practice.
- The association between heparin-calibrated anti-Xa measurements and LC-MS/MS results was strong for all drugs.
- Clinically relevant drug levels were predicted correctly.

INTRODUCTION

The proportion of patients taking direct oral anticoagulants (DOAC) for the prevention and treatment of thromboembolic diseases is rapidly increasing (1, 2). These patients occasionally face clinical situations with a high bleeding risk such as accidents, urgent surgery, and thrombolysis because of acute stroke (3–5). Besides, relevant DOAC drug concentrations contribute to massive bleeding of any cause (3, 6, 7). In addition, unresponsive or demented patients present to the emergency department, and knowledge of anticoagulant treatment is essential in the management. Rapid determination of DOAC drug levels in these situations supports clinical decisions regarding reversal agents, and deferral of interventions (8–10). Additionally, accumulation in the case of renal and/or hepatic failure or even overdosing can be detected (11, 12). Thus, determination of DOAC drug levels in special clinical situations is recommended by major scientific societies such as the International Society on Thrombosis and Haemostasis (9). Furthermore, it might potentially save health care costs associated with the clinical situations mentioned above (13).

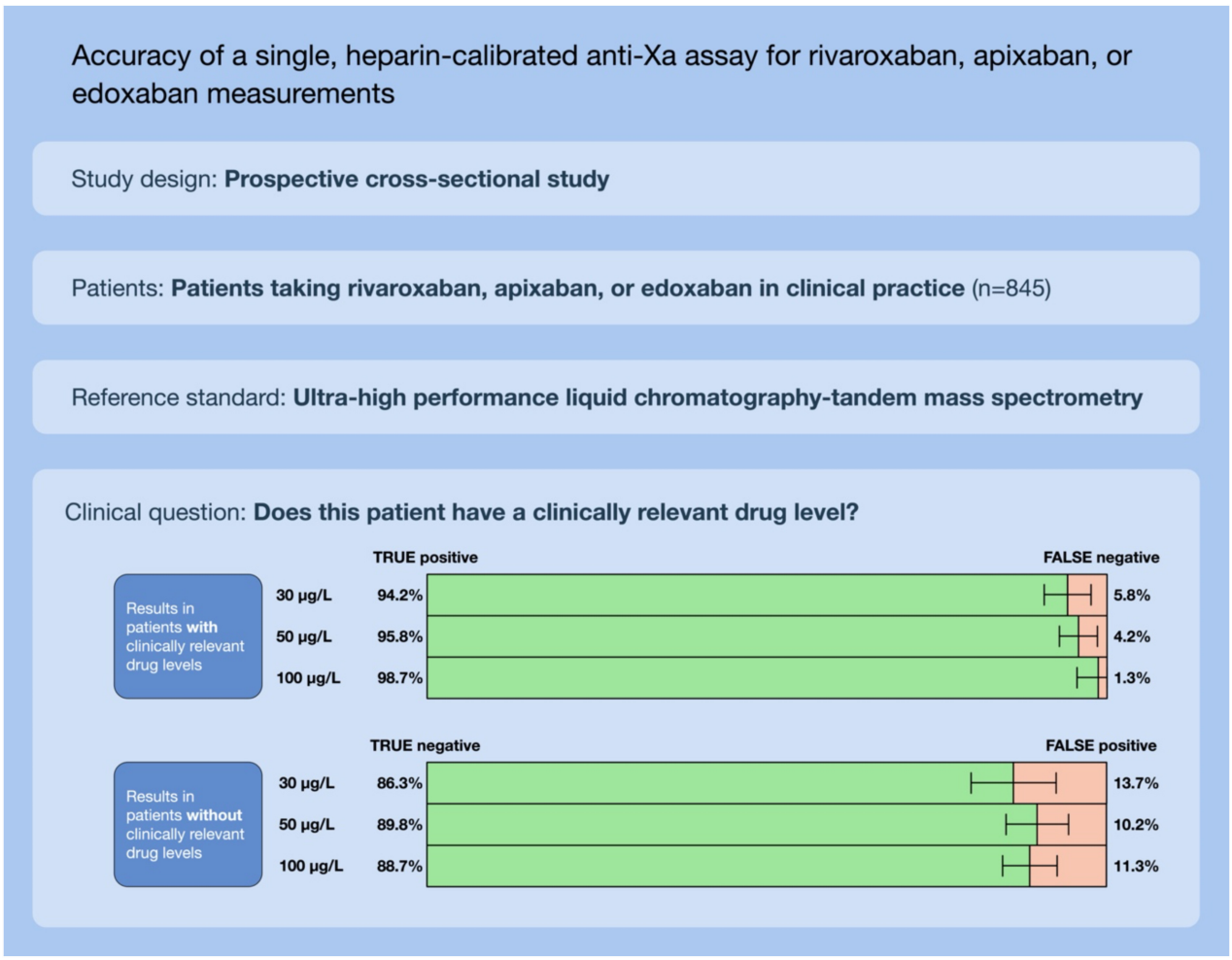
Ideally, a simple laboratory test that accurately determines DOAC plasma levels would be available and implemented in various healthcare settings in a 24/7 service (3). Routine coagulation tests are neither sensitive nor specific in the detection of DOAC (10, 14–16). Various anti-Xa assays are available that measure rivaroxaban, apixaban, or edoxaban concentrations using drug-specific calibration curves (17). However, these tests are still not widely implemented because it is laborious and expensive to provide three different tests (3). We and other authors hypothesized that a single heparin-calibrated anti-Xa assay would be sufficient to accurately and efficiently determine rivaroxaban, apixaban, and edoxaban drug levels (18–20). An essential advantage of this method is that heparin-calibrated assays are already available even in smaller laboratories. Thus, implementing a single-calibration anti-Xa assay for unfractionated heparin, low molecular weight heparin, rivaroxaban, apixaban, and edoxaban would improve laboratory procedures but also the care of patients treated with DOAC. Recently, we demonstrated that a universal, LMWH-calibrated assay can accurately measure DOAC drug levels (21). However, it remains unclear if this can be achieved using a universal heparin-calibrator intended to detect unfractionated heparin and low molecular weight heparins.

With the present multicenter cross-sectional study, we aimed to assess whether the Siemens INNOVANCE® Heparin anti-Xa assay would accurately measure rivaroxaban, apixaban, and edoxaban drug concentrations and correctly predict clinically relevant drug levels. The primary focus was on the clinically significant concentration range between 0 and 300 $\mu g\ L^{-1}$.

MATERIALS AND METHODS

Study Design, Setting, and Population

We conducted a prospective multicenter cross-sectional study including patients in nine hemostasis laboratories affiliated to Swiss tertiary hospitals. Patients treated with rivaroxaban, apixaban, or edoxaban in clinical practice were included between 2018 and 2019 (**Figure 1**, CONSORT flow diagram). Inclusion criteria were (a) 18 years or older, (b) use of rivaroxaban, apixaban, or edoxaban (c) DOAC drug-level requested, and (d) signed general informed consent, if required by local authorities. Exclusion criteria were (a) refused general informed consent, (b) use of heparin, (c) preanalytical issues, (d) use of more than one DOAC, and (e) insufficient sample material. Samples were collected regardless of the time of last drug intake, covering the full range of drug levels observed in clinical practice. Ultra-high performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) measuring rivaroxaban, apixaban, and edoxaban



GRAPHICAL ABSTRACT | Visual summary.

was used as a reference standard (16, 21). The study was approved by the local ethics committees and all hospitals gave local feasibility approval. If required, patients signed a general consent to use their samples and data before enrolment at the respective study center. The study was conducted in accordance with the declaration of Helsinki.

Data Collection and Handling of Samples

Patient characteristics including age, sex, and the DOAC used (rivaroxaban, apixaban, or edoxaban) were collected in a secured REDCap database. Protocols were implemented at all institutions detailing blood-drawing procedures to ensure adequate pre-analytical conditions (22). Venous blood samples were drawn in plastic syringes containing 1 mL trisodium citrate (0.106 mol L^{-1}) per mL of blood (i.e., S-Monovette® Citrate, Sarstedt, Nümbrecht, Germany). Samples were centrifuged according to an established scheme (1,500 *g* for 10–15 min, or 3,137 *g* for 7 min), and aliquots were frozen immediately and stored at −80°C until transportation (22). Samples were shipped on dry ice in one batch per site to the central laboratory and delivered within 3 to 4 h. Samples were kept frozen until the determination of laboratory tests without any freeze-thaw cycle. Laboratory test results were exported automatically to avoid typing errors.

Determination of the Anti-Xa Activity

The Siemens INNOVANCE® Heparin anti-Xa assay was selected for determining the anti-Xa activity. This one-stage chromogenic assay is designed to measure the drug level of unfractionated heparin (UFH) as well as low molecular weight heparin (LMWH) (INNOVANCE® Heparin anti-Xa assay application sheet; Siemens Healthineers, Marburg, Germany). The reagent contains dextran sulfate but not exogenous antithrombin. The instructions provided by the manufacturer were strictly followed. In brief, a five-step calibration curve was applied using the calibrators provided by the manufacturer (0.0, 0.42, 0.86, 1.26, and 1.67 U/ml). Samples were rapidly thawed and gently mixed at 37°C. Patient plasma was pre-diluted (1:2) and added to the reagent containing coagulation factor Xa and a chromogenic substrate. The formation of paranitroaniline was quantified

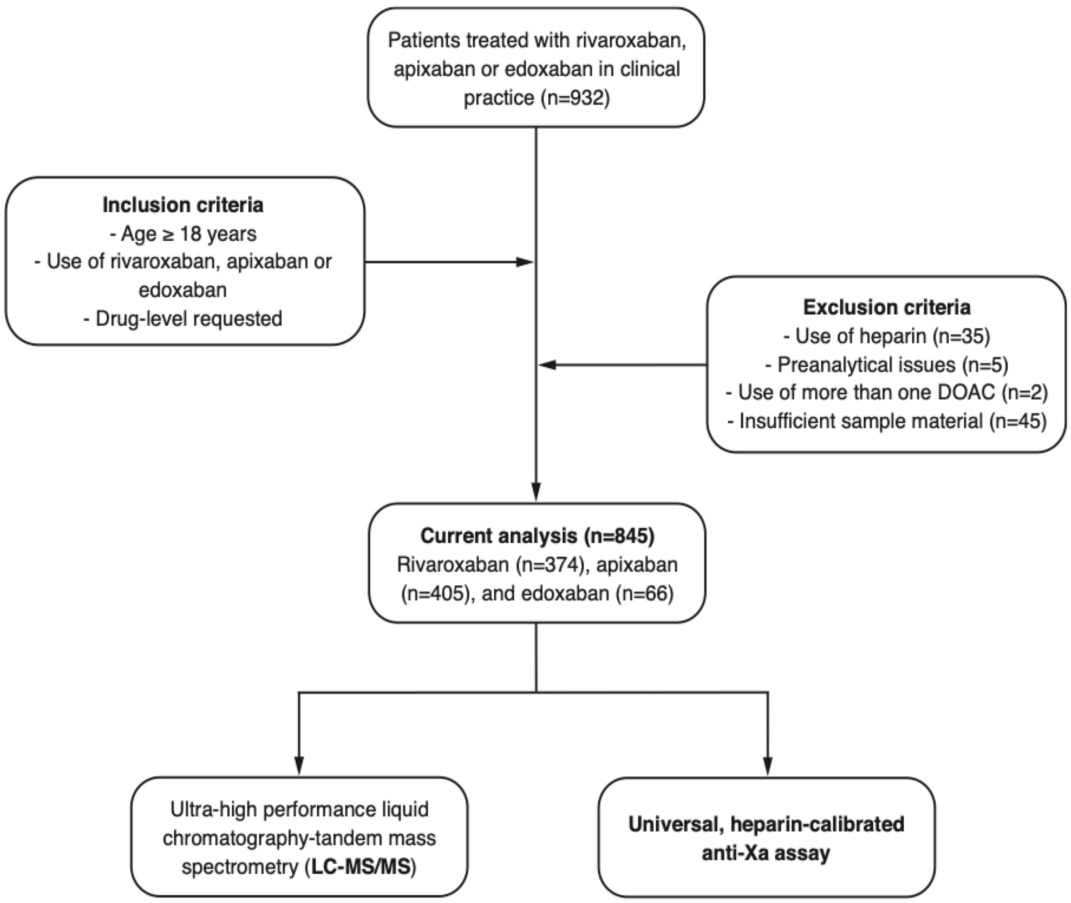


FIGURE 1 | Flow of the patients. A prospective, multicentre cross-sectional study was conducted to test the accuracy of a heparin-calibrated anti-Xa assay for the measurement of rivaroxaban, apixaban, or edoxaban plasma levels in clinical practice.

optically at a wavelength of 405 nm. The measurements were conducted in batches on an Atellica COAG 360 analyzer (Siemens Healthineers, Marburg, Germany) (23). Measurements were performed blinded to the LC-MS/MS test results.

Determination of the Drug Concentration by Liquid Chromatography-Tandem Mass Spectrometry

Liquid chromatography-tandem mass spectrometry was used for the quantification of rivaroxaban, apixaban, edoxaban, and M4 metabolite of edoxaban. For protein precipitation and analyte extraction, plasma acetonitrile:water 1:1 (v/v), extraction buffer (MassTox TDM Series A, Chromsystems, Gräfelfing, Germany), and precipitation reagent (MassTox TDM Series, Chromsystems, Gräfelfing, Germany) containing the isotope labeled internal standards (13C6 rivaroxaban, 13CD3 apixaban, 13CD2 edoxaban; provided by the manufacturers) were added to the plasma. Afterward, the samples were vortexed and centrifuged at 14,000 rcf and 20°C for 4 min. The supernatant was diluted with water:methanol 8:2 (v/v) and stored at 10°C until analysis. The calibrators and QCs were prepared in pooled plasma (Innovative Research, Novi, MI, United States). The extracted samples were analyzed using reversed-phase chromatography (Cortecs UPLC C18 column, 2.1 × 75 mm, 1.7 μm, Waters) on a triple quadrupole mass spectrometer (Xevo TQ-S, Waters, Milford, CT, United States) coupled to a UPLC Acquity I-Class system (Waters, Milford, CT, United States). Edoxaban M4 concentration was summed up with the edoxaban for further analysis.

Statistical Analysis

Variables were described using proportions and percentages or median and interquartile range (IQR) as appropriate. The normality of the data was assessed visually and using a Q-Q plot. The accuracy of the anti-Xa assay was determined by calculating the Spearman's correlation coefficient in relation to the plasma concentration as measured by LC-MS/MS. A correlation coefficient of rs $\geq$ 0.95 was considered as accurate (alternative hypothesis), and a correlation of rs $\leq$ 0.6 was regarded as inadequate (null hypothesis). The Deming regression was used to describe the linear relationship and a modified Bland-Altman plot (ratios were used due to different scales) was created

TABLE 1 | Characteristics of patients treated with rivaroxaban, apixaban or edoxaban (n = 845).

	Patients treated with				
	Rivaroxaban	**Apixaban**	**Edoxaban**	**All**	**Missing data**
Patients *(n/%)*	374 (44.3)	405 (47.9)	66 (7.8)	845 (100)	0
Age *(years; median/IQR)*	74 (63-83)	78 (63-83)	75 (58-82)	76 (66-82)	96
Sex *(n/%)*					8
Male	209 (56.0)	233 (58.4)	36 (55.4)	478 (57.1)	–
Female	164 (44.0)	166 (41.6)	29 (44.6)	359 (42.9)	–

N, number. IQR, interquartile range.

to observe a potential bias over the spectrum of measurements (9). Systematic differences were analyzed by calculating the mean difference and the SD to compute 95% limits of agreement for every level of measurements (average difference ± 1.96 standard deviation of the difference) (24). To assess the diagnostic accuracy of the anti-Xa assay, we determined the sensitivity and specificity of detecting 30, 50, and 100 µg/L, representing clinically relevant drug levels. The dataset was randomly split in half, and the cut-offs of the new test were obtained by a ROC curve analysis in the derivation dataset. As an internal validation, we repeated the ROC curve analysis in the verification dataset and calculated sensitivities and specificities regarding clinically relevant drug levels. An area under the receiver-operating characteristics (ROC) curve ≥ 0.95 and sensitivities/specificities of at least 90% were regarded as adequate. A power analysis for a one-sample correlation test was conducted with a power of 0.9 and an alpha of 0.05. Since many patients were taking rivaroxaban and apixaban, and only a few edoxaban, 932 patients were included until data saturation was reached. Sensitivity analyses considering samples below 3.34 U ml^{-1} only were conducted. All statistical analyses were performed using RStudio (1.3. 1093-1); figures were created using Prism 8 (GraphPad Software, Inc., La Jolla, CA, United States).

RESULTS

Patient Characteristics

Overall, 932 patients were included in this prospective multicenter cross-sectional study; a detailed flow chart is given in **Figure 1**. From this study population, 35 patients were excluded because of heparin use, five patients due to preanalytical issues, two patients using more than one DOAC, and 45 patients due to insufficient sample material. Eventually, samples of 845 patients were used for the current analysis. Of these, 374 patients used rivaroxaban, 405 apixaban, and 66 edoxaban. The median

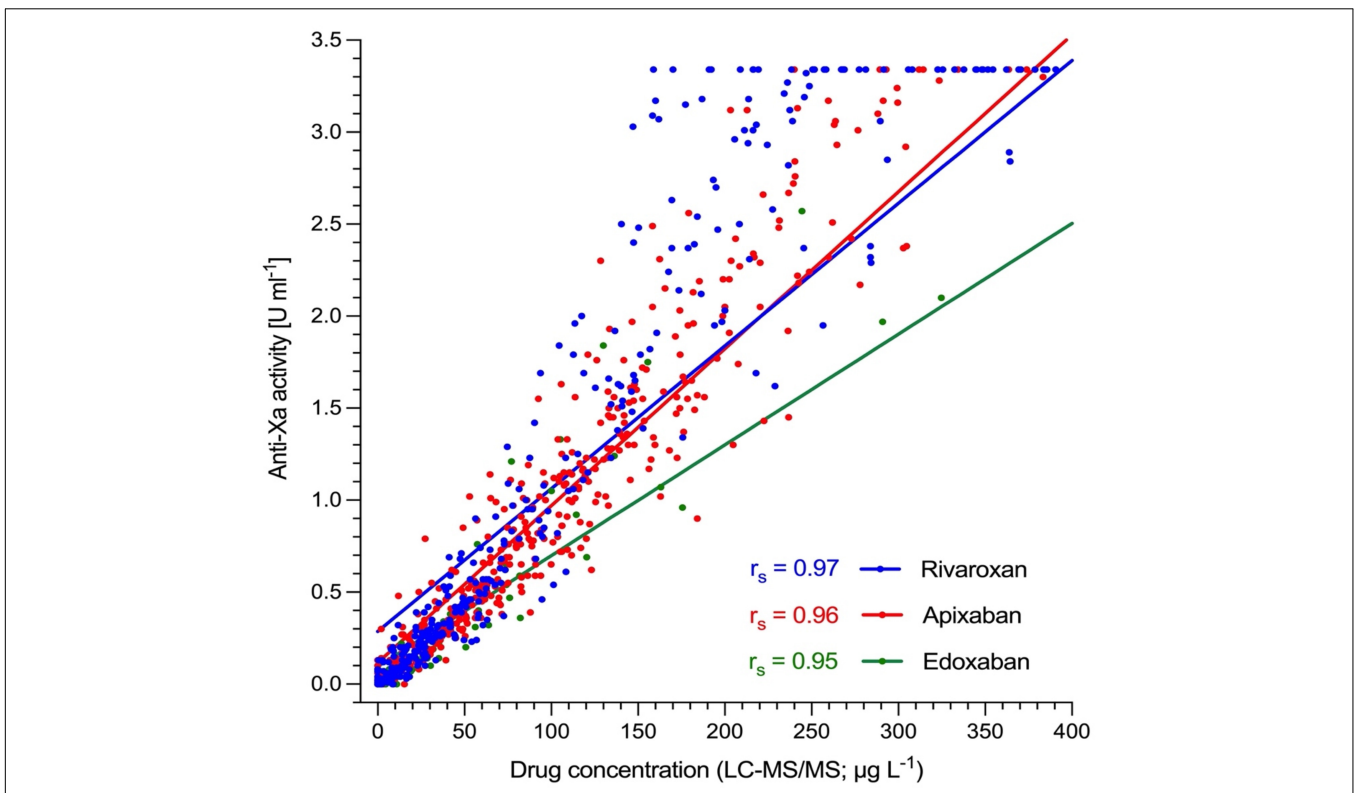


FIGURE 2 | Association of heparin-calibrated anti-Xa measurements with drug concentration in 845 patients taking rivaroxaban, apixaban, or edoxaban in clinical practice. Ultra-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) was used to determine drug levels. Spearman's correlation coefficient (r_s) was 0.97 for rivaroxaban (95% CI 0.97–0.98), 0.96 for apixaban (0.95–0.97), and 0.96 for edoxaban (0.94–0.99). The overall r_s was 0.97 (95% CI, 0.97–0.98).

TABLE 2 | Accuracy of universal, heparin-calibrated anti-Xa assay with regard to drug concentration in 845 patients taking rivaroxaban, apixaban, or edoxaban in clinical practice.

	Overall	Rivaroxaban	Apixaban	Edoxaban
Spearman's correlation coefficient (95% CI)	0.97 (0.97, 0.98)	0.97 (0.97, 0.98)	0.96 (0.96, 0.97)	0.96 (0.94, 0.99)
Deming regression Slope (95% CI)	0.008 (0.006, 0.009)	0.008 (0.007, 0.009)	0.008 (0.007, 0.009)	0.006 (0.005, 0.007)
Y-intercept (95% CI)	0.29 (0.15, 0.42)	0.29 (0.16, 0.40)	0.14 (0.05, 0.23)	0.10 (0.015, 0.18)

Ultra-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) was used to determine drug levels. The Spearman's correlation coefficient is given (r_S), and the coefficients of the Deming regression.

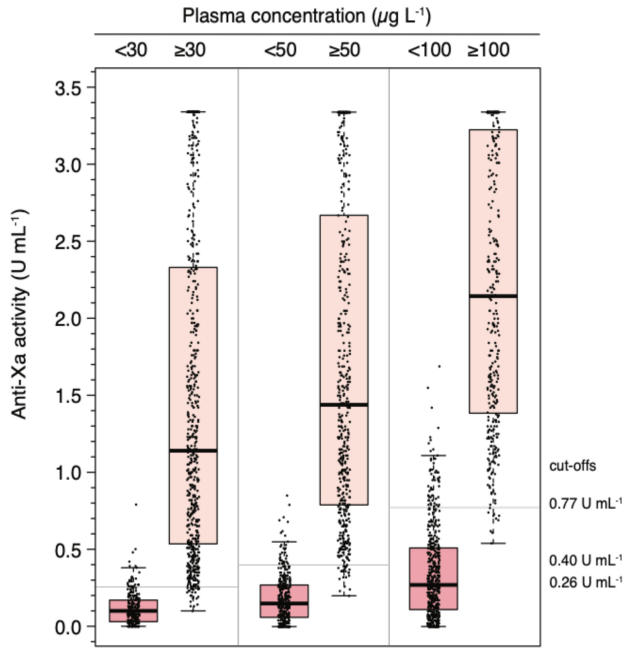


FIGURE 3 | Distribution of universal, heparin-calibrated anti-Xa measurements for the measurement of rivaroxaban, apixaban, and edoxaban drug concentrations in clinical practice (n = 845). Box plot illustrating the distribution of measurement (median, interquartile range, minimum, maximum) at clinically relevant cut-off levels (above and below 30, 50, and 100 μg L^{-1}).

age was 76 years old (IQR, 66 to 82 years), and 42.9% of the patients were female, see **Table 1**.

Association Between Anti-Xa Activity and Drug Concentration

The association between anti-Xa activity and drug concentrations as measured by LC-MS/MS is shown in **Figure 2**, and results of correlation analyses are provided in **Table 2**. The overall Spearman's correlation coefficient (r_s) was 0.97 (95% confidence interval, CI, 0.97 to 0.98). Regarding the individual drugs, r_s was 0.97 (95% CI 0.97–0.98) for rivaroxaban, 0.96 (0.95–0.97) for apixaban, and 0.96 (0.94–0.99) for edoxaban. The overall slope of the regression equation was 0.008 (95% CI 0.007–0.009), 0.008 (0.007–0.009) for rivaroxaban, 0.009 (0.008–0.010) for apixaban, and 0.006 (0.005–0.008) for edoxaban. The overall Y-intercept was 0.21 (95% CI 0.13–0.28), 0.29 (0.16–0.40) for rivaroxaban, 0.12 (0.016–0.022) for apixaban, and 0.10 (0.007–0.16) for edoxaban. The association between anti-Xa activity and drug concentrations over the range of measurements is shown in a modified Bland-Altman plot, see **Supplementary Figure 1**. The overall bias was 0.01, with a lower limit of agreement of −0.01, and an upper limit of agreement of 0.03. The distribution of anti-Xa measurements in patients with and without clinically relevant drug levels (30, 50, and 100 μgL^{-1}) is shown in **Figure 3**.

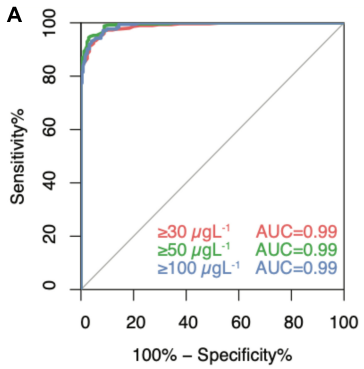
Sensitivity analyses considering samples below 3.34 U ml^{-1} only yielded the following results similar to the values mentioned above: r_s overall 0.97 (95%CI 0.96, 0.97), r_s rivaroxaban 0.97 (0.96, 0.97), r_s apixaban 0.96 (0.95, 0.97), and r_s edoxaban 0.96 (0.93, 0.98). The Deming regression slope was 0.01 (overall; 95% CI 0.01, 0.01), 0.01 (rivaroxaban; 0.01, 0.01), 0.01 (apixaban; 0.01, 0.01), and 0.01 (edoxaban; 0.01, 0.01). The Y-intercept was −0.01 (overall; −0.05, 0.03), −0.03 (rivaroxaban; −0.08, 0.01), −0.01 (apixaban; −0.06, 0.04), and 0.04 (edoxaban; −0.05, 0.13).

Diagnostic Accuracy Regarding Clinically Significant Drug Levels

In the derivation dataset (n = 422), the area under the ROC curve was 0.99 for all clinically relevant drug concentrations (**Figure 4**, panel A); 95% CI were 0.977 to 0.997 in case of 30 μg L^{-1}, 0.981–0.995 in 50 μg L^{-1}, and 0.978–0.994 in 100 μg L^{-1}. Drug levels above 30 μg L^{-1} were detected with a sensitivity of 96.9% (95% CI 94.3–98.5; cut-off value 0.26 U mL^{-1}), drug levels above 50 μg L^{-1} with a sensitivity of 95.2% (95% CI 92.0–97.4; cut-off value 0.40), and drug levels above 100 μg L^{-1} with a sensitivity of 96.2% (95% CI 92.4–98.5; cut-off value 0.77). Specificities were 92.2% (85.1–96.6), 90.6% (84.7–94.8), 88.1% (83.3–92.0), respectively. Confusion matrices are given in **Figure 4**, panel B. In the sensitivity analyses, these measures did not differ significantly.

Internal Validation

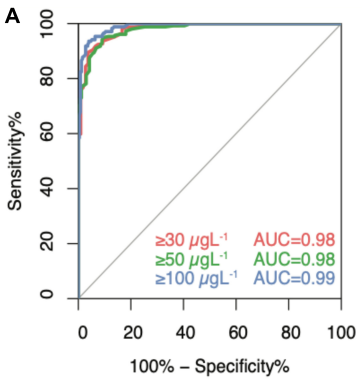
In the verification dataset (n = 423), the area under the ROC curve was 0.98 for both the cut-offs 30 (0.971–0.990) and 50 (0.976–0.993) μg L^{-1} and 0.99 (0.988–0.998) for 100 μg L^{1} (**Figure 5**, panel A). Cut-off levels obtained in the derivation dataset were used to calculate sensitivities and specificities in the verification dataset (n = 423) as an internal validation (**Figure 5**, panel B). Drug levels above 30 μg L^{-1} were detected with a sensitivity of 94.2% (95% CI 90.8–96.6; cut-off value 0.26 U mL^{-1}), drug levels above 50 μg L^{-1}



B

Anti-Xa activity (U mL^{-1})	Plasma concentration (μg L^{-1}) ≥30	<30	≥50	<50	≥100	<100
≥0.26	310	8	≥0.40 260	14	≥0.70 179	28
<0.26	10	94	<0.40 13	135	<0.70 7	208

FIGURE 4 | Diagnostic accuracy of a universal, heparin-calibrated anti-Xa assay for the measurement of rivaroxaban, apixaban, and edoxaban drug concentrations in clinical practice (derivation dataset; n = 422).
(A) Receiver-operating characteristics curve (ROC) showing the diagnostic accuracy. The area under the ROC curve was 0.99 for all cut-offs.
(B) Confusion matrices at each cut-off. Drug levels above 30 μg L^{-1} were detected with a sensitivity of 96.9% (95% CI 94.3, 98.5; cut-off value 0.26 U mL^{-1}), drug levels above 50 μg L^{-1} with a sensitivity of 95.2% (95% CI 92.0, 97.4; cut-off value 0.40), and drug levels above 100 μg L^{-1} with a sensitivity of 96.2% (95% CI 92.4, 98.5; cut-off value 0.77). Specificities were 92.2% (85.1, 96.6), 90.6% (84.7, 94.8), 88.1% (83.3, 92.0), respectively.



B

Anti-Xa activity (U mL^{-1})	Plasma concentration (μg L^{-1}) ≥30	<30	≥50	<50	≥100	<100
≥0.26	275	18	≥0.40 227	19	≥0.70 156	2
<0.26	17	113	<0.40 10	167	<0.70 30	235

FIGURE 5 | Internal validation of a universal, heparin-calibrated anti-Xa assay for the measurement of rivaroxaban, apixaban, and edoxaban drug concentrations in clinical practice (verification dataset; n = 423).
(A) Receiver-operating characteristics curve (ROC) showing the diagnostic accuracy. The area under the ROC curve was 0.98 for both the cut-offs 30 and 50 μg L^{-1} and 0.99 for 100 μg L^{-1}. **(B)** Confusion matrices at each cut-off. Drug levels above 30 μg L^{-1} were detected with a sensitivity of 94.2% (95% CI 90.8, 96.6; cut-off value 0.26 U mL^{-1}), drug levels above 50 μg L^{-1} with a sensitivity of 95.8% (95% CI 92.4, 98.0; cut-off value 0.40), and drug levels above 100 μg L^{-1} with a sensitivity of 98.7% (95% CI 95.5, 99.9; cut-off value 0.77). Specificities were 86.3% (79.2, 91.7), 89.8% (84.5, 93.7), 88.7% (84.2, 92.2), respectively.

with a sensitivity of 95.8% (95% CI 92.4–98.0; cut-off value 0.40), and drug levels above 100 μg L^{-1} with a sensitivity of 98.7% (95% CI 95.5–99.9; cut-off value 0.77). Specificities were 86.3% (79.2–91.7), 89.8% (84.5–93.7), 88.7% (84.2–92.2), respectively. In the sensitivity analyses, these measures did not differ significantly.

DISCUSSION

We conducted a large multicenter cross-sectional study including 845 patients treated with rivaroxaban, apixaban, or edoxaban in clinical practice. Even though minor differences between drugs and some variability in the higher concentrations exist, the association between heparin-calibrated anti-Xa measurements and LC-MS/MS results was strong for all drugs. As an internal validation, clinically relevant drug levels were predicted correctly in the verification dataset using cut-off levels derived in the derivation dataset.

Even though this is the first study analyzing a UFH-calibrated anti-Xa assay in a large cohort, our results are essentially in-line with previous publications. Recently, we analyzed the accuracy of a LMWH-calibrated anti-Xa assay in the same cohort (n = 867) (21). Similarly, the accuracy was high and clinically relevant drug levels were predicted correctly. Studt et al. (17) studied the accuracy and consistency of anti-Xa assays for rivaroxaban plasma concentration in 20 healthy individuals and found a high agreement with drug concentrations measured by LC-MS/MS. Another cross-sectional study (25) showed a strong correlation between heparin anti-factor Xa activity and LC-MS/MS in 30 patients treated with rivaroxaban. In another retrospective study,

TABLE 3 | Implementation of a single, heparin-calibrated anti-Xa assay for the measurement of rivaroxaban, apixaban, and edoxaban drug concentrations.

	Cut-off value	Regression equation
Clinical threshold		
30 μg/L DOAC	0.26 U/mL	
50 μg/L DOAC	0.40 U/mL	
100 μg/L DOAC	0.77 U/mL	
Drug concentrations		
Rivaroxaban		129 × [U/mL] – 37
Apixaban		124 × [U/mL] – 17
Edoxaban		166 × [U/mL] – 16

The cut-off values could be given, which would allow direct clinical decisions to be made. Alternatively, the regression equations can be used to calculate the plasma concentrations of each compound.

a high degree of correlation between a heparin-calibrated anti-Xa assay and LC-MS/MS was observed in 24 patients taking rivaroxaban or apixaban (26). Similar results were also observed in studies assessing the correlation of anti-Xa measurements with LC-MS/MS in spiked samples (27–30). A high correlation between UFH-calibrated anti-Xa measurements and rivaroxaban-/apixaban-calibrated anti-Xa results was found in a study assessing 241 left-over samples (20). Besides, van Pelt and colleagues proposed a universal anti-Xa assay reporting the inhibitory effect rather than drug concentrations (18).

This study is associated with certain strengths and limitations. The sample size is much larger than previous studies ($n = 845$), which increases statistical power and precision. Thus, we were able to split the dataset into a derivation and verification dataset, facilitating internal validation of the results. Another strength is that our study was designed as a multicenter study (nine laboratories) conducted in clinical practice, thus constituting a representative population. Therefore, the results can be translated straightforwardly to clinical practice. Also, LC-MS/MS was used as a reference standard which is considered the most accurate technique to measure DOAC plasma levels (21, 31). As a limitation, only a single heparin-calibrated assay was studied and other heparin-calibrated anti-Xa assays may perform differently. Several previous studies using various study designs found considerable differences among reagents (19, 32, 33). Additionally, the number of edoxaban-treated patients was lower compared to rivaroxaban and apixaban-treated patients. However, we believe that this is compensated by the large sample size.

The question now arises as to how this test can be applied in daily practice. The cut-off values mentioned in **Table 3** can be given so that clinical decisions can be prompted directly (**Table 3**). Alternatively, the regression equations can be used to calculate the plasma concentrations of each compound (**Table 3**). However, the second approach must be used with caution. Minor differences between drugs exist and a certain degree of variability can be observed in higher concentrations. Therefore, drug levels in high concentrations ($\geq$150 μgL^{-1}) can only be measured with limited accuracy and precision (34). Yet, several arguments can be raised in favor of the heparin-calibrated assay: (1) this variation is also present in drug-specific anti-Xa assays (17), (2) typical requirements in terms of correlation coefficients and ROC AUC are fulfilled, and (3) all clinically relevant cut-off thresholds are met with high accuracy. Current guidelines do not distinguish between normal-high and very-high drug levels concerning patient management.

Our results confirm that a single, heparin-calibrated anti-Xa assay accurately measures rivaroxaban, apixaban, and edoxaban drug concentrations and correctly predicts clinically relevant drug levels. Since heparin-calibrated anti-Xa assays are already available in many laboratories, determination of DOAC drug levels can be provided easily. This may foster the widespread implementation of anti-Xa assays to measure DOAC, thus improving care in patients taking these drugs. Future studies should confirm these results in other settings and using other heparin-calibrated assays.

Conclusion

We report results of a large prospective study including patients treated with rivaroxaban, apixaban, or edoxaban in clinical practice. The association of heparin-calibrated anti-Xa measurements with DOAC drug concentrations was strong, and clinically relevant drug levels were predicted correctly. Our results represent a strong argument in favor of the potential application of a universal, heparin-calibrated anti-Xa assay to measure DOAC in clinical practice.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Kantonale Ethikkommission Bern. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TM analyzed the data, interpreted the results, and wrote the manuscript. J-DS, AM, LAl, PF, WW, AS, LG, BG, CB, LAs, UA, and TS collected data, and contributed to study design, protocol, and preparation of the manuscript. CB and UA contributed essential tools and reagents. MN designed the study, wrote the protocol, collected data, analyzed, and interpreted the data, and wrote the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by a research grant of the Research Fund Haematology Cantonal Hospital Lucerne. MN was supported by a research grant of the Swiss National Science Foundation (#179334). Implementation of the LC-MS/MS measurements was supported by the Gottfried & Julia Bangerter-Rhyner-Stiftung. This study was supported by a research grant of Siemens Healthineers. These funders had no role in study design, data collection and analysis, the decision to publish, or manuscript preparation. We thank the following companies for the provision of reagents and/or pure substances: Bayer Healthcare AG, Bristol-Myers Squibb, and Daiichi Sankyo. These companies had no role in study design, data collection and analysis, the decision to publish, or manuscript preparation.

ACKNOWLEDGMENTS

We thank Evelyne Giabbani for organizing the sample collection, Marc Gisi, and Vincent Benites for doing the anti-Xa measurements, Gabriela Mäder for doing the LC-MS/MS measurements, Sarah Phillip for technical support, and Martin Fiedler for providing the infrastructure at Inselspital.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.817826/full#supplementary-material

Supplementary Figure 1 | A modified Bland–Altman plot using ratios to determine a possible systematic bias over the range of measurements. The bias and the upper and lower limit of agreement is shown.

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Conflict of Interest: MN reports research grants from Bayer Healthcare, outside of the submitted work, lecture honoraria from Bayer Healthcare, and Daiichi Sankyo. LAl reports research grants from Bayer, CSL-Behring, Novartis, Novo Nordisk, Roche, Sobi, and Takeda. WW reports research grants from Bayer Healthcare, BMS-Pfizer, Daiichi Sankyo and Sanofi, and honoraria for participating in scientific advisory boards from Bayer, Pfizer, and from Alexion Pharma GmbH, all outside the submitted work. J-DS reports lecture fees and advisory honoraria from Bayer Healthcare, Pfizer, Takeda, Siemens, and Sanofi. TS holds an endowed professorship supported by the Touring Club Switzerland. BG reports non-financial support and funding for accredited continuing medical education program from Axonlab, and from Thermo Fisher Scientific, during the conduct of the study; personal fees and funding for accredited continuing medical education program from Alnylam, grants, personal fees and funding for accredited continuing medical education program from Pfizer, funding for accredited continuing medical education program from Bayer, Bristol Myers Squibb, Daiichi Sankyo, Takeda, Octapharma, SOBI, Janssen, Novo Nordisk, Mitsubishi Tanabe Pharma, outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 18 March 2022
doi: 10.3389/fcvm.2022.846803

Evolving Antithrombotic Treatment Patterns for Patients With Nonvalvular Atrial Fibrillation and Acute Coronary Syndrome or Underwent Percutaneous Coronary Intervention in China: A Cross-Sectional Study

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OPEN ACCESS

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Thrombosis, a section of the journal Frontiers in Cardiovascular Medicine

Received: *31 December 2021*
Accepted: *28 January 2022*
Published: *18 March 2022*

Citation:
Suo N, Yang YM, Wang J, Zhang H, Shao XH, Wu S and Zhu J (2022) Evolving Antithrombotic Treatment Patterns for Patients With Nonvalvular Atrial Fibrillation and Acute Coronary Syndrome or Underwent Percutaneous Coronary Intervention in China: A Cross-Sectional Study. Front. Cardiovasc. Med. 9:846803. doi: 10.3389/fcvm.2022.846803

Objective: Antithrombotic therapy in patients with nonvalvular atrial fibrillation (NVAF) concomitant with the acute coronary syndrome (ACS) or underwent percutaneous coronary intervention (PCI) is challenging and has evolved in recent years. However, real-world data on this issue about antithrombotic regimens at discharge and its evolving trend were relatively scarce, especially in China.

Methods: A total of 2,182 patients with NVAF and ACS/PCI were enrolled from 2017 to 2019. A total of 1,979 patients were finally analyzed and divided in three sequential cohorts: cohort 1 (2017), $n = 674$; cohort 2 (2018), $n = 793$; and cohort 3 (2019), $n = 512$. Baseline characteristics and antithrombotic therapy at discharge were analyzed by cohort.

Results: In our cross-sectional study, the majority of patients (59.6%) received dual antiplatelet therapy (DAPT). Over the 3 years, DAPT prescription reduced from nearly 70% to <50% (P trend < 0.001), while triple therapy (TT)/double therapy (DT) increased from 27.2 to 50.0% (P trend < 0.001). This trend was also seen in different subgroups stratified by CHA2DS2-VASc score, HAS-BLED score, coronary artery disease type, or management type, and was validated after multivariate adjustment. Persistent atrial fibrillation and history of congestive heart failure, hypertension, diabetes mellitus, and stroke/transient ischemic attack/systemic embolism were the independent predictors of TT/DT use, while ACS, PCI, or advanced chronic kidney disease was related with more DAPT prescription.

Conclusion: There is a shift of antithrombotic regime at discharge for patients with NVAF with recent ACS/PCI with reducing DAPT prescription and increasing TT/DT prescription. While the appropriate antithrombotic regimen for patients with NVAF having ACS/PCI is still underused in China.

Keywords: atrial fibrillation, acute coronary syndromes, PCI–percutaneous coronary intervention, antithrombotic therapy, anticoagulation, antiplatelet

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia with increasing prevalence (1) and is associated with a five-fold increase in stroke risk (2). Up to 40% of patients with AF are concomitant with coronary artery disease (CAD) (3). Besides, AF increases the risk of myocardial infarction in patients with and without CAD (4, 5). About 5–15% of patients with AF are known to require percutaneous coronary intervention (PCI) during their entire life (3). Among patients with the acute coronary syndrome (ACS) or undergoing PCI, 2–23% are concomitant with AF (6).

Patients with nonvalvular atrial fibrillation (NVAF) having moderate-to-high stroke risk require chronic oral anticoagulation (OAC) for thromboembolism prevention (7, 8), whereas patients with ACS or undergoing PCI require dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor for coronary ischemic events prevention (9). Therefore, combined therapy is needed in patients with NVAF having ACS/PCI. But combined antithrombotic treatment is related to an increased risk of bleeding at the same time (10). The concomitant presence of these conditions represents a challenge in clinical practice.

Antithrombotic therapy of patients concomitant NVAF and ACS/PCI has evolved in recent years with new evidence from pivotal clinical trials in this field (11–14). Evidence-based guidelines and consensus (7, 15–18) recommended a short course of triple therapy (TT) with OAC and DAPT in combination for patients with NVAF after recent ACS/PCI, and following double therapy (DT) with an OAC and single antiplatelet therapy (SAPT) (15, 16). However, observational studies find that patients with AF and ACS/PCI were less likely to receive appropriate antithrombotic therapy (19) and more likely to experience adverse outcomes (20). This study aims to investigate the evolving trends in antithrombotic regimens in Chinese patients with NVAF and ACS/PCI.

METHODS

Study Design and Participants

This study is a single-center cross-sectional study of adults with AF and concomitant with ACS or who underwent PCI from 2017 to 2019 in Fuwai Hospital, Beijing, China. Men and women aged over 18 years with AF and ACS or who underwent PCI were enrolled to assess eligibility (**Figure 1**). At least one of the following risk factors for stroke was required: history of symptomatic heart failure or left ventricular ejection fraction of no more than 40%; hypertension; an age of at least 65 years; diabetes mellitus; previous stroke, transient ischemic attack, or systemic embolism; prior or newly diagnosed acute myocardial infarction; peripheral artery disease with artery stenosis or occlusion. Patients who died in the hospital, patients with valvular AF (i.e., mechanical heart valves, moderate to severe mitral stenosis), and patients who have no atherosclerosis lesion after coronary angiography were excluded. Patients were enrolled consecutively and divided into three sequential cohorts by year: cohort 1 (2017), cohort 2 (2018), and cohort 3 (2019). This article reports cross-sectional data at baseline including antithrombotic therapy pattern at discharge.

Definitions

The diagnosis of AF was confirmed by reviewing clinical records and electrocardiographic evidence, namely, ECGs, Holter, and rhythm strips. ACS comprised a series of acute coronary diseases, namely, ST-elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), and unstable angina (UA). The diagnosis of ACS was confirmed by clinical physicians based on clinical evaluation, namely, symptoms of cardiac ischemia, 12-lead electrocardiography abnormalities, cardiac biomarkers (cardiac enzyme and cardiac troponin) change, and echocardiography. PCI was defined as percutaneous transluminal coronary revascularization with balloon angioplasty, drug-eluting balloon angioplasty, bare-metal/drug-eluting stent implantation, or unsuccessful coronary intervention attempt.

The definitions of comorbidities are listed as follows. Congestive heart failure was defined with prior symptomatic heart failure and/or left ventricular ejection fraction $<40\%$. Hypertension was defined as a documented history of hypertension or blood pressure over 140/90 mm Hg. Vascular diseases include CAD with prior myocardial infarction (MI), acute MI (AMI), and peripheral artery disease with artery stenosis or occlusion. Prior stroke was defined as a combination of ischemic stroke and hemorrhage stroke.

The CHA2DS2-VASc scores and HAS-BLED scores were used to evaluate the risk of ischemic stroke and bleeding. CHA2DS2-VASc scores were calculated with 1 point for congestive heart failure, hypertension, diabetes, vascular disease, age 65–74 years, and sex category (female), and 2 points for age $\geq$75 years or stroke. HAS-BLED were calculated with 1 point each for uncontrolled hypertension with systolic blood pressure over 160 mm Hg, abnormal renal function, abnormal hepatic function, previous ischemic or hemorrhagic stroke, bleeding history or predisposition, elderly (age $>$ 65 years), concomitant use of antiplatelet or NSAID and excessive alcohol intake per week, and labile international normalized

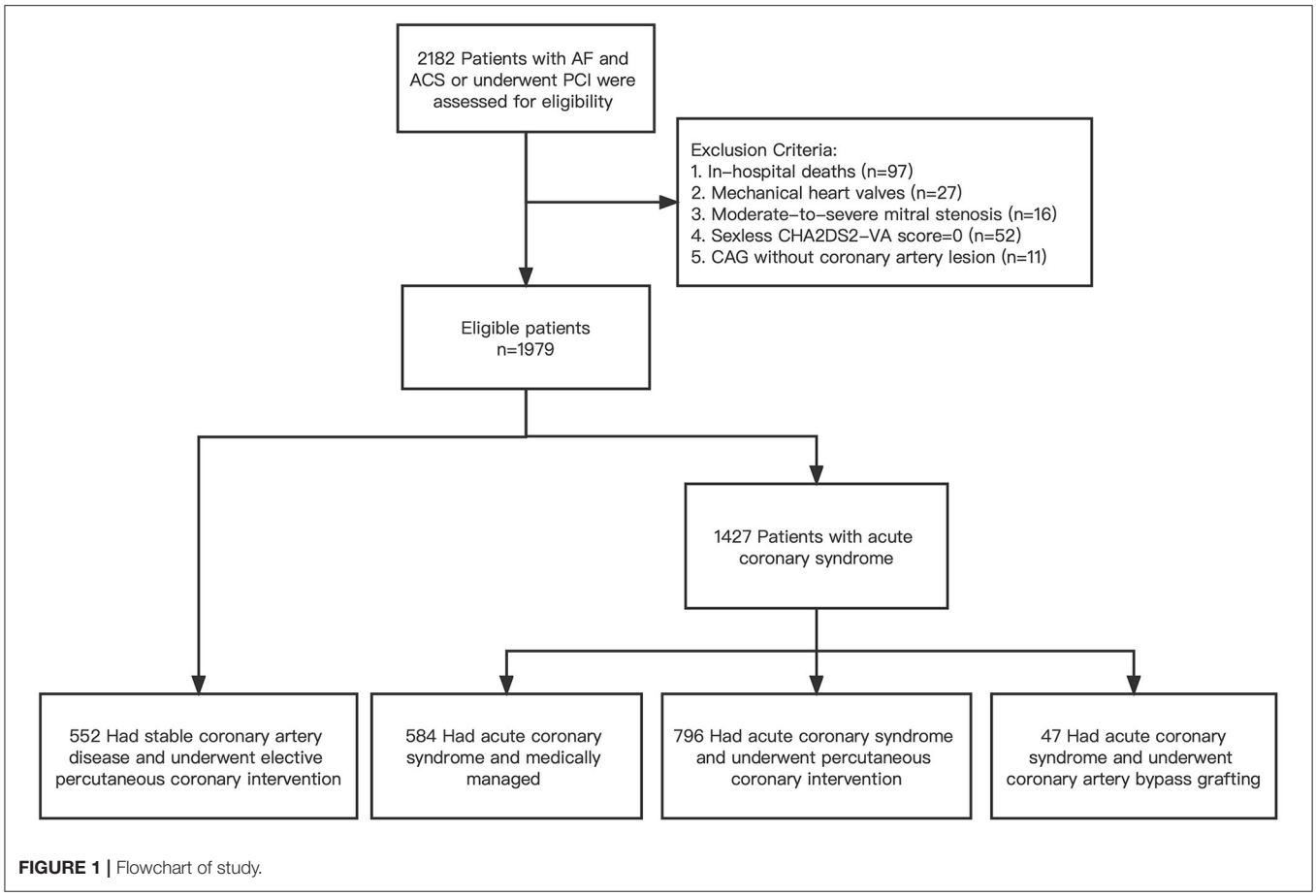

FIGURE 1 | Flowchart of study.

ratio (INR) is applied for patients receiving warfarin with over 3 times INR measurements. The high risk of ischemic thromboembolism was defined as CHA2DS2-VASc score $\geq$2, and the high risk of bleeding was defined as HAS-BLED score $\geq$3.

Antithrombotic Regimens

The antithrombotic regimens were evaluated by the prescription of antithrombotic drugs at discharge including antiplatelet and oral anticoagulants (OACs). The antiplatelet drugs include aspirin, clopidogrel, and ticagrelor, and OACs comprise both vitamin K antagonist (VKA, e.g., warfarin) and nonvitamin K oral anticoagulants (NOACs, e.g., rivaroxaban or dabigatran).

We classified the antithrombotic treatment according to the combination of prescribed drugs into the following six regimens: no treatment, single antiplatelet therapy (SAPT), dual antiplatelet therapy (DAPT), OAC monotherapy, double therapy (DT, with an OAC and SAPT in combination), and triple therapy (TT, with OAC and DAPT in combination). And TT and DT together are called combined therapy. Besides, TT and DT were further classified into NOAC-based TT (NOAC + DAPT), VKA-based TT (VKA + DAPT), NOAC-based DT (NOAC + SAPT), and VKA-based DT (VKA + SAPT).

Data Collection

Data about demographic information, baseline comorbidities, and medication usage were collected by trained research personnel *via* interviewing the participants, reviewing medical records (namely, hospital diagnoses and prescription information), and contacting their treating physicians. Individual CHA2DS2-VASc score and HAS-BLED score were calculated by using the information on comorbidities at baseline retrospectively. And source data verification was conducted by the computer-based patient record management system. The study design and protocol have been approved by the Ethics Committee of Fuwai Hospital (Approved No. 2017-923) and conformed to the Declaration of Helsinki. All the patients have signed consent to participate in this study.

Statistical Analysis

Descriptive statistics were used to summarize and analyze the baseline demographic characteristics, medical history, clinical risk score assessment, and in-hospital invasive treatment by cohort. Besides, the antithrombotic therapy and drug usage were summarized and analyzed by cohort. Then, the temporal trend in antithrombotic therapy was further analyzed by CHA2DS2-VASc score and cohort, by HAS-BLED score and cohort, by CAD type and cohort, and by treatment type and cohort.

To investigate factors affecting the prescription of TT or DT after recent ACS/PCI in patients with AF, baseline demographic characteristics, medical history, clinical risk score, and in-hospital invasive treatment were compared between patients with TT/DT and those with only DAPT. Then logistic regression analysis was performed to investigate the difference in the TT/DT or DAPT prescription across different CHA2DS2-VASc scores and HAS-BLED scores. In addition, multivariable logistic regression analysis was performed using the forward stepwise (LR) method to evaluate the independent predictors of favoring TT/DT over DAPT, with variables comprising year cohort, AF type, CAD type, gender, age, congestive heart failure (CHF), hypertension, diabetes, CAD, PAD, stroke/transient ischemic attack (TIA)/systemic embolism (SE), history of bleeding, advanced chronic kidney disease (CKD) [estimated glomerular filtration rate (eGFR) $<$ 30 ml/min/1.73 m^2], and in-hospital invasive treatment.

The multivariate logistic regression models were applied to verify the independent effect of time trend on TT/DT use by adjusting for potential confounders. Model 1 was the crude model without adjustment. Model 2 was adjusted for AF type, CAD type, and treatment type. Model 3 was further adjusted factors in the CHA2DS2-VASc score, namely, age, sex, CHF, hypertension, diabetes mellitus, stroke/TIA/SE, prior MI, and peripheral arterial disease.

Continuous variables were expressed as mean ± SD or median with interquartile ranges as appropriate and one-way ANOVA or the Mann–Whitney *U*-test was used to compare the difference among groups. Categorical variables were presented as the frequency with percentage and the chi-squared test was used. The significance of the linear time trend over the study period was assessed using linear regression analysis or logistic regression analysis. Statistical significance was set at $p < 0.05$. All the analyses were performed using software packages SPSS (version 26.0).

RESULTS

Study Population

Between January 2017 and December 2019, 2,182 patients with AF and ACS or who underwent PCI were enrolled to assess eligibility. A total of 1,979 patients were included in the final analysis, and divided into three consecutive sequential cohorts by year: cohort 1 (2017), $n = 674$; cohort 2 (2018), $n = 793$; cohort 3 (2019), $n = 512$.

Baseline characteristics and in-hospital treatment strategy were listed in **Table 1**. Among the baseline characteristics, there is a slightly higher prevalence of ACS, prior CAD, alcohol intake, and a slightly lower prevalence of CHF in cohort 2. During the study period, over 90% of patients were at a high stroke risk with a CHA2DS2-VASc score ≥2, and over 1/3 of patients were at a high bleeding risk with HAS-BLED score ≥3. Considering in-hospital invasive treatment, over two-thirds of patients had undergone PCI and the prevalence of PCI increased over time (P trend = 0.014), while the rest variables were similar among the groups.

Trend in Antithrombotic Therapy and Drug Usage

Table 2 shows the prescribing pattern at discharge for patients concomitant with NVAF and ACS/PCI in all three cohorts. Although the majority of patients were prescribed DAPT without OAC at discharge, the proportion of DAPT reduced from nearly 70 to <50% over the 3 years (P trend < 0.001). The combined therapy (OAC with single or dual antiplatelet) was increased from cohort 1 (27.2%) to cohort 3 (50.0%) (P trend < 0.001). Both the proportion of TT (from 14.4 to 30.5%, P trend < 0.001) and DT (12.8%−19.5%, P trend < 0.001) increased over time. The rise was due to the prevalence use of NOAC, as the prescription of both NOAC + DAPT (from 6.1 to 25.0%, P trend < 0.001) and NOAC + SAPT (from 6.5 to 17.6%, P trend < 0.001) increased over the study period. At the same time, there was a decline in the use of VKA, regardless of VAK + DAPT (from 8.3 to 5.5%, P trend = 0.034) or VKA + SAPT (from 6.2 to 2.0%, P trend < 0.001). While the proportion of patients not receiving antithrombotic therapy remained unchanged ($p = 0.274$, P trend = 0.161). Considering the drug-specific prescription, there is a decreasing trend in aspirin (from 87.2 to 79.5%, P trend < 0.001) and VKA (from 14.7 to 7.6%, P trend < 0.001) use. And there is an increasing trend in NOACs (from 13.5 to 42.8%, P trend < 0.001) use, especially for rivaroxaban (from 8.5 to 37.3%, P trend < 0.001) use. While the prescription rate of clopidogrel, ticagrelor, and dabigatran stayed almost the same.

Subgroup Analysis of Trend in Antithrombotic Therapy

The increasing trend of TT/DT prescription was observed regardless of CHA2DS2-VASc score level (**Figure 2A**), HAS-BLED score level (**Figure 2B**), CAD type (**Figure 2C**), or management type (**Figure 2D**). Patients with CHA2DS2-VASc score ≥2 and patients treated medically had higher TT/DT prescription rates regardless of cohort year when compared with those with CHA2DS2-VASc score = 1 or those treated invasively, while the difference in antithrombotic prescription between patients with different inclusion events (SCAD or ACS) was not obvious. And an incremental relationship was observed between CHA2DS2-VASc score and TT/DT prescription (P for trend < 0.001, **Figure 3A**). While, the proportion of patients on TT/DT stayed the same across different HAS-BLED scores (P for trend = 0.058, **Figure 3B**). When compared with the low bleeding risk subgroup (HAS-BLED score = 0–2), patients with high bleeding risk (HAS-BLED score ≥3) processed a borderline increased likelihood of TT/DT prescription [odds ratio (OR) 1.21, 95%CI 1.00–1.46, **Figure 3B**].

Predictors of Favoring TT/DT Over DAPT

Table 3 compares the baseline characteristics and invasive treatment between patients with TT/DT and those with only DAPT. Patients on TT/DT were more likely to be with persistent AF ($p < 0.001$), CHF ($p < 0.001$), hypertension ($p < 0.001$), DM ($p < 0.001$), prior history of stroke/TIA/SE ($p < 0.001$), and possessed higher CHA2DS2-VASc score ($p < 0.001$). Besides, patients with TT/DT were more likely treated conservatively

TABLE 1 | Baseline characteristics of the study population.

Variable	Total 2017–2019 *n* = 1,979	Cohort 1 2017 *n* = 674	Cohort 2 2018 *n* = 793	Cohort 3 2019 *n* = 512	*p*-value
Demographic characteristics					
Sex (female sex)	552 (27.9%)	203 (30.1%)	211 (26.6%)	138 (27.0%)	0.281
BMI	25.7 ± 3.4[a]	25.6 ± 3.5[b]	25.7 ± 3.5[c]	25.7 ± 3.2[d]	0.813
Age at diagnosis	67.7 ± 9.6	68.3 ± 9.9	67.4 ± 9.5	67.6 ± 9.5	0.224
AF type					
New-onset	166 (8.6%)	57 (8.7%)	69 (8.9%)	40 (8.0%)	0.838
Pre-existing	1,759 (91.4%)	596 (91.3%)	703 (91.1%)	460 (92.0%)	0.838
PAF	1,312 (68.2%)	438 (67.1%)	521 (67.5%)	353 (70.6%)	0.389
PeAF	613 (31.8%)	215 (32.9%)	251 (32.5%)	147 (29.4%)	0.389
CAD type					
SCAD	552 (27.9%)	211 (31.3%)	186 (23.5%)	155 (30.3%)	0.001
ACS	1,427 (72.1%)	463 (68.7%)	607 (76.5%)	357 (69.7%)	0.001
Medical history					
CHF	414 (20.9%)	139 (20.6%)	131 (16.5%)	144 (28.1%)	<0.001
Hypertension	1,541 (77.9%)	511 (75.8%)	633 (79.8%)	397 (77.5%)	0.179
DM	837 (42.3%)	279 (41.4%)	332 (41.9%)	226 (44.1%)	0.607
STROKE/TIA/SE	513 (25.9%)	177 (26.3%)	212 (26.7%)	124 (24.2%)	0.581
Stroke/TIA	498 (25.2%)	169 (25.1%)	206 (26.0%)	123 (24.0%)	0.728
SE	31 (1.6%)	15 (2.2%)	12 (1.5%)	4 (0.8%)	0.138
PAD	316 (16.0%)	101 (15.0%)	129 (16.3%)	86 (16.8%)	0.670
Prior-CAD	1,347 (68.1%)	444 (65.9%)	566 (71.4%)	337 (65.8%)	0.036
Prior-MI	544 (27.5%)	172 (25.5%)	233 (29.4%)	139 (27.1%)	0.251
Prio-PCI	578 (29.2%)	195 (28.9%)	250 (31.5%)	133 (26.0%)	0.097
Prior-CABG	139 (7.0%)	52 (7.7%)	59 (7.4%)	28 (5.5%)	0.273
Prior-Bleeding	139 (7.0%)	47 (7.0%)	58 (7.3%)	34 (6.6%)	0.896
CKD (eGFR < 30 ml/min)	41 (2.1%)	15 (2.2%)	10 (1.3%)	16 (3.1%)	0.066
Cancer	63 (3.2%)	26 (3.9%)	25 (3.2%)	12 (2.3%)	0.338
Current smoker	474 (24.0%)	155 (23.0%)	209 (26.4%)	110 (21.5%)	0.102
Current drinker	438 (22.1%)	155 (23.0%)	196 (24.7%)	87 (17.0%)	0.004
Clinical risk score					
CHA2DS2-VASc score	4 (2–5)	4 (3–5)	3 (2–5)	4 (2–5)	0.284
HAS-BLED score	2 (2–3)	2 (2–3)	2 (2–3)	2 (2–3)	0.598
CHA2DS2-VASc score ≥ 2	1,791 (90.5%)	607 (90.1%)	723 (91.2%)	461 (90.0%)	0.706
HAS-BLED score ≥ 3	723 (36.5%)	246 (36.5%)	284 (35.8%)	193 (37.7%)	0.788
Invasive treatment					
CAG	1,608 (81.3%)	539 (80.0%)	637 (80.3%)	432 (84.4%)	0.108
PCI	1,348 (68.1%)	444 (65.9%)	531 (67.0%)	373 (72.9%)	0.026
Stent	1,204 (60.8%)	398 (59.1%)	475 (59.9%)	331 (64.6%)	0.115
DEB	96 (4.9%)	24 (3.6%)	46 (5.8%)	26 (5.1%)	0.133
CABG	47 (2.4%)	20 (3.0%)	22 (2.8%)	5 (1.0%)	0.053
None	584 (29.5%)	210 (31.2%)	240 (30.3%)	134 (26.2%)	0.147

[a] *128 patients missing.*
[b] *48 patients missing.*
[c] *40 patients missing.*
[d] *40 patients missing.*
Data are presented as number (%) or mean ± SD.
AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; SCAD, stable coronary artery disease; ACS, acute coronary syndrome; BMI, body mass index; CHF, congestive heart failure; DM, diabetes mellitus; TIA, transient ischemic attack; SE, systemic embolism; PAD, peripheral arterial disease; CAD, stable coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; DEB, drug eluting balloon; CABG, coronary artery bypass graft, CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CAG, coronary angiography.

TABLE 2 | Trends of antithrombotic therapy and drug usage of patients with AF concomitant with ACS or underwent PCI.

Variable	Total 2017–2019 *n* = 1,979	Cohort 1 2017 *n* = 674	Cohort 2 2018 *n* = 793	Cohort 3 2019 *n* = 512	*p*-value	*P*-value for trend*
Anti-thrombotic therapy						
OAC + DAPT	423 (21.4%)	97 (14.4%)	170 (21.4%)	156 (30.5%)	<0.001	<0.001
NOAC + DAPT	297 (15.0%)	41 (6.1%)	128 (16.1%)	128 (25.0%)	<0.001	<0.001
VKA + DAPT	126 (6.4%)	56 (8.3%)	42 (5.3%)	28 (5.5%)	0.039	0.034
OAC + SAPT	305 (15.4%)	86 (12.8%)	119 (15.0%)	100 (19.5%)	0.006	0.002
NOAC + SAPT	229 (11.6%)	44 (6.5%)	95 (12.0%)	90 (17.6%)	<0.001	<0.001
VKA + SAPT	76 (3.8%)	42 (6.2%)	24 (3.0%)	10 (2.0%)	<0.001	<0.001
Combined therapy (OAC + DAPT/SAPT)	728 (36.8%)	183 (27.2%)	289 (36.4%)	256 (50.0%)	<0.001	<0.001
OAC	16 (0.8%)	7 (1.0%)	7 (0.9%)	2 (0.4%)	0.446	0.229
DAPT	1,184 (59.8%)	460 (68.2%)	477 (60.2%)	247 (48.2%)	<0.001	<0.001
SAPT	46 (2.3%)	24 (3.6%)	17 (2.1%)	5 (1.0%)	0.013	0.003
None	5 (0.3%)	0 (0.0%)	3 (0.4%)	2 (0.4%)	0.274	0.161
Drug usage						
ASA	1,677 (84.7%)	588 (87.2%)	682 (86.0%)	407 (79.5%)	0.001	<0.001
Clopidogrel	1,694 (85.6%)	576 (85.5%)	664 (83.7%)	454 (88.7%)	0.046	0.166
Ticagrelor	194 (9.8%)	60 (8.9%)	84 (10.6%)	50 (9.8%)	0.555	0.564
OAC use	744 (37.6%)	190 (28.2%)	296 (37.3%)	258 (50.4%)	<0.001	<0.001
VKA	206 (10.4%)	99 (14.7%)	68 (8.6%)	39 (7.6%)	<0.001	<0.001
Dabigatran	102 (5.2%)	34 (5.0%)	40 (5.0%)	28 (5.5%)	0.932	0.756
Rivaroxaban	436 (22.0%)	57 (8.5%)	188 (23.7%)	191 (37.3%)	<0.001	<0.001

*OAC, oral anticoagulants; DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy; NOAC, nonvitamin K antagonist oral anticoagulants; VKA, vitamin K antagonist. *p value for trend was calculated using linear regression analysis.*

without invasive treatment ($p < 0.001$) and with less stent implantation ($p < 0.001$).

Then, the multivariate logistic regression analysis was performed to evaluate the independent predictors associated with the prescription of TT/DT or DAPT (**Figure 4**). The increased cohort year, persistent AF type, and history of CHF, hypertension, diabetes mellitus, and stroke/TIA/SE were associated with a higher prescription of TT/DT. In addition to increased cohort year, persistent AF was the most significant predictor of TT/DT [oddsratio(OR), 3.27; 95%CI, 2.62–4.10]. While ACS, PCI, or CKD with eGFR < 30 ml/min/1.73 m^2 was associated with underuse of the combined therapy, the most significant predictor of DAPT was PCI (OR, 0.29, 95% CI, 0.22–0.38), while age, sex, history of vascular diseases, and previous bleeding events had little effect on the choice of antithrombotic therapy.

Verification of Temporal Trend in Evolving Antithrombotic Treatment

The multivariate logistic regression model was applied to verify the independent effect of time trend on TT/DT use. The association between yearly trends and TT/DT use is shown in **Table 4**. In the crude model, using cohort 1 as a reference, patients in cohort 2 (OR 1.56, 95% CI 1.24–1.96, $p < 0.001$) and cohort 3 (OR 2.73, 95% CI 2.14–3.50, $p < 0.001$) has a higher prescription rate of TT/DT and is increasing over time (P trend < 0.001). The results remained statistically significant after adjustment for confounders in Model 2–3. In the full adjusted model, the association between year cohort and TT/DT remained statistically significant (OR 1.76, 95% CI: 1.36–2.27, cohort 2 vs. cohort 1; OR 3.43, 95% CI: 2.59–4.54, cohort 3 vs. cohort 1; P trend < 0.001).

DISCUSSION

In this study, we investigated the evolving trend in antithrombotic therapy, and our principal findings were as follows: (1) The majority of patients were administered DAPT without OAC; (2) Both the TT and DT prescriptions showed a gradual increment over time, and the total amount of TT/DT prescriptions surpassed 50% in 2019; (3) An incremental relationship between CHA2DS2-VASc score and combined therapy prescription was identified; (4) The predictors of TT/DT use were persistent AF type and history of CHF, hypertension, diabetes mellitus, and stroke/TIA/SE. ACS or PCI and CKD with eGFR < 30 ml/min/1.73 m^2 were associated with underuse of the combined therapy; and (5) Temporal trend was the independent factor related to the incremental use of TT/DT.

The choice of antithrombotic therapy for patients concomitant of AF and ACS/PCI presents a great challenge in the real-world clinical scenario. The risk of ischemic events and the risk of bleeding need to be balanced carefully. Plenty of efforts have been made to explore this issue since 2013. Based on the result of WOEST (21), ISAR-TRIPLE (22),

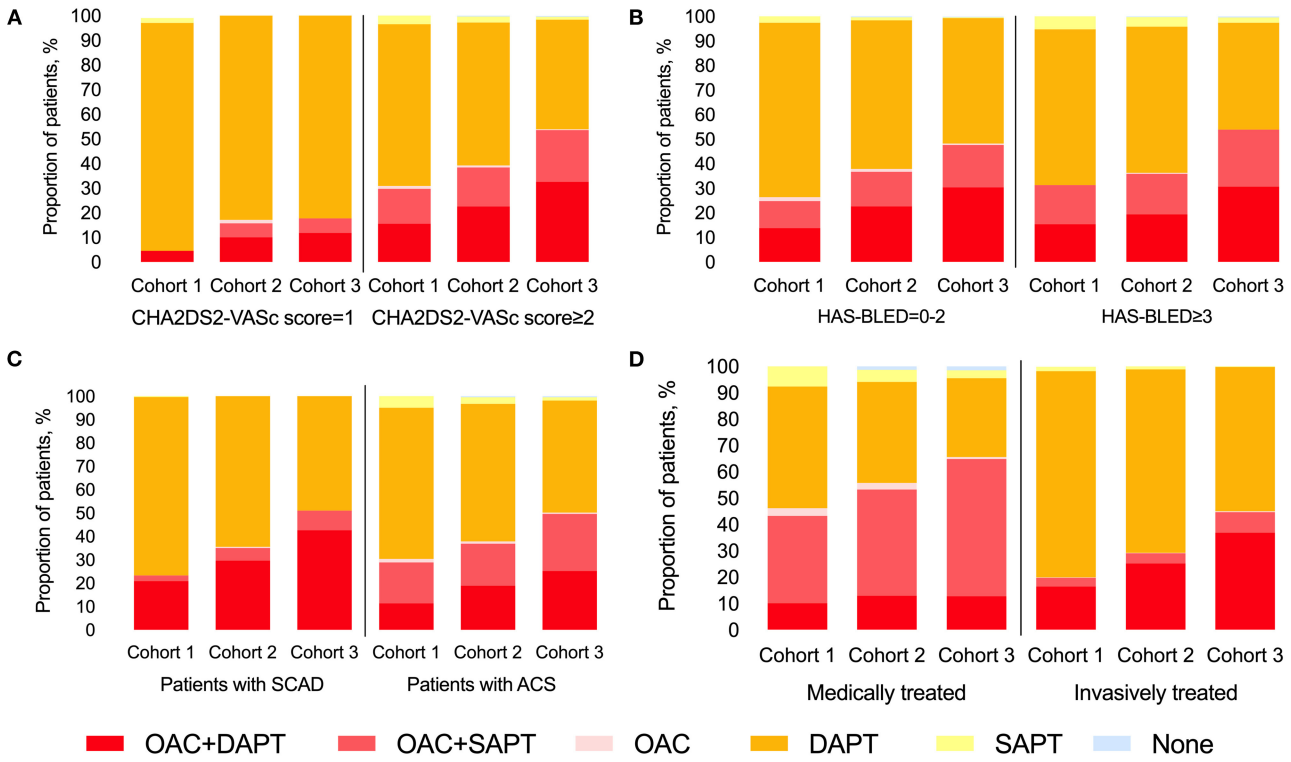

FIGURE 2 | Trend of antithrombotic treatment at discharge stratified by CHA2DS2-VASc score and cohort **(A)**, by HAS-BLED score and cohort **(B)**, by CAD type and cohort **(C)**, and by treatment type and cohort **(D)**. CAD, coronary artery disease; SCAD, stable coronary artery disease; ACS, acute coronary syndrome; OAC, oral anti-coagulants; DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy.

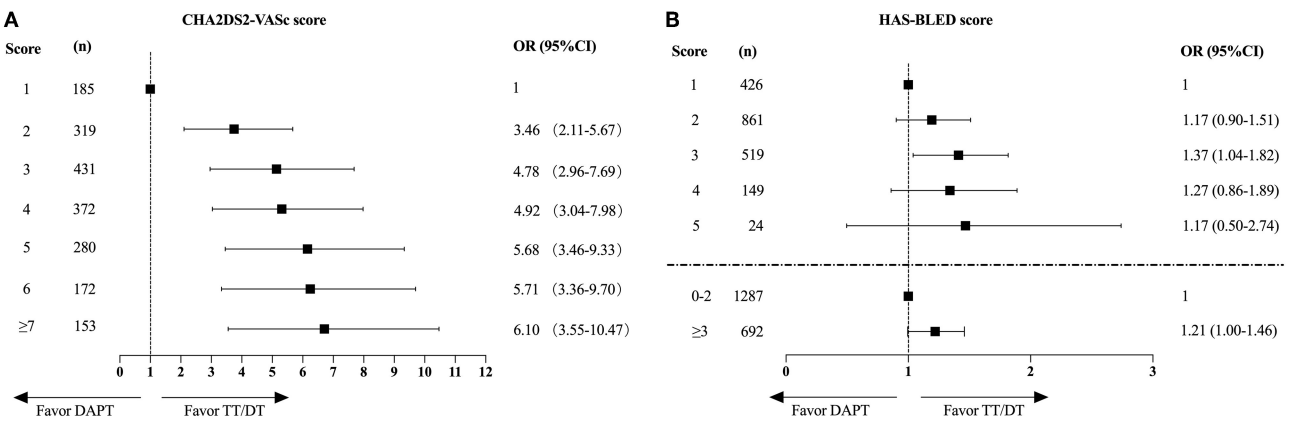

FIGURE 3 | The impact of CHA2DS2-VASc scores **(A)** or HAS-BLED scores **(B)** on the choice of antithrombotic therapy. CHA2DS2-VASc score of 1 and HAS-BLED score of 1 served as the reference respectively. OR, odds ratio; CI, confidence interval; DAPT, dual antiplatelet therapy; TT, triple therapy; DT, double therapy.

and four pivotal NOAC-based RCTs (11–14), guidelines and consensus documents updated from the North American (16, 17), European (7, 15), and Chinese (18) recommended combined therapy with short-course TT and following DT in patients with NVAF and ACS/PCI. Besides, NOACs are preferred over VKA, and clopidogrel is the most advocated P2Y12 inhibitor.

However, the data on detailed temporal trends in real-world clinical practice were relatively scarce, especially in China. Our study shows a clear gap between real-world everyday medical practice and guideline recommendations. In our study, DAPT was the most commonly prescribed regimen at discharge (59.8%), rather than the guideline-recommended TT/DT. And there is a small proportion of patients were prescribed with

TABLE 3 | Baseline characteristics of patients by DATP or TT/DT treatment type.

Variable	DAPT $n = 1,184$	TT/DT $n = 728$	*p*-value
Demographic characteristics			
Sex (female sex)	315 (26.6%)	214 (29.4%)	0.185
BMI	25.6 ± 3.4[a]	25.8 ± 3.4[b]	0.447
Age at diagnosis	67.5 ± 9.9	67.7 ± 8.9	0.565
AF type			
New-onset	99 (8.6%)	59 (8.3%)	0.838
Pre-existing	1,053 (91.4%)	650 (91.7%)	0.838
PAF	900 (78.1%)	367 (51.8%)	<0.001
PeAF	252 (21.9%)	342 (48.2%)	<0.001
CAD type			
SCAD	357 (30.2%)	193 (26.5%)	0.088
ACS	827 (69.8%)	535 (73.5%)	0.088
Medical history			
CHF	162 (13.7%)	231 (31.7%)	<0.001
Hypertension	898 (75.8%)	597 (82.0%)	<0.001
DM	461 (38.9%)	349 (47.9%)	<0.001
STROKE/TIA/SE	263 (22.2%)	227 (31.2%)	<0.001
Stroke/TIA	259 (21.9%)	218 (29.9%)	<0.001
SE	8 (0.7%)	16 (2.2%)	0.004
PAD	174 (14.7%)	130 (17.9%)	0.066
Prior-CAD	821 (69.3%)	486 (66.8%)	0.238
Prior-MI	301 (25.4%)	224 (30.8%)	0.011
Prior-PCI	367 (31.0%)	198 (27.2%)	0.077
Prior-CABG	72 (6.1%)	63 (8.7%)	0.033
Prior-Bleeding	66 (5.6%)	57 (7.8%)	0.051
CKD (eGFR < 30 ml/min)	22 (1.9%)	14 (1.9%)	0.919
Cancer	43 (3.6%)	16 (2.2%)	0.078
Current smoker	305 (25.8%)	157 (21.6%)	0.037
Current drinker	279 (23.6%)	148 (20.3%)	0.099
Clinical risk score			
CHA2DS2-VASc score	3 (2–5)	4 (3–5)	<0.001
HAS-BLED score	2 (2–3)	2 (2–3)	0.058
Invasive treatment			
CAG	1,034 (87.3%)	544 (74.7%)	<0.001
PCI	931 (78.6%)	407 (55.9%)	<0.001
Stent	848 (71.6%)	352 (48.4%)	<0.001
DEB	63 (5.3%)	30 (4.1%)	0.236
PTCA	18 (1.5%)	18 (2.5%)	0.137
CABG	24 (2.0%)	15 (2.1%)	0.96
None	229 (19.3%)	306 (42.0%)	<0.001

[a] *96 patients missing.*

[b] *23 patients missing.*

Data are presented as number (%) or mean ± SD.

AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; SCAD, stable coronary artery disease; ACS, acute coronary syndrome; BMI, body mass index; CHF, congestive heart failure; DM, diabetes mellitus; TIA, transient ischemic attack; SE, systemic embolism; PAD, peripheral arterial disease; CAD, stable coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; DEB, drug eluting balloon; PTCA, percutaneous transluminal coronary angiography; CABG, coronary artery bypass graft; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CAG, coronary angiography.

merely OAC, SAPT, or no treatment. These results highlight the undertreated status of patients with NVAF and ACS/PCI in China and are in line with other countries. A Korean study (23) reported their nationwide registries from 2013 to 2018, and OAC in patients with AF after PCI were underprescribed. Besides, this phenomenon was also prevalent in western populations. A nationwide Danish study (24) retrospectively analyzed the antithrombotic treatment of 8,659 patients with AF admitted with a MI ($n = 6,362$) and/or underwent PCI ($n = 2,297$) from 2011 to 2017, finding <1/2 patients were treated with DT/TT ($n = 3,222$). The underprescription of OAC-based TT/DT in our study might be caused by concerns of physicians in China. As TT/DT has been shown to increase the risk of bleeding (25), Asians are more prone to suffer from anticoagulant-related bleeding and intracranial hemorrhage when compared with Caucasians (26, 27). For the sake of safety, physicians were hesitant to add OAC on top of antiplatelet therapy. Bedsides, this grim status is partially related to the insufficient awareness of thromboembolism risk and exaggerated concern of bleeding risk in Chinese patients with AF (28). The need for regular INR monitoring and excessive interaction with other medication or foods were related to the reluctance of patients to receive warfarin. Although NOACs have been proved to possess a favorable safety, efficacy, and convenience, the less well-off economic status and insufficient healthcare expenditure limited the wide application of NOACs in China (29). These indicate that better academic education and health policies are required to improve the management status for patients with AF and ACS/PCI.

Then, we investigate the difference in the TT/DT or DAPT prescription across different CHA2DS2-VASc scores and HAS-BLED scores by utilizing logistic regression analysis. The CHA2DS2-VASc score was significantly related to the prescription of TT/DT, and the association was more pronounced in higher risk score subgroups. While, the bleeding risk evaluated by HAS-BLED score has little effect on the choice of antithrombotic regimens, as the proportion of patients on TT/DT stayed almost the same across different HAS-BLED scores. Besides, patients with higher bleeding risk (HAS-BLED score ≥3) possessed a borderline increased likelihood of TT/DT prescription. This might due to the fact that bleeding risk factors frequently overlap with thromboembolism risk factors. Those patients with high bleeding risk often possess high thromboembolic risk as well. Besides, clinical guidelines suggest that HAS-BLED scores should be utilized to assess the risk of bleeding, rather than define whether a patient should be treated with OAC (16). By using the HAS-BLED score, potentially modifiable bleeding risk factors can be identified and altered by treatment or by changing lifestyle. So, the prescription rate of TT/DT did not decrease in patients with high bleeding risk (HAS-BLED score ≥3) in this study.

Moreover, we explored the independent predictors of TT/DT prescription and the factors associated with the suboptimal use of combined therapy by using multivariable logistic regression analysis. In addition to the temporal trend of TT/DT use, persistent AF type and history of CHF, hypertension, diabetes mellitus, and stroke/TIA/SE were associated with a higher prescription of TT/DT. This is in line with a previous study utilizing Korea nationwide registry data, which also found traditional thromboembolism risk factors, namely, female

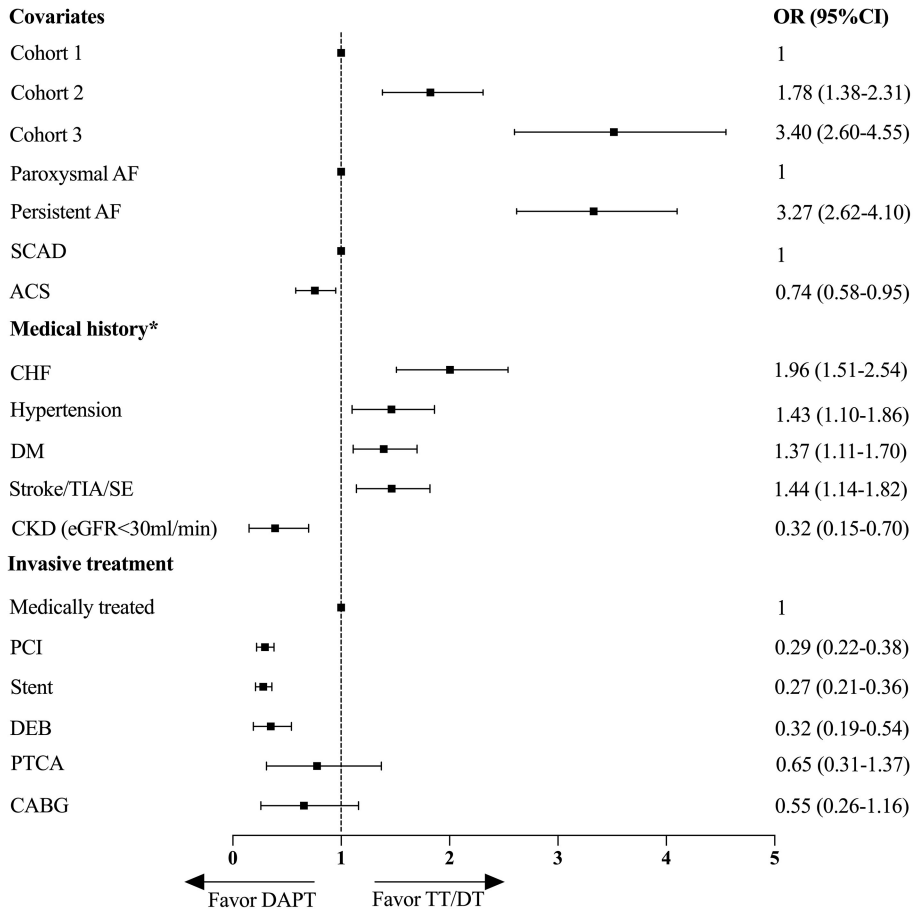

FIGURE 4 | Multivariate logistic regression analysis for factors associated with the prescriptions of TT/DT or DAPT. *Reference group is patient with no medical history or no invasive treatment. OR, odds ratio; CI, confidence interval; DAPT, dual antiplatelet therapy; TT, triple therapy; DT, double therapy; AF, atrial fibrillation; SCAD, stable coronary artery disease; ACS, acute coronary syndrome; CHF, congestive heart failure; DM, diabetes mellitus; TIA, transient ischemic attack; SE, systemic embolism; CKD, chronic kidney disease; PCI, percutaneous coronary intervention; DEB, drug eluting balloon; PTCA, percutaneous transluminal coronary angiography; CABG, coronary artery bypass graft.

gender, DM, prior cerebrovascular accident, and CHF are significant determinants of OAC use (30). And patients with persistent AF possessed higher thromboembolism risk when compared with those with paroxysmal AF (31). Our results indicate that more AF burden and traditional thromboembolism risk factors have more impact on clinical antithrombotic strategy making, and patients with these factors were more inclined to receive combined therapy. While ACS or PCI and advanced CKD stage were associated with underuse of the combined therapy. The prevalent use of DAPT for patients with NVAF having recent coronary ischemic events or coronary intervention indicates intensive attention was on coronary ischemic events prevention and insufficient awareness was on thromboembolism prophylaxis. As DAPT is the default treatment to prevent coronary ischemic events after PCI, and TT/DT increased the risk of bleeding compared with DAPT, physicians were hesitant to add OAC on top of antiplatelet therapy. With evolving evidence and guidelines recommendations, more and

TABLE 4 | Odds ratio (OR) and 95%CI for TT/DT antithrombotic treatment according to year cohort.

	Cohort 1 2017 *n* = 674	Cohort 2 2018 *n* = 793	Cohort 3 2019 *n* = 512	*P*-value for trend*
Model 1:	1.00 (Ref)	1.56 (1.24 to 1.96)	2.73 (2.14 to 3.50)	<0.001
p-values		<0.001	<0.001	
Model 2	1.00 (Ref)	1.77 (1.38 to 2.26)	3.57 (2.73 to 4.67)	<0.001
p-values		<0.001	<0.001	
Model 3	1.00 (Ref)	1.76 (1.36 to 2.27)	3.43 (2.59 to 4.54)	<0.001
p-values		<0.001	<0.001	

Association between year cohort with TT/DT antithrombotic treatment.
*Model 1 was crude model, with no adjustment. Model 2 was adjusted for AF type, CAD type and treatment type. Model 3 was further adjusted for factors in CHA2DS2-VASc score, namely, age, sex, CHF, hypertension, diabetes mellitus, stroke/TIA/SE, prior-myocardial infarction, and peripheral arterial disease. *p-value for trend was calculated using logistic regression analysis.*

more physicians gradually realize that DAPT alone was not sufficient for thromboembolism prevention. This situation has been gradually improved during our study period with an increasing trend of TT/DT prescription. Although CKD is a prothrombotic and prohemorrhagic factor among patients with AF. Anticoagulant therapy was associated with a decreased risk of stroke or systemic thromboembolism among patients concomitant with AF and CKD (32). While, this is still a conundrum in clinical practice, and associated with the underuse of combined therapy. Knowledge regarding these factors related to the selection of antithrombotic therapy is important and necessary for further improving the treatment for patients with NVAF having ACS/PCI.

Another important finding in this study was that a pronounced change in the pattern of antithrombotic therapy prescription has been made in China. There is a shift of antithrombotic regime with reducing DAPT prescription and increasing combined therapy (TT/DT) prescription. This trend was also seen in different subgroups stratified by CHA2DS2-VASc score, HAS-BLED score, CAD type (ACS or SCAD), or management type (invasive treated or medically treated). Moreover, this trend stayed validated after adjusting for confounders, namely, AF type, CAD type, and treatment type, factors in the CHA2DS2-VASc score. This phenomenon demonstrated that clinical practice has been influenced by evolving evidence and guidelines recommendations, which is in line with the result from Taiwan (33). This paradigm shift in prescribing practice has been driven in part by the prevalence use of NOACs with a better risk-to-benefit ratio of NOAC-based DT than VKA-based TT (34). In addition, this trend might also be driven by the realization that DAPT alone was not sufficient for thromboembolism prevention (25).

Strengths

There are several strengths in this study. First, this study was conducted in the largest medical center for cardiovascular diseases in China, representing the most advanced level of clinical practice in our country. To the best of our knowledge, this is the largest cross-sectional study conducted in China until now in this field. Second, a great deal of clinically important information was collected, namely, patient baseline characteristics, previous history, bleeding profile, and specific treatment strategy. In addition, source data verification was conducted by the computer-based patient record management system to ensure validity.

Limitations

This study also has some limitations. First, since our data were derived from a single medical center, there may be a discrepancy between the drug prescription habit of this single center and the overall population of China. Generalizing the antithrombotic utilization patterns beyond this level of healthcare setting warrants caution. Second, the prescription of TT/DT might be overestimated as some OAC prescription was due to transient purposes like cardioversion or AF ablation. Third, patients with AF may have some specific angiographic characteristics (35). The severity of coronary lesions may influence the choice of antithrombotic regimen. While in this study, procedure-related characteristics in PCI or CABG were not documented and we cannot conduct further relevant analysis. In addition, this study shares the limitations of the cross-sectional study. Duration of therapy, switch of antithrombotic regimens, and clinical outcomes, namely, recurrent thrombotic events, major bleeding events, mortality, and other major adverse clinical events for each regimen were not evaluated. Besides, as NOACs are associated with reduced major adverse outcomes in patients with NVAF (36), future studies can focus on and further investigate the difference in clinical outcome between those treated with NOACs and those treated with VKA in patients with NVAF and ACS/PCI. Lastly, there could still be residual confounding due to unmeasured variables or inadequate control, although substantial efforts have been made in variable collection and adjustments.

CONCLUSION

The antithrombotic treatment at discharge for patients with NVAF having recent ACS/PCI has noticeably changed in recent years. There is a shift of antithrombotic regimen with reducing DAPT prescription and increasing combined therapy (TT/DT) prescription. The predictors of TT/DT use ware persistent AF type and history of CHF, hypertension, diabetes mellitus, and stroke/TIA/SE, while ACS or PCI and CKD with eGFR < 30 ml/min/1.73 m^2 were associated with underuse of the combined therapy. Further studies are warranted to elucidate the clinical outcome with different antithrombotic treatment regimes in Chinese real-world clinical practice.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Fuwai Hospital (Approved No. 2017-923) and conformed to the Declaration of Helsinki. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NS collected the data, performed the statistical analysis, drafted, and wrote the manuscript. Y-mY and JZ designed the study and revised the manuscript. JW, HZ, X-hS, and SW collected the data. All authors read and approved the final manuscript.

FUNDING

This work was supported by Capital's Funds for Research and Application of Clinical Diagnosis and Treatment Technology (Grant/Award Number: Z191100006619121).

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frontiers in Cardiovascular Medicine

MINI REVIEW
published: 29 March 2022
doi: 10.3389/fcvm.2022.864899

Uninterrupted DOACs Approach for Catheter Ablation of Atrial Fibrillation: Do DOACs Levels Matter?

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Most patients present for catheter ablation of atrial fibrillation (CAAF) with residual or full effect of vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs). In daily practice, it has been observed that the activated clotting time (ACT) was actually poorly sensitive to the effect of DOACs and that patients on DOACs required more unfractionated heparin (UFH) to achieve the ACT target of 300 s during the procedure, leading some authors to worry about potential overdosing. Conversely, we hypothesize that these higher doses of UFH are necessary to achieve adequate hemostasis during CAAF regardless of the residual effect of DOACs. During CAAF, thrombosis is promoted mainly by the presence of thrombogenic sheaths and catheters in the bloodstream. Preclinical data suggest that only high doses of DOACs are able to mitigate catheter-induced thrombin generation, whereas low dose UFH already do so. In addition, the effect of UFH seems to be lower in patients on DOACs, compared to patients on VKAs, explaining part of the differences observed in heparin requirements. Clinical studies could not identify increased bleeding risk in patients on DOACs compared to those on VKAs despite similar efficacy during CAAF procedures. Moreover, targeting a lower ACT was associated with an increased periprocedural thrombotic risk for both DOAC and VKA patients. Therefore, the low sensitivity of the ACT to the residual effect of DOACs should not be a major concern in its use in the interventional cardiology laboratory.

Keywords: atrial fibrillation, catheter ablation, direct oral anticoagulant, unfractionated heparin, activated clotting time

OPEN ACCESS

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Thrombosis, a section of the journal Frontiers in Cardiovascular Medicine

Received: *29 January 2022*
Accepted: *28 February 2022*
Published: *29 March 2022*

Citation:
Hardy M, Douxfils J, Dincq A-S, Sennesael A-L, Xhaet O, Mullier F and Lessire S (2022) Uninterrupted DOACs Approach for Catheter Ablation of Atrial Fibrillation: Do DOACs Levels Matter? Front. Cardiovasc. Med. 9:864899. doi: 10.3389/fcvm.2022.864899

INTRODUCTION

Atrial fibrillation (AF) is associated with a significant thrombotic risk, requiring long-term anticoagulation in patients with intermediate or high thrombotic risk (1–4). Nowadays, vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) are the main anticoagulants for stroke prevention in non-valvular AF (1–3). Over the years, catheter ablation of atrial

fibrillation (CAAF) has become a first- or second-line treatment for symptomatic AF (5). However, the procedure is associated with a thrombotic risk and requires the administration of high-dose unfractionated heparin (UFH; between 50 and 120 units per kg just before or immediately after transseptal puncture), exposing patients to a risk of bleeding (5); reported incidences of bleeding (e.g., groin bleeding/hematoma, cardiac tamponade) and embolic (e.g., transient ischemic attacks, strokes) complications during hospitalization being ∼1.9 and 0.2%, respectively (6). Before ablation, most patients receive anticoagulation for at least 3 weeks to reduce the thromboembolic risk associated with CAAF (5).

Historically, VKAs therapy was interrupted and "bridged" with low molecular weight heparins (LMWH) before and after CAAF. In 2014, the COMPARE randomized trial identified a lower rate of periprocedural stroke and minor bleeding when warfarin was continued with an INR in the therapeutic range (i.e., between 2.0 and 3.0) throughout the periprocedural period, compared with discontinuation with LMWH bridging (7). With the introduction of DOACs in non-valvular AF patients, due to the concern of potentially major bleeding and the lack of a convenient reversal agent, DOACs were discontinued in the preprocedural period. Since then, several randomized trials have compared CAAF with uninterrupted DOAC vs. uninterrupted VKA approaches and found no significant differences between the two groups in terms of thrombotic and bleeding complications (8–15). This approach is now recommended over discontinuation and bridging (5). An acceptable alternative to avoid high DOAC peak plasma concentrations during CAAF is to skip one or two DOAC doses before the procedure (16). However, clinical trials that analyzed uninterrupted or minimally interrupted approaches for DOACs were all underpowered.

During the procedure, repeated measurements of the activated clotting time (ACT) each 10–15 min intervals until therapeutic anticoagulation and then at 15–30 min intervals are recommended to guide UFH administration (5). The test, which consists in measuring the time to clot formation in whole blood after complete activation of the contact pathway (e.g., celite or kaolin), is poorly sensitive to DOACs, especially to direct factor Xa inhibitors, even at high concentrations corresponding to the peak effect (17). An ACT maintained above 300 s is recommended during CAAF on VKA therapy based on studies visualizing a lower incidence of thrombi in left heart chambers and according to observational studies (5, 18–20). This threshold is applied similarly for CAAF on DOAC therapy despite a lower level of evidence. However, higher UFH doses are required to achieve the ACT goal of 300 s when DOACs are on board, compared to VKAs (8, 15, 18, 21–27), which corresponds to a potential overdosage according to some authors (21, 28). Conversely, we hypothesize that these higher doses of UFH are necessary to achieve adequate hemostasis during the procedure and that considering the residual effect of DOACs would not be as important as expected. The following paper will get some insights into the mechanisms of thrombosis during CAAF and the possibilities to manage them.

DISCUSSION

Mechanisms of Thrombosis During CAAF by Thermocoagulation

In addition to possible pre-existing thrombi that may be dislodged by the catheters or by fluctuations in heart rhythm during the procedure, several mechanisms have been advocated to explain thrombi formation during CAAF (29, 30). First, direct endothelial damage may result from the passage of sheaths and catheters from the femoral vein to the left atrium and from thermal injuries during the ablation procedure; radiofrequency ablation could be more thrombogenic than cryoablation by this mean (31). Second, the contact pathway is activated on the surface of foreign materiel (sheaths, catheters) in the bloodstream (**Figure 1**) and by cell debris such as DNA or polyphosphates released during thermoablation. Occasionally, emboli may also arise from coagulum or char formation on the ablation electrode, which can be limited by proper technique and does not seem to depend on hemostasis and anticoagulation (32). Of those thrombus/coagulum sources, those formed in the left atrium are particularly dangerous because they are more likely to embolize into the systemic circulation, whereas emboli formed in peripheral veins or right chambers can only embolize into the systemic circulation through an interatrial communication.

During CAAF, intracardiac ultrasound can be used to directly visualize thrombi formed in the cardiac chambers. Small observational studies identified that thrombi form primarily on transseptal sheaths or on mapping catheters (19, 20, 33–36). Less frequently, thrombi are also seen in the left atrium, pulmonary vein or left atrial appendix; however, as some of these thrombi can be extracted by strong suction through the sheath during its removal, some authors emphasized that those thrombi could have been initially related to the sheath or the catheter itself (35). It should be noted that no thrombi are generally observed on the ablation lesion itself during the procedure and radiofrequency ablation is not associated with an increase in *in vivo* thrombin generation markers (such as thrombin-antithrombin complexes), compared with the mapping phase or with single electrophysiological studies (33, 37–39). Taken together, these data suggest that sheaths/catheters may be the main source of intracardiac thrombus formation during CAAF.

The thrombogenicity of catheters has been studied in preclinical models (40–46). Yau et al. demonstrated *in vitro* that clot forms three times faster in the presence of catheters than in their absence (41). They identified that coagulation was activated on the surface of catheters via the contact pathway, as the procoagulant effect of the catheters was reduced or reversed by corn trypsin inhibitor, in plasma deficient in factor XI or XII, or in rabbits treated with antisense oligonucleotide for factor XII or XI (41, 42, 45). Another research group demonstrated that *Ixodes ricinus Contact Pathway Inhibitor (Ir-CPI)* also has the potential to reduce the procoagulant effect of catheters *in vitro* (46). Interestingly, they showed that catheters were still able to induce a procoagulant effect in factor XII deficient plasma which could be abolished by the presence of Ir-CPI, suggesting that factor XII is not the only coagulation factor implicated in the activation of the coagulation cascade by catheters (46). As Ir-CPI

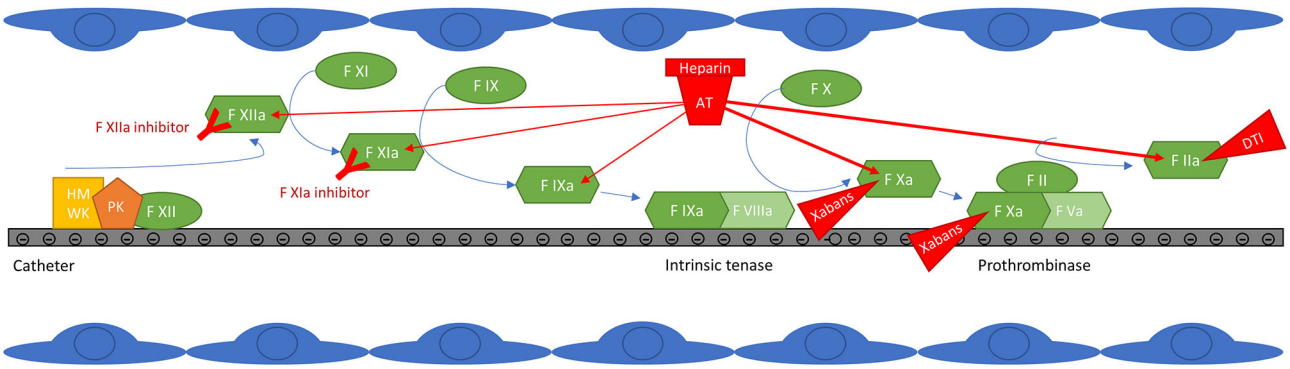

FIGURE 1 | Contact pathway activation at the surface of catheters and targets of anticoagulant drugs. Factor XIIa auto-activates on contact with negatively charged surfaces. High molecular weight kininogen (HMWK) is also adsorbed and serves as a cofactor for FXIIa auto-activation. FXIIa then activates FXI to initiate thrombin generation, but also prekallikrein (PK) to kallikrein, resulting in further FXIIa generation. FXIa activates FIX, which forms the intrinsic tenase with FVIIIa. Intrinsic tenase and prothrombinase complexes form on negatively charged surfaces, classically on the surface of activated platelets, but possibly also on the surface of catheters. The thrombin generated then amplifies the reaction by promoting the activation of factors XI, VIII and V, but it is also a potent platelet activator. In addition to the generation of thrombin initiated by FXIIa, other thrombotic mechanisms take place on the surface of catheters (not shown in the figure): the adsorption of proteins such as fibrinogen, which promotes the adhesion and activation of platelets and leukocytes, potentially increasing thrombin generation and thrombogenesis (47–51). FXIIa, kallikrein and thrombin also activate the complement system which promotes platelet activation and thrombin generation (53–57). The effect of anticoagulant drugs is also depicted: unfractionated heparin (UFH) potentiates the inhibitory effect of antithrombin (AT) mainly on free activated factors X and II, but also to a lesser extent on free activated factors IX, XI and XII (86); clot-bound FXa and FIIa, and FXa within the prothrombinase complex, are less accessible to inhibition by AT (87–89). Direct oral anticoagulants (direct F Xa inhibitors (xabans) and the direct thrombin inhibitor (DTI) dabigatran) directly inhibit activated factor II or X, free, within the prothrombinase complex and clot-bound (89–92). Contact pathway inhibitors specifically target factor XI or XII; truncated antibodies against FXIa or FXIIa are shown in the figure, but this category also includes small inhibiting molecules, antisense oligonucleotides and small interfering RNAs (82).

is a dual inhibitor of both factor XII and factor XI, it is suggested that factor XI is also involved in the thrombogenesis mechanism of catheter-induced thrombosis.

As catheters are the primary site of thrombus formation during CAAF and as these catheters generate thrombin via the contact pathway, contact pathway inhibition may represent the primary target of anticoagulation during CAAF. Although tissue factor (TF) pathway could also contribute to thrombogenesis during the procedure (endothelial lesions by the passage of the sheaths and following cellular destruction during transseptal puncture or the application of thermal energy), UFH at concentrations required to block contact activation would also provide protection on TF-initiated thrombin generation.

Besides direct activation of coagulation upon contact with negatively charged surfaces, other mechanisms can contribute to thrombin generation during CAAF. First, proteins such as fibrinogen are adsorbed to the catheter surface, which promotes platelet adhesion and activation (47–49). Leukocytes can also adhere to adsorbed fibrinogen and platelets (50, 51); leukocytes may then degranulate and promote inflammation. Neutrophils extracellular traps can also activate the coagulation contact pathway and contribute to thrombin generation (52). In addition, the complement system may be activated by FXIIa, kallikrein and thrombin, which may then promote thrombosis through platelet activation and direct thrombin generation (53–57). However, it is less clear to what extent these mechanisms would contribute to thrombogenesis and how clinicians might manage them. Finally, direct measurement of haemostasis proteins/biomarkers in cardiac chambers could be more sensitive and help to understand pathogenesis more precisely (58, 59).

Pharmacological Prevention of Contact Phase Activation

Among the conventional anticoagulants, heparins are preferred for contact inhibition in the acute setting [e.g., CAAF, extracorporeal circuits, mechanical heart valves (MHV)] (**Figure 1**). Previous work identified that inhibition of catheter-induced thrombin generation was more effective with UFH than with LMWH and poorly effective with fondaparinux, which was also ineffective at blocking FXIIa- and FXIa-initiated thrombin generation (41). Similar results were also observed in a rabbit model of catheter thrombosis (41). This could be due to the greater anti-IIa activity of UFH, compared to LMWH or fondaparinux, or to its upstream effect on free FIXa (60).

Whereas, UFH strongly inhibits contact-initiated thrombin generation, the ability of DOACs to do so may be much less. For example, only dabigatran concentrations of 200 ng/mL and above were able to attenuate *in vitro* polyurethane catheter-induced thrombin generation, whereas UFH concentrations as low as 0.02 IU/mL could already do so (43). No data are available regarding the ability of direct anti-Xa to mitigate catheter-induced thrombin generation. However, preclinical studies are available in other contact pathway activation models such as mechanical heart valves (MHV). As with catheters models, dabigatran, but also apixaban and rivaroxaban had limited ability to suppress MHV-induced thrombin generation at concentrations consistent with those observed in therapeutically anticoagulated patients (61, 62). Therefore, it is questionable whether full consideration of residual DOACs levels is relevant for thrombosis prevention during CAAF.

Another important aspect to consider is the pharmacodynamic interaction between UFH and oral anticoagulants. Unfortunately, few data are available regarding this topic. A pharmacokinetic-pharmacodynamic study performed in CAAF patients identified that the response to intravenous UFH was similar between patients on dabigatran and patients without baseline anticoagulation (same ACT increase for a given UFH bolus), but was enhanced in patients on VKAs (increased ACT increase for a given UFH bolus) (63). However, dabigatran was often skipped for one dose before the procedure, probably resulting in low plasma concentrations, which limits the findings of the study. Using thrombin generation, other authors identified a reduced response to the *in vitro* addition of 0.1 IU/mL UFH to the plasma of patients on DOACs (both at Cpeak and Ctrough), compared with the plasma of patients on VKA or healthy volunteers. The response to UFH was greater for samples with dabigatran than for samples with direct anti-Xa inhibitors (64). Finally, Yau et al. identified a synergistic effect on delaying the time to catheter occlusion in rabbits when low-dose dabigatran and UFH were administered concomitantly (43).

Monitoring of UFH During CAAF—The Activated Clotting Time

During CAAF, UFH administration is guided using the ACT. A variety of devices and cartridges are available, differing in the activator used (e.g., celite, kaolin, glass beads or a combination of these) and the method of measurement (e.g., rotation of a tube, a plunger or movement through capillaries) (17). Systematic differences exist between available ACT devices [which may be more than 100 s in heparinized patients (65–68)], which cannot be used interchangeably (65–71). However, in clinical guidelines, fixed ACT targets (i.e., 300 s) are proposed without differentiating devices (5), which adds variability in the level of anticoagulation achieved from center to center. In addition, various preanalytical variables may influence the ACT, such as blood collection technique (e.g., site of blood collection, amount of blood discarded before sampling, velocity of aspiration during sampling) and processing (e.g., time-interval between collection and analysis, agitation of the sample, prewarming of the reagent) (72, 73). As a result, this could also lead to huge variations in UFH dose administered.

Although the excellent correlation between ACT and UFH concentrations with *in vitro* spiking of whole blood (74, 75), the association between ACT and *ex vivo* heparin levels assessed with an anti-Xa assay is poor, especially at high UFH concentrations such as those used during CAAF (i.e., 1–2 IU/mL) (76). Unlike UFH, the ACT shows poor sensitivity to DOACs *in vitro*, especially to direct factor Xa inhibitors (inability to achieve ACTs >200 s even at supratherapeutic concentrations), whereas its sensitivity to dabigatran, the only direct factor IIa inhibitor, is better (77). When using samples from patients on DOAC, the correlation with direct factor Xa inhibitors levels is even worse (28). As a result, and because of uninterrupted preoperative anticoagulation attitudes, some patients may present in the interventional cardiology laboratory with therapeutic DOACs blood levels with only small ACT prolongations, especially for direct factor Xa inhibitors (78, 79).

Outcomes in Clinical Studies

Some authors suggested that the higher doses of UFH administered to patients on DOACs, compared with patients on VKAs, could be detrimental by adding to the residual effect of uninterrupted DOACs, putting patients at increased bleeding risk (21, 28). However, meta-analyses of randomized trials and observational studies comparing uninterrupted VKA and DOAC treatment approaches are reassuring, identifying no increase in bleeding risk with DOACs compared with VKAs (80, 81); dabigatran was even safer than VKAs in the RE-CIRCUIT randomized trial [absolute risk difference −5.3% (95% confidence interval: −8.4 to −2.2%), $p < 0.001$] (10). Furthermore, these increased doses of UFH appear to be necessary to prevent thrombosis during CAAF. Indeed, another meta-analysis identified that, similarly to the uninterrupted VKAs approach, achieving an ACT >300 s for patients on DOAC therapy was associated with a reduced risk of thromboembolic events, compared with an ACT target of <300 s (18). Overall, this suggests that the lack of integration of DOACs levels by the ACT and the hassle of administrating higher UFH doses with the uninterrupted DOAC approach are not worrying in terms of clinical endpoints. Worse, aiming for lower ACTs for fear of overanticoagulation could be deleterious by increasing thrombotic risk.

Future Directions

Due to the expected predominant role of the contact pathway in procedural thrombosis, contact pathway inhibitors are attractive for anticoagulation during CAAF. Contact pathway inhibitors are pharmacologic agents targeting specifically factor XII or XI using truncated antibodies, small inhibiting molecules, antisense oligonucleotides (ASO) or small interfering RNAs (82). These molecules are able to profoundly block contact activation with no effect on hemostasis initiated by TF exposure. At present, these molecules have been used successfully in preclinical models of extracorporeal life support (83, 84), and were associated with excellent thrombosis prevention with minimal bleeding risk (sometimes lower than UFH). In human, FXI ASO were more effective than LMWH to prevent venous thrombosis after total knee arthroplasty with a lower incidence of clinically relevant bleeding (85). However, the utilization of these molecules during CAAF should be done with caution as the contribution of TF-induced thrombin generation to thrombosis during the procedure remains unresolved. Whether this mechanism does significantly contribute to thrombosis, and whether residual VKAs or DOACs concentrations in the context of uninterrupted approaches would be enough to counter this specific risk would deserve to be carefully studied.

CONCLUSION

Although the activated clotting time is poorly sensitive to the effect of direct factor Xa inhibitors, the latter may not be very effective in mitigating catheter-induced thrombin

generation, at least at concentrations encountered in the interventional cardiology laboratory. Furthermore, the higher UFH doses required to achieve the ACT target of 300 s in patients on uninterrupted DOAC therapy, compared with those required in an uninterrupted VKA approach, do not appear to dangerously compromise the hemostatic competence of those patients, as evidenced by available randomized controlled trials and meta-analysis. Although the reliability of the ACT for assessing overall coagulation in the presence of high-dose heparin may still be questioned, its low sensitivity to the residual effect of direct factor Xa inhibitors is not a major concern in its use in the interventional cardiology laboratory.

AUTHOR CONTRIBUTIONS

MH, FM, and SL wrote the first draft of the manuscript. All authors contributed to manuscript writing, revision, read, and approved the submitted version.

ACKNOWLEDGMENTS

The authors would like to thank Professor Thomas Lecompte (Université de Nancy) for providing very sound and helpful advice on the content of the manuscript. The authors also thank the Fondation Mont-Godinne for the research grant awarded to MH.

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Conflict of Interest: JD is the CEO and founder of QUALIblood s.a., a contract research organization manufacturing the DP-Filter, is a coinventor of the DP-Filter (patent application number: PCT/ET2019/052903) and reports personal fees from Daiichi-Sankyo, Mithra Pharmaceuticals, Stago, Roche and Roche Diagnostics outside the submitted work. FM reports institutional fees from Stago, Werfen, Nodia, Roche Sysmex and Bayer. He also reports speaker fees from Boehringer Ingelheim, Bayer Healthcare, Bristol-Myers Squibb, Pfizer, Stago, Sysmex and Aspen all outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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OPINION
published: 06 April 2022
doi: 10.3389/fcvm.2022.884063

Anticoagulation Management in High Bleeding-Risk ECMO in Adults

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Keywords: ECMO, cardiac surgery, heparin, bleeding, hemostasis

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a life-saving therapy that has increasingly been used in recent years for the treatment of severe respiratory failure or cardiogenic shock, in the veno-venous (VV) or veno-arterial (VA) configuration, respectively (1). ECMO is a complex procedure not without significant complications, including both thrombosis and bleeding. The use of an extracorporeal circuit for cardiopulmonary support exposes blood to non-biologic, thrombogenic surfaces, and for this reason, ECMO protocols recommend systemic anticoagulation. The presence of active bleeding or a high bleeding-risk scenario is a common occurrence in the typical critically ill, ECMO-candidate patient making the choice of the anticoagulation strategy very challenging.

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Thrombosis, a section of the journal Frontiers in Cardiovascular Medicine

Received: *25 February 2022*
Accepted: *03 March 2022*
Published: *06 April 2022*

Citation:
De Paulis S and Cavaliere F (2022) Anticoagulation Management in High Bleeding-Risk ECMO in Adults. Front. Cardiovasc. Med. 9:884063. doi: 10.3389/fcvm.2022.884063

ECMO ANTICOAGULATION GUIDELINES

The Extracorporeal Life Support Organization (ELSO) guidelines for anticoagulation during ECMO recommend unfractionated heparin (UFH) as 50–100 units per kg bolus at the time of cannulation, followed by a continuous infusion of 20–50 units/kg/h to achieve an activated clotting time (ACT) of 180–220 s (2). Anticoagulation should ideally inhibit clot formation in the extracorporeal circuit to prevent embolism and/or ECMO dysfunction while preserving adequate procoagulant activity to avoid bleeding in the patient. The desirable hemostatic balance often proves difficult to be achieved and may become a nearly impossible task in a high bleeding-risk setting.

MINIMAL OR NO ANTICOAGULATION ECMO

Bleeding is a frequent complication of ECMO, with a reported incidence ranging from 27 to 60%. In adult patients with ECMO, the risk factors for bleeding have been identified: postsurgical (especially postcardiotomy) ECMO, recent trauma, type of cannulation (surgical, especially intrathoracic, and arterial at increased risk), ECMO duration, pre-ECMO coagulation abnormalities, and on-ECMO aPTT (>72 s), fibrinogen (<2 g/L), and platelets count (<38,000/mm^3) (3, 4). The clinical spectrum of ECMO bleeding includes intracranial hemorrhage, surgical site bleeding, gastrointestinal and pulmonary hemorrhage, and cannulation site bleeding. In these scenarios, case reports and case series have reported successful management of bleeding of patients with ECMO with prolonged periods of no anticoagulation. Technological advances in ECMO circuits, oxygenators, and pumps have improved biocompatibility and theoretically reduced the risk of thrombotic complications. Consequently, reduced anticoagulation protocols have been introduced and pilot randomized trials have proven the feasibility of future randomized controlled trials of low vs. standard anticoagulation during ECMO. Based on the available data, systematic reviews, and meta-analyses offer an insight into the effectiveness of this new approach.

Olson et al. (5), in their systematic review, reported a total incidence of thrombosis of 22.9% in a group of 201 patients with ECMO without systemic anticoagulation for a median of 4.75 days and a total duration of anticoagulant-free ECMO of 304.7 days. Thrombotic events were circuit-related in 13.4% (mainly oxygenator thrombosis requiring exchange) and patient-related in 9.5% of the cases, with a predominance of arterial thrombosis in VA-ECMO. The reported incidence of circuit thrombosis during standard anticoagulation in the 2017 ELSO report is 15.6 and 22.1% in VA and VV-ECMO, respectively, and in two recent meta-analyses ranges from 12.8 to 29%. The bleeding events, during these anticoagulation-free ECMO periods, affected 32.8% of patients, the surgical site bleeding being the most common event. Of patients who bled, 27.3% were on antiplatelet and/or prophylactic dose anticoagulant. The reported incidence of bleeding during standard anticoagulation in the 2017 ELSO report is 39.4 and 51% for VV and VA-ECMO, respectively, and in two meta-analyses 29.3 and 33%.

Lv et al. (6), in their meta-analysis of low (target ACT 140–160 s) vs. standard anticoagulation ECMO, found no significant difference between the two groups in the incidence of deep vein thrombosis, pulmonary embolism, clots in the oxygenator or pump, and intracardiac thrombus. On the other hand, gastrointestinal tract and surgical site hemorrhage were significantly lower in the low anticoagulation group.

DISCUSSION

ECMO perturbs the balance of hemostasis inducing both a pro-thrombotic state and a bleeding diathesis. The triggering of coagulation and inflammatory cascades and platelets activation by the non-biologic circuit surface, the consequently almost universal thrombocytopenia and platelet dysfunction, and the abnormal flow-mediated loss of high-molecular-weight von Willebrand multimers and hypofibrinogenemia all contribute to clinical thrombotic and bleeding events. The standard approach to mitigate these phenomena is anticoagulation with UFH, titrated to primarily inhibit circuit thrombosis while preserving patient clotting capacity. However, ECMO frequently needs to be instituted in a high bleeding-risk context or even in a bleeding patient, making guidelines-driven anticoagulation management a real challenge.

A growing experience with low- or even no-anticoagulation protocols in bleeding settings has emerged and recent data support the adoption of reduced-intensity anticoagulation protocols. The incidence of thrombosis in the standard anticoagulation ELSO registry and other meta-analyses was comparable with the data reported by Olson et al. Data from the meta-analysis of Lv et al. confirmed the comparable thrombotic rates between standard and low anticoagulation protocols and showed a reduced incidence of bleeding events.

With the pending results of RCTs, comparing standard vs. low anticoagulation regimens for ECMO, it seems reasonable to tailor anticoagulation to the specific patient condition, allowing periods of no anticoagulation in the actively bleeding patients and shifting to low anticoagulation protocols in the case of high bleeding risk.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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OPINION
published: 13 April 2022
doi: 10.3389/fcvm.2022.884076

Emergency Cardiac Surgery in Patients on Direct Oral Anticoagulants

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Keywords: direct oral anticoagulants, cardiac surgery, cardiopulmonary bypass, bleeding, hemostasis

INTRODUCTION

Cardiac surgery carries a high risk of perioperative bleeding and emergency surgery is one of the most significant factors in the determination of this risk. When perioperative bleeding ensues, blood products administration, and surgical re-exploration are generally required, with concomitant increase in perioperative morbidity and mortality (1). Bleeding risk is amplified in patients on anticoagulants and the expanding indication for direct oral anticoagulants (DOACs) has confronted perioperative physicians with new challenges related to the peculiar pharmacology of these agents. Guidelines for the management of bleeding patients taking DOACs are available but many uncertainties remain for their application to the cardiac surgery setting.

PERIOPERATIVE BLEEDING IN CARDIAC SURGERY

Emergency cardiac surgery has an inherently higher bleeding risk related to the pathology (aortic dissection, endocarditis), the intraoperative strategy (hypothermia) or the context (coronary revascularization after antiplatelet loading dose). Hemostatic balance during cardiac surgery is a rollercoaster ride: initial surgical dissection is best accomplished with a normal coagulation profile, cannulation and cardiopulmonary bypass require complete anticoagulation while final surgical hemostasis and the patient's course in the early post-operative period clearly benefit from complete restoration of hemostatic activity. Guidelines and consensus statements on the laboratory assessment of coagulation profile and optimal pharmacological treatment options have been released (2, 3). In this scenario the recent intake of therapeutic doses of DOACs poses additional burden on a complex task.

ASSESSING PREOPERATIVE COAGULATION PROFILE

Knowledge of the degree of anticoagulation determined by DOACs serum levels is important to decide the most appropriate treatment strategy. Standard coagulation tests like international normalized ratio (INR), prothrombin time (PT) and activated partial thromboplastin time (aPTT) have limited value because of the poor correlation with clinical hemostasis. Thrombin time is extremely sensitive to dabigatran, with significant influence even from subtherapeutic levels of drug. Standard thromboelastography/thromboelastometry assays are not sensitive enough to guide management, although newly developed tests that can detect DOACs are available but need clinical validation (4). Quantitative monitoring requires liquid chromatography/tandem mass spectrometry or, for direct thrombin inhibitors like dabigatran, an ecarin chromogenic assay or,

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Edited by:
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Specialty section:
This article was submitted to Thrombosis, a section of the journal Frontiers in Cardiovascular Medicine

Received: *25 February 2022*
Accepted: *01 March 2022*
Published: *13 April 2022*

Citation:
De Paulis S, Bruno P and Massetti M (2022) Emergency Cardiac Surgery in Patients on Direct Oral Anticoagulants. Front. Cardiovasc. Med. 9:884076. doi: 10.3389/fcvm.2022.884076

TABLE 1 | Treatment options.

Medication	Action	Treatment		
		Before CPB	During CPB	After CPB
Dabigatran	Direct thrombin inhibitor	• Activated charcoal • 4F-PCC • Consider Idarucizumab	Hemofiltration	Supportive care for cardiac surgery
Apixaban, edoxaban, rivaroxaban, betrixaban	Factor Xa inhibitor	• Activated charcoal • 4F-PCC	Hemoadsorption	• Consider Andexanet-alfa • Supportive care for cardiac surgery

for factor Xa inhibitors like apixaban, an anti-factor Xa activity assay (3). These quantitative tests are not readily available and have long turnaround time that makes them unavailable in an emergency setting.

TREATMENT OPTIONS

Activated oral charcoal (50 g orally) can be given if DOAC was last ingested within 2–4 h to reduce residual drug absorption.

Different antidotes are available for the thrombin inhibitor and anti-factor Xa inhibitor DOACs. Idarucizumab is an anti-dabigatran monoclonal antibody fragment given as a 5 g initial dose (a second dose may be given if required) that rapidly corrects quantitative assays results even though rebound rise in clotting time after 12–24 h has been reported. Limited use in cardiac surgery before cardiopulmonary bypass has been described with no apparent thromboembolic complications (5). Andexanet alfa is a genetically modified factor Xa variant that prevents binding to factor Xa by all inhibitors (including low-molecular-weight heparin and fondaparinux). It is administered as a bolus dose followed by continuous infusion for up to 2 h and rapidly reduces anti-factor Xa activity. Andexanet alfa binds to heparin-antithrombin complexes preventing proper anticoagulation with heparin, so that alternative anticoagulation with bivalirudin has been suggested if the antidote is given before cardiopulmonary bypass (3).

Non-specific prohemostatic agents, such as four-factor prothrombin concentrate (4F-PCC), are a second line reversal strategy that has been associated with adequate bleeding control in DOACs-related bleeding (6). The dose ranges from 25 to 50 IU/kg and it can be used before cardiopulmonary bypass with no later interference with heparin anticoagulation.

During cardiopulmonary bypass hemoadsorption of apixaban with Cytosorb® has been reported (it also binds antiplatelet drugs), while modified ultrafiltration could be effective only for dabigatran that has a low protein-bound fraction (7).

Supportive care with fresh frozen plasma, platelets, fibrinogen concentrate, desmopressin and antifibrinolytics, if necessary, should be provided in adherence with protocols for cardiac surgery (2) (**Table 1**).

DISCUSSION

Guidelines have been established for patients on DOACs undergoing emergency non-cardiac surgery which recommend correction of hemostatic imbalance before skin incision (8). Cardiac surgery has the unique challenge of cardiopulmonary bypass that requires complete anticoagulation and at the same time aggravates the hemostatic profile via activation of coagulation and inflammatory cascade. Data on the safety and efficacy of DOACs antidotes given before cardiopulmonary bypass are scarce and heparin resistance has been reported with the use of andexanet alfa (9). Their use may be postponed to the end of surgery in case of persistent bleeding that is refractory to conventional coagulation supportive measures. Reports from the cardiac surgery literature indicate that pre-operative correction of hemostatic imbalance with 4F-PCC seems a reasonable initial approach that combines efficacy with safety and does not interfere with heparin anticoagulation during bypass (10). With the start of extracorporeal circulation, blood purification techniques may be instituted to enhance drugs removal. Hemofiltration can achieve significant clearance for dabigatran only while hemoadsorption with Cytosorb® may be effective for removal of DOACs and antiplatelet agents.

One more thing to consider while managing anticoagulation during cardiopulmonary bypass is the fact that DOACs may interfere with activated clotting time (ACT) giving falsely low values that do not reflect actual anticoagulation (11).

The strategy of post-operative management should result from an assessment of the hemorragic and thromboembolic risks; as an example, the amount of chest tubes drainage that can be tolerated in the first post-operative hours. This would be a case-by-case assessment to decide how aggressive the correction of coagulopathy must be but also to choose timing and modality of post-operative anticoagulation that needs to be restarted.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SYSTEMATIC REVIEW
published: 09 May 2022
doi: 10.3389/fcvm.2022.833329

Direct Oral Anticoagulants vs. Vitamin K Antagonists in Atrial Fibrillation Patients at Risk of Falling: A Meta-Analysis

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Specialty section:
This article was submitted to Thrombosis, a section of the journal Frontiers in Cardiovascular Medicine

Received: *11 December 2021*
Accepted: *04 March 2022*
Published: *09 May 2022*

Citation:
Gao X, Huang D, Hu Y, Chen Y, Zhang H, Liu F and Luo J (2022) Direct Oral Anticoagulants vs. Vitamin K Antagonists in Atrial Fibrillation Patients at Risk of Falling: A Meta-Analysis. Front. Cardiovasc. Med. 9:833329. doi: 10.3389/fcvm.2022.833329

Background: Direct oral anticoagulants (DOACs) and warfarin are usually used for people with atrial fibrillation (AF). However, for the AF patients at risk of falling, the effectiveness and safety outcomes of DOACs compared with warfarin remain unclear. Therefore, we performed a meta-analysis regarding the effectiveness and safety of DOACs vs. warfarin in AF patients at risk of falling.

Methods: A search of the PubMed and Embase databases until November 2021 was performed. We included studies if they satisfied the following criteria: (1) study type: randomized clinical trials or observational cohort studies. (2) Comparisons: effectiveness and/or safety of DOACs (dabigatran, rivaroxaban, apixaban, or edoxaban) compared with warfarin. (3) Study data: the sample size, the number of events in the VKAs or DOACs groups, adjusted risk ratios (RRs), and 95% confidence intervals (CIs). (4) Study outcomes: stroke or systemic embolism (SSE), ischemic stroke, myocardial infarction (MI), all-cause death, and cardiovascular death; major bleeding, major or clinically relevant non-major (CRNM) bleeding, intracranial bleeding, gastrointestinal bleeding, and any bleeding. (5) Study population: patients at risk of falling. According to the Morse Fall Scale, the risk of falling relates to the history of falling, secondary diagnosis, ambulatory aids, intravenous therapy, type of gait, and mental status. In this meta-analysis, if the patient's MFS score is $\geq$25 points, he will be thought of as having the risk of falling. The adjusted risk ratios (RRs) and 95% confidence intervals (CIs) were pooled by a random-effects model with an inverse variance method.

Results: Three cohort studies were included in our study. For the effectiveness outcomes, the use of DOACs was only associated with a significantly reduced risk of hemorrhagic stroke (RR = 0.28, 95%CI:0.10–0.75) compared with warfarin, but there were no significant differences in stroke or systemic embolism (SSE) (RR = 0.87, 95%CI:0.70–1.08), cardiovascular death (RR = 0.97, 95%CI:0.73–1.29) and all-cause

death (RR = 0.90, 95%CI:0.72–1.11). For the safety outcomes, the use of DOACs was significantly associated with reduced risks of major or clinically relevant non-major bleeding (RR = 0.77, 95%CI:0.61–0.98) and intracranial bleeding (RR = 0.26, 95%CI:0.11–0.66) but not major bleeding (RR = 0.78, 95%CI:0.58–1.06).

Conclusions: Compared with warfarin, the use of DOACs in AF patients at risk of falling is significantly associated with reduced risks of hemorrhagic stroke, major or clinically relevant non-major bleeding, and intracranial bleeding.

Keywords: atrial fibrillation, fall, direct oral anticoagulants, warfarin, meta-analysis

INTRODUCTION

As the most common arrhythmia, the incidence, and prevalence of atrial fibrillation have increased for the last 20 years and might keep this growing tendency in the next 30 years (1). And AF as an accompanying state is associated with a 1.5- to 1.9-fold mortality risk after adjustment for the former cardiovascular disease (2). Patients with AF have increased risks of death, stroke, heart failure (HF), and cognitive dysfunction (3), thus they have significantly poorer life quality compared with other patients with only coronary heart disease or healthy people (4). With the advancement of medical management and ablation procedures, AF hospitalization-related mortality has decreased from 7.5% in 2006 to 4.3% in 2015 (approximately by 42%), but hospital costs per year have increased exponentially by 468% during this 10 years period (5), which means AF has become one of the largest epidemic and public health problems in the world. Atrial fibrillation (AF) affects 60 million people worldwide (6), resulting in embolism events, deterioration of cardiac function, and a significant increase in overall mortality (7).

The incidence of AF rises as the age increases from 60-years-old, so does the risk of falling (8, 9). DOACs and warfarin are generally used in AF patients to prevent stroke. The advantage of DOACs over warfarin in reducing SSEs, hemorrhagic stroke, all-cause mortality, and intracranial hemorrhage has been studied by several previous studies (10). The risk of falling should not be a decisive factor for withholding anticoagulation as nowadays' anticoagulation guidelines seem to pay more attention to bleeding complications than the risk of stroke (11, 12). In addition, the evidence certifying the deleterious effects of warfarin and DOACs on bone health is insufficient (13). However, the effectiveness and safety outcomes comparing warfarin and DOACs use in AF patients at risk of falling are still unclear. Therefore, this meta-analysis aimed to compare the effectiveness and safety of DOACs with warfarin in AF patients at risk of falling.

METHODS

We performed this meta-analysis based on the protocol and reporting of the results from the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. We put the PRISMA 2020 Checklist in **Supplementary Table 1**.

Literature Retrieval

PubMed and Embase were systematically searched until November 2021 for relevant studies through the following search terms: (atrial fibrillation) AND (non-vitamin K antagonist oral anticoagulants OR direct oral anticoagulants OR dabigatran OR rivaroxaban OR apixaban OR edoxaban) AND (vitamin K antagonists OR warfarin) AND (fall or falling). We applied no linguistic restrictions to the literature. The literature search strategy is shown in **Supplementary Table 2**.

Inclusion and Exclusion Criteria

We included studies if they satisfied the following criteria: (1) study type: randomized clinical trials or observational cohort studies. (2) Comparisons: effectiveness and/or safety of DOACs (dabigatran, rivaroxaban, apixaban, or edoxaban) compared with warfarin. (3) Study data: the sample size, the number of events in the VKAs or DOACs groups, adjusted risk ratios (RRs), and 95% confidence intervals (CIs). (4) Study outcomes: stroke or systemic embolism (SSE), ischemic stroke, myocardial infarction (MI), all-cause death, and cardiovascular death; major bleeding, major or clinically relevant non-major (CRNM) bleeding, intracranial bleeding, gastrointestinal bleeding, and any bleeding. (5) Study population: patients at risk of falling. According to the Morse Fall Scale, the risk of falling relates to the history of falling, secondary diagnosis, ambulatory aids, intravenous therapy, type of gait, and mental status. In this meta-analysis, if the patient's MFS score is $\geq$25 points, he will be thought of as having the risk of falling (14). Studies were excluded if: (1) certain publication types such as reviews, case reports, case series, editorials, letters, and meeting abstract meta-analyses. (2) Studies with no sufficient data. (3) Studies with duplicate data.

Study Selection and Data Extraction

Two authors (Hu Y.T. and Chen Y.Y.) screened all the retrieved studies by titles and abstracts firstly to find eligible studies. Then we read the full texts in more detail according to the inclusion and exclusion criteria. We solved the disagreements through discussion or consultation with another author. The data extraction is according to the standardized form. The following data of each study will be collected: the first author and publication year, study design, country, data source, follow-up time, patient age and sex, sample size, types of DOACs, effectiveness and safety outcomes used in the study, and adjusted risk ratios (RRs) and 95% confidence intervals (CIs).

TABLE 1 | Baseline characteristics of included studies.

Included study	Study design	Country	Data source	Follow-up time (y)	Antiplatelet agents use rate	Sample size	Age, median (25th, 75th), years	Female sex, No. (%)	Definition of the risk of falling	DOACs	Safety outcomes	Effectiveness outcomes	Confounder	Warfarin-naïve or warfarin-users
Rao et al. (25)	Cohort study	USA	Duke Clinical Research Institute	1.8	0%	753	75 (67, 79)	357 (47.4)	Patients with a history of falling	Apixaban	Major bleeding, major or CRNM bleeding and intracranial bleeding	SSE, cardiovascular death, all-cause death and hemorrhagic stroke	Comorbidities (e.g., cerebrovascular disease, peripheral vascular disease, congestive heart failure, prior MI), medication at randomization (ACE inhibitors/ARBs, Beta-blockers)	Unclear
Steffel et al. (27)	Cohort study	USA	ENGAGE AF–TIMI 48	2.8	0%	900	77 (72, 82)	445 (49.4)	Having any of the following eight criteria at randomization: 1) prior history of falls; 2) lower extremity weakness; 3) poor balance; 4) cognitive impairment; 5) orthostatic hypotension; 6) use of psychotropic drugs; 7) severe arthritis; or 8) dizziness.	Edoxaban	Major bleeding, major or CRNM bleeding and intracranial bleeding	SSE, cardiovascular death, all-cause death and hemorrhagic stroke	History of stroke or TIA, history of hypertension, history of coronary artery disease, history of coronary heart failure, aspirin use at randomization, dose reduced at randomization	Warfarin-naïve and warfarin-users

(Continued)

TABLE 1 | Continued

Included study	Study design	Country	Data source	Follow-up time (y)	Antiplatelet agents use rate	Sample size	Age, median (25th, 75th), years	Female sex, No. (%)	Definition of the risk of falling	DOACs	Safety outcomes	Effectiveness outcomes	Confounder	Warfarin-naïve or warfarin-users
Miao et al. (26)	Cohort study	USA	United States (US) Truven MarketScan	1.4	18.0%	25,144	83(47.87)	10,297(41.0)	A predicted 2-year fall-risk ≥ 15% per the algorithm developed and validated by Homer et al.	Apixaban, edoxaban and rivaroxaban	Intracranial bleeding	SSE	Comorbidities (e.g., acute decompensated heart failure, genital urinary bleeding, ischemic stroke, cognitive artery bypass grafting, heart failure, coagulopathy) smoker, medication use like antiplatelet drugs	Warfarin-naïve

DOACs, direct oral anticoagulants; CRNM, clinically relevant nonmajor bleeding; SSE, stroke or systemic embolism; NOS, Newcastle-Ottawa Scale.

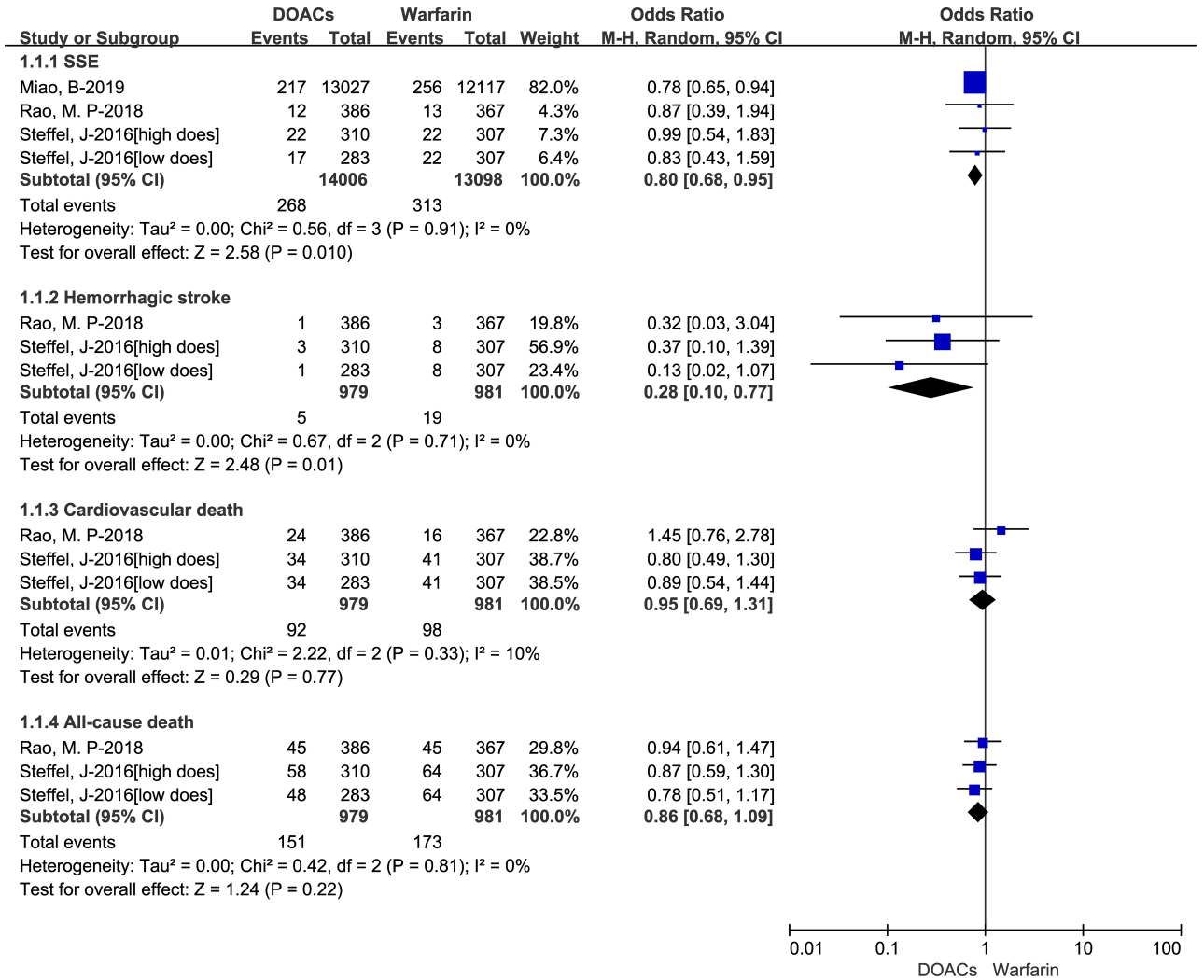

FIGURE 1 | Crude effectiveness event rates of direct oral anticoagulants compared with warfarin among atrial fibrillation patients at risk of falling. DOACs, direct oral anticoagulants; SSE, stroke or systemic embolism.

Study Quality Assessment

Because each included study belonged to a cohort study, we use the Newcastle–Ottawa Scale (NOS) tool to evaluate the quality. This scoring scale involved three domains: the selection of cohorts (0–4 points), the comparability of cohorts (0–2 points), and the assessment of the outcomes (0–3 points). A study with a NOS score of <6 was defined as low quality (15, 16).

Statistical Analysis

We used the Manager Version 5.4 (The Nordic Cochrane Center, The Cochrane Collaboration, 2014, Copenhagen, Denmark; https://community.cochrane.org/) to conduct the statistical analysis. If a *P*-value is < 0.05, we admit it's statistically significant. The Cochrane Q-test and I^2 statistic were chosen by us to evaluate consistency, in this way, a $P < 0.1$ for Q-test and $I^2 > 50\%$ indicated a substantial heterogeneity. We calculated and pooled the natural logarithms of RRs and standard errors of the studies by a random-effects model using an inverse variance method. Firstly, the number of patients and events of two groups were collected to calculate corresponding crude effectiveness and safety outcomes rates. The results of DOACs or group warfarin groups were shown by odds ratios (ORs) and 95% CIs. Secondly, we used the adjusted RRs to further eliminate the influence of confounders and to evaluate the outcomes.

RESULTS

Study Selection

The process of literature retrieval is shown in **Supplementary Figure 2**. A total of 111 studies were found through electronic searches. Removing the duplicate studies, 81 studies were used for the title/abstract screening. Then

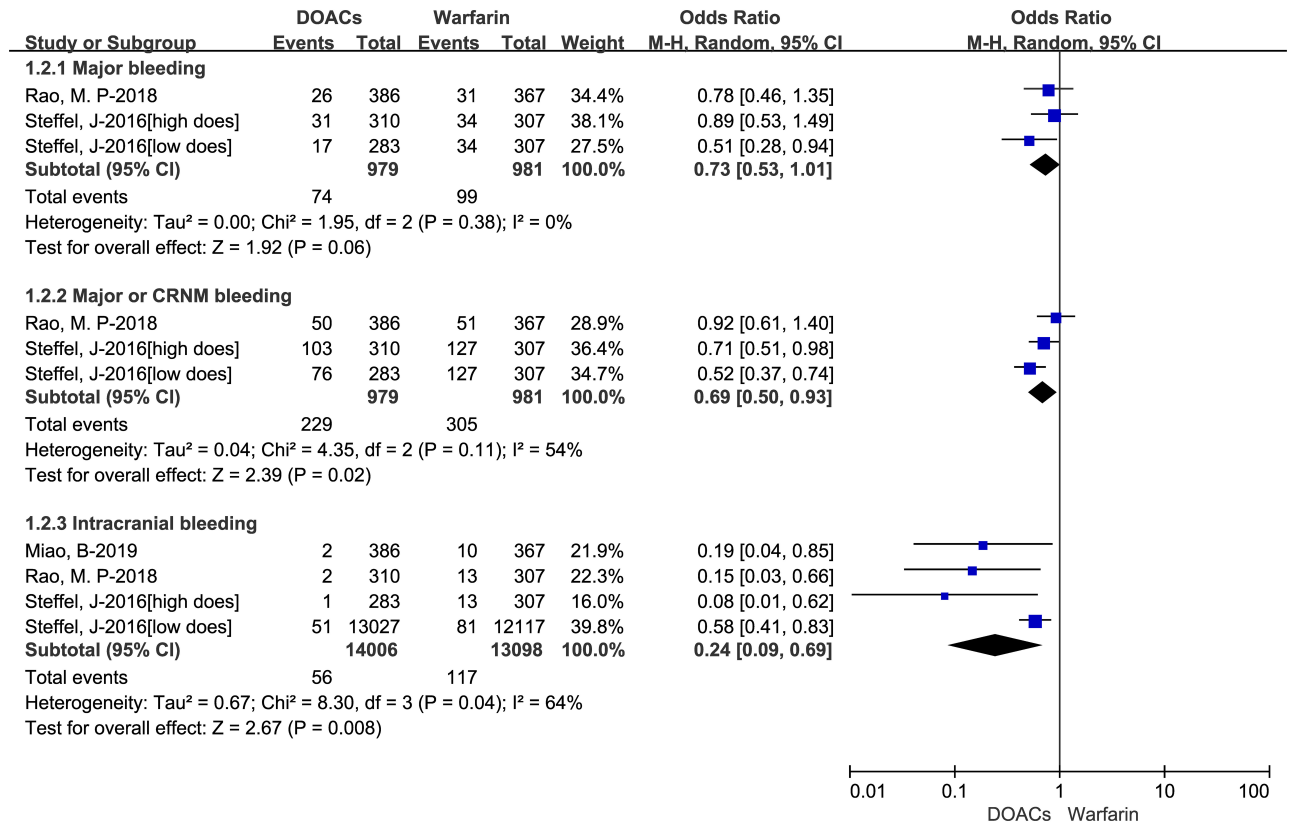

FIGURE 2 | Crude safety event rates of direct oral anticoagulants compared with warfarin among atrial fibrillation patients at risk of falling. DOACs, direct oral anticoagulants; CRNM, clinically relevant nonmajor bleeding.

13 remaining studies need to be assessed in more detail. Ten studies (11, 12, 17–24) were excluded because (1) mathematical model (n = 3); (2) case-control study (n = 1); (3) participants without AF (n = 1); (4) intervention is only warfarin (n =1); (5) studies without available data (n = 1); (6) studies' outcomes are the risk of falling (n = 2); (7) studies' outcomes are prescriptions (n = 1). Finally, a total of three cohort studies (25–27) were included in our meta-analysis.

Baseline Characteristics of the Included Studies

The baseline characteristics of included studies are shown in **Table 1**. All of them are cohort studies and meet our inclusion criteria. For quality assessment, these three included studies had a moderate-to-high quality with a Newcastle-Ottawa Scale score of ≥6 points. The study by Rao et al. (25) included 753 patients with a mean age of 75 years old using apixaban in the DOACs therapy. The study by Steffel et al. (27) included 900 patients with the use of edoxaban at the mean age of 77. And the last study by Miao et al. (26) included a total of 25,144 patients receiving three kinds of DOACs (apixaban, edoxaban, and rivaroxaban) at the mean age of 83. More details of these included studies' characteristics are shown in **Supplementary Table 4**. Although the three cohort studies were performed in the US, it did not mean all the patients were Americans. In the study by Rao et al., the patients come from America, Europe and Asia. The study by Steffel et al. included multinational patients. Therefore, we didn't discuss the limitations or generalizability of the patient ethnicity. Therefore, we didn't discuss the limitations or generalizability of the patient ethnicity.

Crude Event Rates Between DOACs and Warfarin

We put the effectiveness outcomes of three included studies in **Figure 1**. The use of DOACs is associated with lower event rates of SSE (1.91 vs. 2.39%, OR = 0.80, 95%CI:0.68–0.95), and hemorrhagic stroke (0.51 vs. 1.94%, OR = 0.28, 95%CI:0.10–0.77). But there were comparable rates of cardiovascular death (9.40 vs. 9.99%, OR = 0.95, 95%CI:0.69–1.31), and all-cause death (15.42 vs. 17.64%, OR = 0.86,95%CI:0.68–1.09). The safety outcomes of DOACs vs. warfarin are shown in **Figure 2**. Compared with warfarin-users, DOACs users had significantly lower event rates of major or CRNM bleeding (23.39 vs. 31.09%, OR = 0.69, 95%CI:0.50–0.93), and intracranial bleeding (0.40 vs. 0.89%, OR = 0.24, 95%CI:0.09–0.69). However, there were no significant differences in major bleeding (7.56 vs. 10.09%, OR = 0.73, 95%CI:0.53–1.01).

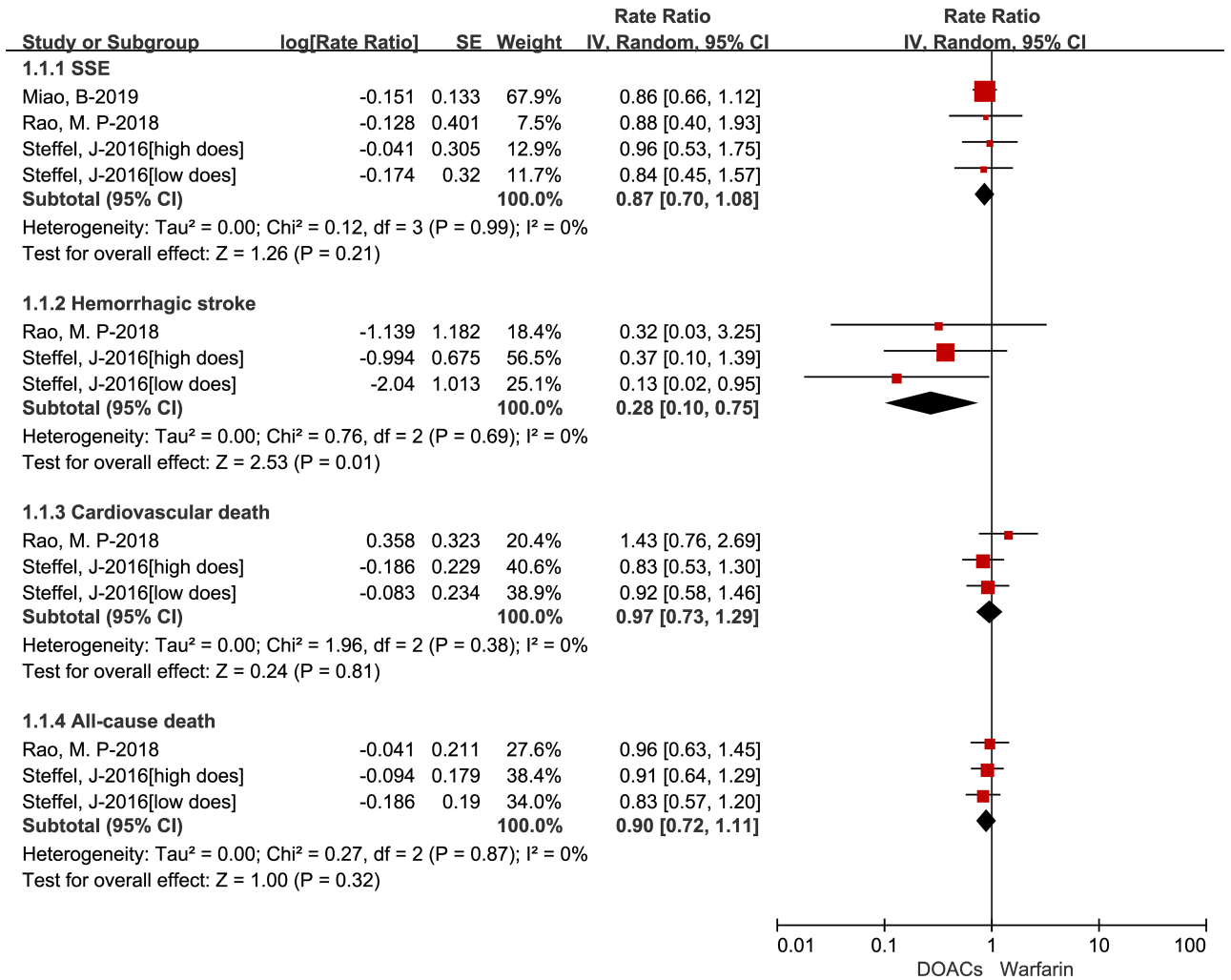

FIGURE 3 | Adjusted effectiveness data of direct oral anticoagulants compared with warfarin among atrial fibrillation patients at risk of falling. DOACs, direct oral anticoagulants; SSE, stroke or systemic embolism.

Adjusted Data of Outcomes Between DOACs vs. Warfarin

The adjusted data of effectiveness and safety outcomes among the three included studies are put in **Figures 3**, **4**, respectively. For effectiveness outcomes, the use of DOACs was significantly associated with reduced risks of hemorrhagic stroke (RR = 0.28, 95%CI:0.10–0.75, I = 0%) compared with warfarin. But there were no significant differences in SSE (RR = 0.87, 95%CI:0.70–1.08, I = 0%), cardiovascular death (RR = 0.97, 95%CI:0.73–1.29, I = 0%), and all-cause death (RR = 0.90, 95%CI:0.72–1.11, I = 0%). For safety outcomes, users of DOACs had a significant association with decreased risks of major or CRNM bleeding (RR = 0.77, 95%CI:0.61–0.98, I = 46%) and intracranial bleeding (RR = 0.26, 95%CI:0.11–0.66, I = 52%) but not major bleeding (RR = 0.78, 95%CI:0.58–1.06, I = 0%) compared with warfarin-users.

Given the huge heterogeneity in sample size between the study by Miao et al. and the other two studies, we deleted the study and then assessed the effectiveness and safety of DOACs vs. VKAs in AF patients at risk of falling by using the adjusted RRs. The adjusted data of effectiveness and safety outcomes about the two included studies were presented in **Supplementary Figures 3, 4**. According to the **Supplementary Figures 3, 4**, if we deleted the Miao study, the outcomes turned to be stable.

Publication Bias

Publication bias assessment should not be performed by the funnel plot approach when the number of studies is < 10 because such meta-analyses are underpowered to detect such bias.

Grade

The overall evidence for the observational studies was qualified using GRADE (grading of recommendations assessment, development, and evaluation) system categories. GRADE ratings of the quality of evidence in the three cohort studies are provided in **Supplementary Table 5**. According to GRADE system

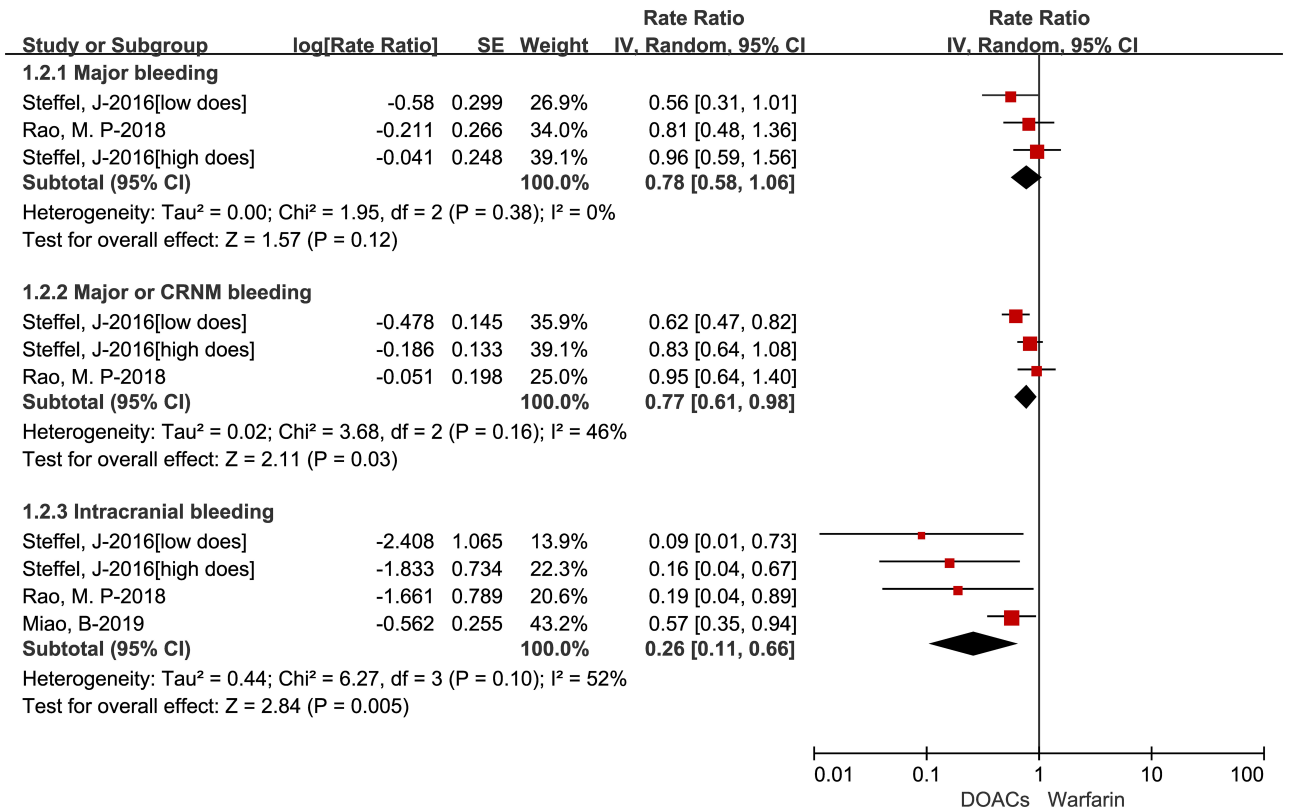

FIGURE 4 | Adjusted safety data of direct oral anticoagulants compared with warfarin among atrial fibrillation patients at risk of falling. DOACs, direct oral anticoagulants; CRNM, clinically relevant nonmajor bleeding.

categories, the quality of evidence for outcomes we included was moderate.

DISCUSSION

The main findings of our meta-analysis are listed as follows: (1) The use of DOACs was significantly associated with reduced risk of hemorrhagic stroke compared with warfarin; (2) The use of DOACs resulted in significantly lower rates of major or CRNM bleeding and intracranial bleeding; (3) Compared with warfarin, DOACs showed comparable rates of SSE, cardiovascular death, all-cause death, intracranial bleeding, and major bleeding.

Due to the unique clinical features of AF patients at risk of falling, anticoagulation for these patients is contentious. For example, patients at high risk for falls with atrial fibrillation are at substantially increased risk of intracranial hemorrhage, especially traumatic intracranial hemorrhage (28). There was apparent underuse of anticoagulant therapy in AF patients at risk of falling, especially in the elderly, as there was inconsistency in opinion among clinicians on who should receive anticoagulation (29). Previous data suggested that physicians' decisions were guided more by their concerns over bleeding than an evaluation of the patient's risk of stroke (30). Global Anticoagulant Registry in the FIELD (GARFIELD) registry has demonstrated that falling risk and fear of bleeding are frequent reasons why clinicians chose to restrict anticoagulant therapy in AF patients despite guideline recommends anticoagulant therapy (31). In addition, some findings suggest that the risk of falling is not a valid reason to avoid oral anticoagulants in AF patients (32). Of note, European Society of Cardiology guidelines (33) did not suggest falling risk was an absolute contraindication to anticoagulation, but rather recommend withholding anticoagulation only in patients who experience "severe uncontrolled falls" such as those related to epilepsy and advanced multisystemic atrophic related-backward falls. Several studies have indicated an overall benefit from anticoagulation in AF patients at increased risk of falling, indicating that the risk of severe bleeding is counterbalanced by a similar reduction in the risk of stroke (27). Furthermore, the study by Acanfora et al. has been calculated that elderly patient should fall more than 300 times a year before overcoming the clinical benefit of oral anticoagulation (34).

Compared with warfarin, DOACs have more benefits. In terms of pharmacodynamics, DOACs might have natural advantages over warfarin since their mode of action does not affect factor VII and initiation of the coagulation cascade, with a potential reduction in the risk of bleeding in case of trauma, particularly intracranial bleeding. In addition, the shorter half-life time of DOACs might help to limit traumatic bleeding (35). Based on their ability to reduce the risk of intracranial hemorrhage compared with warfarin, oral factor Xa inhibitors

like apixaban should be considered as strong alternatives to warfarin in AF patients deemed at higher risk of falling (26). Therefore, DOACs appear to have a better overall benefit-risk profile compared with warfarin (36). However, there are arguments regarding regular follow-up assessment in patients on DOACs, particularly the monitoring of relevant comorbidities such as renal failure, older age, or frailty (37) as DOACs exhibit predictable pharmacokinetic characteristics with fewer drug-drug interactions, which might reduce the need for routine coagulation monitoring and dose adjustment. Therefore, a part of physicians supported that extra attention and regular reviews are only required in elderly and frail patients to ensure safe and effective anticoagulation (38). Recent data displays that there has been an increase in the amount of newly diagnosed patients with AF at risk of stroke receiving guideline-recommended therapy since DOACs were introduced, predominantly driven by increased use of DOACs and reduced use of vitamin K antagonist (VKA) ± antiplatelet (AP) or AP alone (39). DOACs represented more than 60% of newly introduced anticoagulants in 2018. One study by Jurin et al. (40) anticipated that this trend of administrating DOACs would continue as the prices of these agents decline and as they become available for all patients' groups with indications for their use. Among the DOACs, apixaban is the preferred strategy from a public payer perspective for stroke prevention in older patients with atrial fibrillation and increased fall risk according to the health state transition model by Wong et al. (23).

The effectiveness and safety of DOACs compared with warfarin in AF patients at risk of falling have been explored in several recent studies. One systematic review by Grymonprez et al. (41) supported that the preserved efficacy and safety outcomes of apixaban and edoxaban in geriatric AF patients may warrant their use in this population prone to fall, especially because of the significantly lower intracranial bleeding risk. Unfortunately, it concluded only through two secondary analyses of phase III RCT studies. Besides this systematic review, no other systematic review or meta-analysis has been performed so far specifically comparing the effectiveness and safety of DOACs vs. warfarin in AF patients at risk of falling. Our meta-analysis was the largest and latest study comparing the effectiveness and safety outcomes of DOACs vs. warfarin in AF patients at risk of falling, potentially suggesting that DOACs might be considered more suitable for this special population.

LIMITATIONS

First of all, only three cohort studies included in our meta-analysis, in the future, more studies will be added to confirm our findings. Secondly, the clinical characteristics of patients in different included studies were heterogeneous, because the probability of falling in each study was different and we didn't discuss the limitations or generalizability of the patient ethnicity. Thirdly, we ignored the different pharmacological properties and clinical effectiveness and safety of different DOACs, but regarding them together as one group, so we did not conduct a subgroup analysis of DOACs and warfarin in AF patients at risk of falling. Fourthly, the protocol of the systematic review and meta-analysis were not registered in PROSPERO. Fifthly, in the warfarin users, the time in the therapeutic range was not considered because the study Miao et al. didn't compare the NOACs vs. warfarin with a time in the therapeutic range $\geq$ 60%. Sixthly, one study included patients who were warfarin-naïve only, and one study included patients who were warfarin-naïve and warfarin-users, the last one was unclear. Finally, because we did not perform subgroup analysis based on whether or not antiplatelet drugs were used, in the future, we will study antiplatelet drugs for subgroup analysis.

CONCLUSION

Based on our meta-analysis, AF patients at risk of falling using DOACs have a significant association with reduced risks of hemorrhagic stroke, major or CRNM bleeding, and intracranial bleeding.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

ACKNOWLEDGMENTS

We sincerely thank Dr. Wengen Zhu (Department of Cardiology, the First Affiliated Hospital of Sun Yat-sen University, Guangzhou of Guangdong, China) for the directions in study design, data collection, and data interpretation.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.833329/full#supplementary-material

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frontiers | Frontiers in Cardiovascular Medicine

SYSTEMATIC REVIEW
published: 19 May 2022
doi: 10.3389/fcvm.2022.874795

Is the Risk of Diabetes Lower in Patients With Atrial Fibrillation Treated With Direct Oral Anticoagulant Compared to Warfarin?

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OPEN ACCESS

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Reviewed by:
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Dana Huskens, Synapse BV, Netherlands

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Specialty section:
This article was submitted to Thrombosis, a section of the journal Frontiers in Cardiovascular Medicine

Received: 13 February 2022
Accepted: 25 April 2022
Published: 19 May 2022

Citation:
Liu X, Feng S, Chen Z, Zhou Y, Yin K, Xue Z and Zhu W (2022) Is the Risk of Diabetes Lower in Patients With Atrial Fibrillation Treated With Direct Oral Anticoagulant Compared to Warfarin? Front. Cardiovasc. Med. 9:874795. doi: 10.3389/fcvm.2022.874795

Background: The use of anticoagulants is an established strategy to prevent stroke, embolism, and cardiovascular mortality in patients with atrial fibrillation (AF), but its role in the prevention of incident diabetes is unclear. We aimed to investigate this question by using participant data from cohort studies.

Methods: We conducted a meta-analysis of participants to investigate the impact of direct oral anticoagulants (DOACs) on the risk of new-onset diabetes in AF patients. The collection of related data was performed in the PubMed and EMBASE databases until December 2021, including studies associated with evaluating the correlation between DOACs and incident diabetes. The hazard ratios (HRs) and 95% confidence intervals (CIs) were adjusted by the random-effects model with an inverse variance method.

Results: Two cohort studies with a total of 24,434 patients were included in this study (warfarin: n = 6,906; DOACs: n = 17,528). Compared with warfarin, the use of DOACs could reduce the incident diabetic risk in AF patients (HR = 0.75, 95%CI: 0.68–0.82). Investigations about the effects of three major classes of DOACs showed that the individual use of dabigatran (HR = 0.76, 95%CI: 0.64–0.90), rivaroxaban (HR = 0.74, 95%CI: 0.64–0.87), apixaban (HR = 0.74, 95%CI: 0.60–0.92) and the combined use of rivaroxaban and apixaban (HR = 0.74, 95%CI: 0.66–0.84) could reduce the risk of new-onset diabetes compared with warfarin. This risk reduction effect could be observed in both male and female groups (HR = 0.73, 95%CI: 0.64–0.84, $P < 0.00001$; HR = 0.82, 95%CI: 0.82–0.99, $P = 0.04$).

Conclusions: Treatment with DOACs compared with warfarin reduced the risk of new-onset diabetes in both male and female patients with AF.

Keywords: atrial fibrillation, non-vitamin K antagonist oral anticoagulants, diabetes mellitus, warfarin, meta-analysis

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the clinic, characterized by high rates of thromboembolic complications and related mortality.

An integrated approach of AF care mainly contains rhythm and rate control therapy, anticoagulation therapy (OAC), and comprehensive upstream therapy (1). Among them, OAC is of vital importance in AF-related stroke prevention. As a traditional oral anticoagulant, vitamin K antagonists such as warfarin plays their role by antagonizing vitamin K epoxide reductase complex. Warfarin has a narrow therapeutic range, multiple drug and food interactions, and requires frequent blood monitoring of the international normalized ratio (INR) (2). Therefore, direct oral anticoagulants (DOACs, sometimes referred to as non-vitamin K antagonist anticoagulants) have been introduced in the clinic, reducing the risk of stroke or systemic embolism and bleeding compared with warfarin among patients with AF (3–5).

Patients with comorbid AF and DM have a higher risk of stroke, thromboembolism, and cardiovascular mortality (3, 6–9). Vitamin K has been suggested to regulate the activity of vitamin K-dependent proteins (VKDP) such as osteocalcin, which effectively improve β cell proliferation and insulin secretion to reduce the risk of new-onset DM (9–14). Due to the different effects of warfarin and DOACs on vitamin K, the use of DOACs was considered with the potential of reducing DM risk in AF patients. Two cohort studies have been conducted to compare the risk of DM induction in AF patients treated by warfarin and DOACs (9, 15). The study of Cheung et al. included the data of 13,688 DOACs new users from the Clinical Data Analysis and Reporting System (CDARS) managed by the Hong Kong Hospital Authority (HA). Their results showed that dabigatran was significantly related to incident diabetes risk reduction, and for Xa inhibitor anticoagulants, only the combination use of rivaroxaban and apixaban rather than individual drugs could decrease this risk. In this study, males were the only gender with a diabetic risk-reduction effect. While in a cohort analysis performed by Huang et al., a total of 10,746 AF patients from Taiwan's National Health Insurance Research Database (NHIRD) were fitted into the study. All of the three different DOACs (dabigatran, rivaroxaban, apixaban) were reported with the incident diabetic reduction effect compared with warfarin. In this study, a similar trend of lowering new-onset DM risk was observed in both male and female groups treated with DOAC vs. warfarin. We used individual participants' data from the two cohort studies to assess the impact of DOACs on new-onset diabetes risk in AF patients.

METHODS

The preferred reporting items for systematic review and meta-analysis (PRISMA) 2020 guidelines were used to conduct our present meta-analysis. Only published publications were included in our meta-analysis, so we did not need ethical permission. Readers can contact the corresponding authors for data, techniques, and materials to recreate the results or the program.

Literature Retrieval

Two databases PubMed and Embase were used for systemic search in this study, retrieval keywords included (1) atrial fibrillation OR AF AND (2) incident diabetes OR new-onset diabetes AND (3) Direct oral anticoagulants OR DOAC OR DOAC OR oral anticoagulants OR dabigatran OR rivaroxaban OR apixaban AND (4) vitamin K antagonists OR warfarin OR VKA.

Inclusion and Exclusion Criteria

The literature inclusion criteria of this study include (1) randomized controlled trials or observational cohort studies focusing on the risk of developing DM in AF patients treated by warfarin vs. DOACs (Apixaban, dabigatran, rivaroxaban or edoxaban), (2) The outcomes of studies include the appearance of new-onset diabetes, which meets the International Classification of Diseases, the use of anti-diabetic medication, or death occurred during the investigation period. (3) All of the patients included in the cohort study were treated with at least one type of anticoagulant after AF diagnosis. The clinical follow-up time was unlimited. Specific literature forms including reviews, case reports, case series, editorials, meeting abstracts, and insufficient clinical data were excluded.

Study Selection and Data Extraction

Two independent researchers extracted data independently through screening the titles and abstracts to select potential studies for meta-analysis. Then full-text screening was carried out subsequently. Controversies were resolved by discussing with the third researcher. If multiple screened studies suitable for meta-analysis were from the same data source, the study that was more in line with predefined criteria was included. Studies with later publication years and longer follow-up times were preferentially included. The relevant information of each available study included the first author, publication year, study design, outcomes, types of DOACs, follow-up period, the sample size and the number of events in the warfarin or DOACs groups, hazard ratio (HR) and 95% confidence intervals (CI) were collected independently by the fourth author.

Study Quality Assessment

Newcastle-Ottawa Scale (NOS) was used by authors to assess the quality of included studies. A total of nine points were divided into three domains, including the cohort selection (0–4 points), cohort comparability (0–2 points), and the outcomes evaluation (0–3 points) were assessed by the NOS tool. Studies with the NOS results < 6 points were considered as low quality.

Statistical Analysis

We chose the Cochrane Q-test and I^2 statistic to assess the consistency of the included studies. A $P < 0.1$ for the Q-test or $I^2 \geq 50\%$ result was considered as the existence of substantial heterogeneity. The Review Manager Version 5.3 (The

Nordic Cochrane Center, The Cochrane Collaboration, 2014, Copenhagen, Denmark[1]) was used for all statistical analyses; $P < 0.05$ was considered statistically significant. First, we collected the sample size and number of events in the warfarin or DOACs groups, then the crude events rates of DM induction risk were carried out and expressed by HRs and 95% CIs. Second, the HR of DM induction was calculated in both the warfarin group and DOACs group with respect to gender differences. The adjusted HRs were converted to the natural logarithms and standard errors. The inverse variance method was used to incorporate random effect models.

RESULTS

Study Selection

The retrieval flow chart of this meta-analysis is shown in **Figure 1**. A total of **205** studies were acquired through online searching in the PubMed and Embase databases. After removing repeated investigations, 25 studies were chosen to develop title/abstract screening. Then 10 studies were evaluated in detail. On the basis of predefined criteria, finally, two eligible cohort studies were included in our meta-analysis (9, 15). Exhibited in **Table 1** was the baseline information of patients in the included studies. A total of 24,434 individual participants (warfarin: n = 6,906; DOACs: n = 17,528) from two cohort studies were included in our meta-analysis. The data of included cohort studies were from Taiwan's National Health Insurance Research Database (NHIRD) and Clinical Data Analysis and Reporting System (CDARS) managed by the Hong Kong Hospital Authority (HA). Their study periods were not less than 5 years and the medical use conditions that may influence patients' DM risk were recorded in the baseline characteristic table. Both of these two studies could meet our screening criteria. For the quality assessment, the NOS scores of both included studies were ≥ 6 points. The number of included studies was less than 10. Thus, there was no need for publication bias assessment.

[1]https://community.cochrane.org/

Crude Event Rates Between Direct Oral Anticoagulants vs Warfarin

The crude rates of the occurrence of the incident DM in AF patients treated by warfarin or DOACs were reported in both cohort studies, shown in **Table 2**. Compared with warfarin, the incidence of new-onset diabetes was relatively lower in DOACs treated group (6.78% vs 7.68%). Both coagulation factor Xa inhibitors apixaban (5.38% vs 6.14%), rivaroxaban (8.03% vs 8.05%) and thrombin inhibitor dabigatran (6.73% vs 8.49%) show the effectiveness in reducing the incidence of new-onset diabetes in AF patients, and this effect in coagulation factor Xa inhibitors combination group also exist (6.82% vs 7.23%).

Adjusted Data of Outcomes Between Direct Oral Anticoagulants vs Warfarin

Both included studies have reported the adjusted data of new-onset DM in AF patients treated by DOACs vs warfarin (9, 15). The outcomes displayed in **Figure 2** were able to confirm that compared with warfarin, DOACs can reduce the risk of diabetes in AF patients (HR = 0.75, 95%CI: 0.68–0.82). Moreover, the outcomes of the gender subgroup according to the included studies are shown in **Supplementary Figure 1**. Compared with warfarin, the tendency of DOACs to reduce the incidence of new-onset diabetes can be observed in both male and female groups (male: HR = 0.73, 95%CI: 0.24–0.84; female: HR = 0.82, 95%CI: 0.68–0.99).

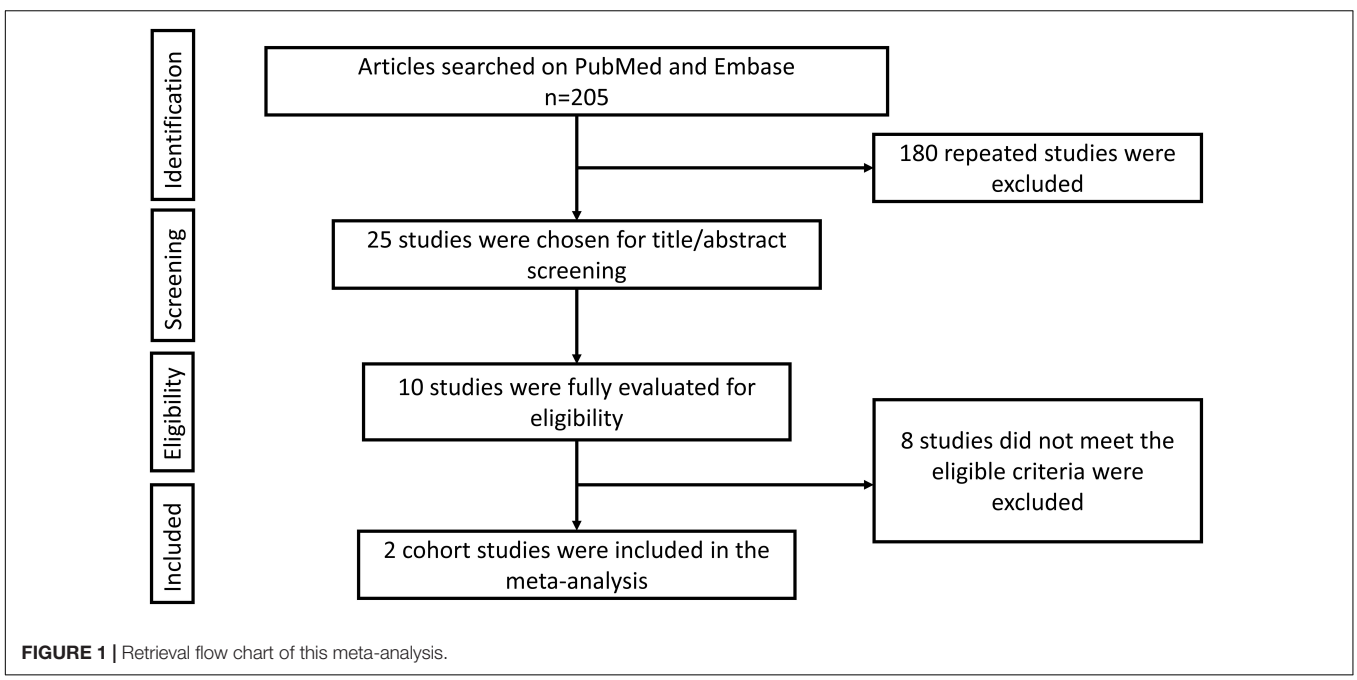

FIGURE 1 | Retrieval flow chart of this meta-analysis.

TABLE 1 | Main baseline characteristics of DOACs and warfarin treated patients in the included cohort studies.

	Huang et al. (9)		Cheung et al. (15)			Warfarin
	DOACs	Warfarin	DOACs			
			Apixaban	Dabigatran	Rivaroxaban	
Basal characteristics						
Sample size, n	4,596	3,452	3,335	4,210	2,689	3,454
Age	70.9 (± 12.0)	70.6 (± 12.9)	78.1 (± 10.8)	74.4 (± 10.3)	74.9 (± 10.8)	72.9 (± 12.2)
Female Sex,%	40.0	39.2	50.9	47.9	47.7	44.9
Median follow-up duration	2.4 year	2.3 years	363 (106–648) days	363 (84–700) days	392 (98–730) days	222 (36–704) days
Data source	From Taiwan's National Health Insurance Research Database (NHIRD)		Clinical Data Analysis and Reporting System (CDARS) managed by the Hong Kong Hospital Authority (HA)			
Country	Taiwan, China		Hong Kong, China			
Study period	5 years		6 years			
Outcomes	new-onset DM requiring treatment with an anti-diabetic drug		ICD-9-CM 250.xx including type 1 and type 2 diabetes or a prescription of anti-diabetic medication.			
Comorbidities, n (%)						
Congestive heart failure	766 (31.1)	737 (29.9)	636 (19.1)	576 (13.7)	413 (15.4)	741 (21.5)
Stroke	742 (30.1)	681 (27.6)	706 (21.2)	797 (18.9)	460 (17.1)	525 (15.2)
COPD	357 (14.5)	350 (14.2)	304 (9.1)	338 (8.0)	215 (8.0)	313 (9.1)
Fall	–	–	637 (19.1)	617 (14.7)	420 (15.6)	566 (16.4)
Fracture	–	–	299 (9.0)	282 (6.7)	214 (8.0)	251 (7.3)
Chronic liver disease/liver cirrhosis	55 (2.2)	56 (2.3)	16 (0.5)	14 (0.3)	4 (0.1)	23 (0.7)
Osteoporosis	–	–	65 (1.9)	51 (1.2)	41 (1.5)	37 (1.1)
Rheumatoid arthritis	20 (0.8)	22 (0.9)	39 (1.2)	36 (0.9)	22 (0.8)	29 (0.8)
Chronic kidney disease	292 (11.9)	280 (11.4)	79 (2.4)	42 (1.0)	49 (1.8)	187 (5.4)
Hypertension	1,616 (65.6)	1,619 (65.7)	–	–	–	–
Coronary artery disease	821 (33.3)	801 (32.5)	–	–	–	–
Hyperlipidemia	646 (26.2)	613 (24.9)	–	–	–	-
Dementia	142 (5.8)	136 (5.5)	–	–	–	–
Gout	265 (10.8)	251 (10.2)	–	–	–	–
Malignancy	185 (7.5)	194 (7.9)	–	–	–	–
Medication use condition						
ACE inhibitors	–	–	1,455 (43.6)	1,529 (36.3)	1,088 (40.5)	1,504 (43.5)
Beta blockers	1,472 (59.7)	1,502 (60.9)	1,959 (58.7)	2,490 (59.1)	1,649 (61.3)	2,019 (58.5)
Proton pump inhibitors	–	–	1,396 (41.9)	1,321 (31.4)	877 (32.6)	1,169 (33.8)
Systemic corticosteroids	–	–	324 (9.7)	341 (8.1)	222 (8.3)	377 (10.9)
Anti-depressants	–	–	202 (6.1)	199 (4.7)	128 (4.8)	162 (4.7)
Statins	143 (5.8)	134 (5.4)	–	–	–	–
Thiazides	199 (8.1)	191 (7.8)	–	–	–	–
Antipsychotics	143 (5.8)	141 (5.7)	–	–	–	–
Steroid	143 (5.8)	134 (5.4)	–	–	–	–
Index year						
2012	45 (1.8)	45 (1.8)	–	–	–	–
2013	476 (19.3)	476 (19.3)	–	–	–	–
2014	593 (24.1)	593 (24.1)	90 (2.7)	403 (9.6)	371 (13.8)	704 (20.4)
2015	694 (28.2)	694 (28.2)	256 (7.7)	578 (13.7)	525 (19.5)	727 (21.0)
2016	657 (26.7)	657 (26.7)	486 (14.6)	785 (18.6)	621 (23.1)	670 (19.4)
2017	–	–	886 (26.6)	1,045 (24.8)	547 (20.3)	630 (18.2)
2018	–	–	1,163 (34.9)	1,174 (27.9)	524 (19.5)	628 (18.2)
2019	–	–	454 (13.6)	225 (5.3)	101 (3.8)	95 (2.8)

COPD, Chronic Obstructive Pulmonary Disease; DOACs, direct oral anticoagulants.

As shown in **Table 2**, the subgroup analysis of different types of DOAC were also analyzed in our study. All of the three evaluated DOACs associated with the decreased risk of inducing incident diabetes (Apixaban: HR = 0.74, 95% CI: 0.60–0.92; Dabigatran: HR = 0.76, 95% CI: 0.66–0.88; Rivaroxaban: HR = 0.74, 95% CI: 0.64–0.86). After pooling the data of rivaroxaban and apixaban,

TABLE 2 | Pooled HRs of diabetes between DOACs vs. warfarin in patients with AF.

	DOACs	Dabigatran	Rivaroxaban	Apixaban	Rivaroxaban + Apixaban
Crude event rates	6.78% vs. 7.68%	6.73% vs. 8.49%	8.03% vs. 8.05%	5.38% vs. 6.14%	6.82% vs. 7.23%
HRs and 95% CIs	0.75 (0.68–0.82)	0.76 (0.66–0.88)	0.74 (0.64–0.86)	0.74 (0.60–0.92)	0.74 (0.66–0.84)
P value	<0.00001	0.001	0.0001	0.007	<0.00001
I^2 statistic	0%	30%	1%	0%	0%

AF, atrial fibrillation; HR, hazard ratio; CI, confidence interval; DOACs, Direct oral anticoagulants.

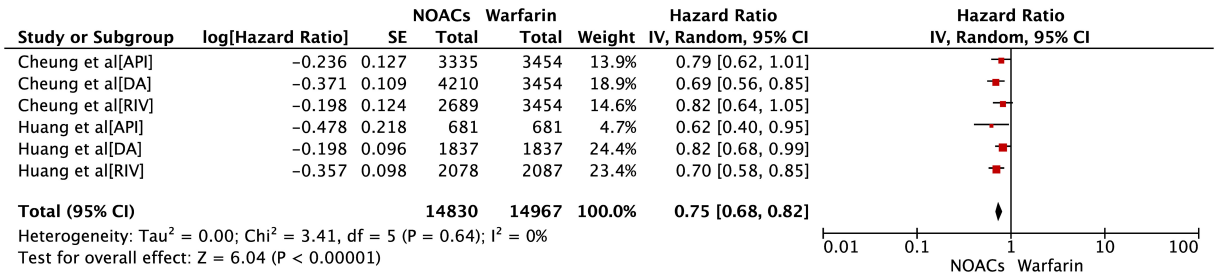

FIGURE 2 | Comparing the primary outcomes of incident diabetes in DOACs vs. warfarin. DOACs, direct oral anticoagulants; HR, hazard ratio; CI, confidence interval; SE, standard error; IV, inverse of the variance.

a similar effect could also be detected (HR = 0.74, 95% CI: 0.66–0.84), which confirms the reducing-effect of coagulation factor Xa inhibitors on the risk of new onset diabetes.

DISCUSSION

The primary findings of this study included (1) Compared with warfarin, DOACs including thrombin inhibitor dabigatran, coagulation factor Xa inhibitor rivaroxaban and apixaban could reduce the risk of new-onset diabetes in AF patients. (2) The DM-reduced effect of DOACs vs. warfarin can be observed in both male and female groups.

Compared with DOACs, warfarin has various limitations in the process of anticoagulant treatment. The changing international standardized ratio (INR) control and dose adjustment, various dietary or drug interactions (16, 17), narrow therapeutic window (17) result in the restrictions of warfarin in clinical use. Several meta-analyses and randomized controlled trials have reported the contrasts with the effectiveness and safety between DOACs and warfarin (18–20). The role of reducing AF and diabetes-associated risk factors including major bleeding, renal decline and cardiac valve calcification can be observed in the use of DOACs rather than warfarin (21–25).

Warfarin plays its role by antagonizing vitamin K, which is an important influence factor of glucose homeostasis and insulin sensitivity. In animal tissues, vitamin K homolog menaquinone-4 (MK-4) might act as an incretin-like nutrient and a cofactor of microsomal γ-glutamyl carboxylase (14, 26, 27). It contributes to the post-translational carboxylation process of transferring glutamate to γ-carboxyglutamate (Gla) residues of VKDP. Insulin production could be promoted by VKDP–osteoblast-specific secreted osteocalcin in a bone-pancreas endocrine loop to regulate glucose metabolism (14). The insulin resistance ameliorating effect of vitamin K was suggested through the inactivation of the NF-κβ signaling pathway to inhibit inflammatory responses and lipid-decreasing effect (11, 12). Considering the vitamin K antagonizing function of warfarin, it can influence the incidence of diabetes. However, the anticoagulation process of DOACs does not influence the vitamin K concentration in the circulatory system. Therefore, using DOACs compared with warfarin could reduce the risk of new-onset diabetes in AF patients.

In 2017, a novel drug betrixaban was approved by FDA as the fifth DOAC that can be used in clinic. With low renal clearance and minimal hepatic metabolism, betrixaban was considered particularly beneficial for patients with renal or hepatic dysfunction (28). However, the lack of an effective reversal agent makes betrixaban has a longer terminal half-life compared with other approved DOACs (28, 29). The impact of betrixaban on the risk of new-onset diabetes has not been evaluated in current studies, and the relevant results are expected to be supplemented in the future.

Our study was based on two cohort studies with a total sample size of 24,434, which is the most comprehensive and latest study according to the risk of DOACs vs. warfarin in inducing new-onset diabetes in AF patients. The result in the cohort study from Cheung et al. (15) proposed that only dabigatran was significantly associated with incident diabetes risk reduction, our results support that three of existing approved DOAC dabigatran, apixaban, and rivaroxaban with the function of reducing incident diabetic risk. At the same time, this effect in factor Xa inhibitors rivaroxaban and apixaban were not obvious, and our findings confirmed that all of these three drugs with the risk reduction ability. Also, in the outcomes of Cheung et al., only a specific gender of AF patients with the advantage of incident diabetic risk reduction in DOACs treatment, whereas the result of our investigation suggested that this effect could be observed in

both male and female groups. In addition, the estimated crude events rates of new-onset diabetes were evaluated during our investigation process. Although available data is insufficient to support the effect of vitamin K in ameliorating prediabetes (the impaired glucose tolerance, fasting blood sugar, fasting serum insulin level would not be restored), the glucose and insulin levels of 2-h post-oral glucose tolerance test could be reduced by stable vitamin K support (10, 30, 31), which indicate that DOACs may not induce the rapid deterioration of prediabetes compared with warfarin. Also, the clinical trials have demonstrated that the new anti-diabetic drug sodium-glucose linked transporter inhibitors (SGLTi) with a beneficial effect on cardiovascular disease (32–34), regardless if diabetes exists or not (34). In the aspect of AF, SGLTi can counteract the production of cellular ROS in cardiomyocytes, which may change atrial remodeling and reduce the burden of AF (34). This suggests that the new anti-diabetic drug SGLTi and new oral anticoagulants DOAC may have similar effects on the prevention of new-onset diabetes during AF treatment.

The results of our study suggested that DOACs could reduce the risk of incident diabetes, which is probably more suitable for AF patients with a higher risk of new-onset diabetes. More prospective clinical data about the risk of incident DM in AF patients treated by DOACs and warfarin could prove our point.

LIMITATIONS

This meta-analysis still had several limitations: (1) Only two cohort studies were included in our study, and the data were relatively limited, therefore the evaluation of the effect of edoxaban and betrixaban on incident diabetes was not supported. (2) The included population in our study only contain AF patients from Hong Kong and Taiwan, thus the evaluation of new-onset diabetes risk just considered Asian AF patients. (3) The subtypes of DM were not be distinguished in this study, whether DOACs have the same effect in reducing the risk of type 1 and type 2 diabetes in AF patients is still not clear. (4) The confounding factors cannot be completely excluded in observational studies. According to clinical guidelines, patients with rheumatic heart disease, congenital heart disease, or valve replacement surgery are more likely to be treated with warfarin rather than DOAC (9). This group that may induce selection bias was not completely excluded in our study. Future research could carry out propensity score matching on the basis of incorporating more data to minimize the impact of confounding factors.

CONCLUSION

Our findings of current analysis suggested that treatment with DOACs compared with warfarin reduced the risk of new-onset diabetes in both male and female patients with AF.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

FUNDING

This study was funded by the National Natural Science Foundation of China (82100273).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.874795/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Cardiovascular Medicine

SYSTEMATIC REVIEW
published: 01 June 2022
doi: 10.3389/fcvm.2022.813419

Intraocular Bleeding in Patients With Atrial Fibrillation Treated With NOACs VS. Warfarin: A Systematic Review and Meta-Analysis

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OPEN ACCESS

Edited by:
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Reviewed by:
Elena Campello, University of Padua, Italy
Olga Germanova, Samara State Medical University, Russia

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Specialty section:
This article was submitted to Thrombosis, a section of the journal Frontiers in Cardiovascular Medicine

Received: *11 November 2021*
Accepted: *02 May 2022*
Published: *01 June 2022*

Citation:
Liu F, Zhang Y, Luo J and Zhou Y (2022) Intraocular Bleeding in Patients With Atrial Fibrillation Treated With NOACs VS. Warfarin: A Systematic Review and Meta-Analysis. Front. Cardiovasc. Med. 9:813419. doi: 10.3389/fcvm.2022.813419

Background Intraocular bleeding is a devastating adverse event for patients with atrial fibrillation (AF) receiving anticoagulant therapy. It is unknown whether non-vitamin K oral anticoagulants (NOACs) compared with warfarin can reduce the risk of intraocular bleeding in patients with AF. Herein, we conducted a meta-analysis to evaluate the effect of NOACs vs. warfarin on intraocular bleeding in the AF population.

Methods: Studies were systematically searched from the Embase, PubMed, and Cochrane databases until April 2022. We included studies if they enrolled patients with AF and compared the intraocular bleeding risk between NOACs and warfarin and if they were randomized controlled trials (RCTs) or observational cohort studies. The random-effects model was chosen to evaluate the pooled odds ratios (ORs) and 95% confidence intervals (CIs).

Results: A total of 193,980 patients with AF from 5 randomized controlled trials (RCTs) and 1 cohort study were included. The incidence of intraocular bleeding among AF patients treated with warfarin and NOACs was 0.87% (n = 501/57346) and 0.61% (n = 836/136634), respectively. In the pooled analysis with the random-effects model, the use of NOACs was not significantly associated with the risk of intraocular bleeding (OR = 0.74; 95% CI 0.52–1.04, $P = 0.08$) compared with warfarin use. In addition, the sensitivity analysis with the fixed-effects model suggested that NOAC users had a lower incidence of intraocular bleeding than patients with warfarin (OR = 0.57; 95% CI 0.51–0.63, $P < 0.00001$).

Conclusions: Our current meta-analysis suggested that the use of NOACs had no increase in the incidence of intraocular bleeding compared with warfarin use in patients with AF. Whether the use of NOACs is superior to warfarin needs more research to confirm.

Keywords: atrial fibrillation, non-vitamin K oral anticoagulants, warfarin, intraocular bleeding, meta-analysis

INTRODUCTION

Atrial fibrillation (AF) has become the most common arrhythmia that affects people worldwide. Patients who have been diagnosed with AF are more prone to suffer from thromboembolic events (1, 2). As such, we urgently need to find an appropriate treatment that can prevent the risk of thromboembolism in patients with AF (3, 4). Although warfarin, a kind of vitamin K antagonists, has already proven to be practical for thromboprophylaxis (5), it still has many disadvantages (e.g., interactions with other drugs or food, frequent monitoring of international normalized ratio) (6, 7). Recently, non-vitamin K oral anticoagulants (NOACs; i.e., dabigatran, rivaroxaban, apixaban, and edoxaban) have been widely used in patients with AF. Newly published guidelines consistently recommend the use of NOACs as the criterion for anticoagulant therapy in patients with AF in terms of their effectiveness and safety compared with warfarin (2, 3, 8).

Although NOACs are safer than warfarin for AF-related stroke prevention (9), the concern of bleeding risks still remains in the NOAC users. In patients with AF receiving anticoagulant therapy, a rare but serious complication of NOACs is intraocular bleeding (10, 11), which may cause visual acuity impairment and sometimes require surgical intervention if it deteriorates. Although three prior meta-analyses by Caldeira et al. (12), Sun et al. (13), and Phan et al. (14) have compared the risk of intraocular bleeding caused by NOACs and warfarin, they have yielded different results. Sun et al. (13) included 12 studies with a sample size of 102,627 patients with AF or venous thromboembolism (VTE) and found that NOACs could reduce the incidence of intraocular bleeding by up to 20% compared with warfarin. In contrast, Caldeira et al. (12) included 17 studies with 117,563 patients with AF or VTE, and claimed that there was no difference in intraocular bleeding between NOACs and warfarin. Phan et al. (14) conducted a network meta-analysis by including 102,617 patients with AF or VTE from 12 RCTs (11,746 treated with apixaban, 18,132 with edoxaban, 11,893 with rivaroxaban, 16,074 with dabigatran, 18,389 with switched NOACs and 44,764 with warfarin). They concluded that only edoxaban was associated with a significantly diminished risk of intraocular bleeding compared with warfarin. Moreover, a prospective cohort study conducted by Campello et al. (15), enrolling 275 cases and 322 controls, found that there was a slightly increased incidence of bleeding in thrombophilia patients treated with NOACs. Subsequently, a large observational cohort study by Park et al. (16) enrolled 27,496 patients with warfarin and 93,691 NOAC users and concluded that the risk of intraocular bleeding was lower in the NOAC group. It is still unclear whether the use of NOACs compared with warfarin can reduce the risk of intraocular bleeding in patients with AF. In the present meta-analysis, we re-evaluated the effect of NOACs vs. warfarin on intraocular bleeding in the AF population. Furthermore, we only included patients diagnosed with AF, rather than patients with AF or VTE. Not only RCTs but also observational cohort studies were included in our analysis.

METHODS

This meta-analysis and systematic review were performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) items (17). Since the results of studies included in this meta-analysis have been published, we did not need to provide ethical approval.

Strategy of Literature Search

In order to find studies comparing the effects of NOACs and warfarin on patients with AF, we conducted a systematic search of articles published in the PubMed, Embase, and Cochrane databases before April 2022. The search terms were included as follows: 1) novel oral anticoagulants, non-vitamin K oral anticoagulants, direct oral anticoagulants, apixaban, edoxaban, dabigatran, rivaroxaban; 2) vitamin K antagonists, warfarin; and 3) atrial fibrillation. The detailed search strategies based on electronic databases were provided in **Supplementary Table 1**. There were no language restrictions in the search process.

Eligibility Criteria

We included randomized controlled trials (RCTs) or observational cohort studies that reported the effect of NOACs (dabigatran, rivaroxaban, apixaban, or edoxaban) compared with warfarin in non-valvular AF patients. We chose studies that used intraocular bleeding as the outcome, which was defined as major bleeding. In this meta-analysis, only subretinal hemorrhage, vitreous hemorrhage, hyphema, and suprachoroidal hemorrhage were considered the major bleeding event, precluding minor uncomplicated bleedings (e.g., subconjunctival hemorrhages), which met the criteria set by the International Society on Thrombosis and Hemostasis (18). Studies focusing on AF patients with ablation, cardioversion, or left-atrial appendage were excluded. Certain publication types with insufficient data (e.g., comments, reviews, letters, case reports, expert opinions, and editorials) were also excluded.

Data Extraction

After retrieving the literature, two reviewers screened them independently through title and abstract for the potential studies and then did a full-text reading to find the literature that met the requirements. Disagreements were resolved through discussion or consultation with a third researcher. Two reviewers extracted the following data: author, the year of publication, data source, study design, patient information, type and dosage of NOACs, follow-up period, number of events, and sample size.

Quality Assessment

The bias risk of RCTs was assessed using the Cochrane Collaboration's tool on the selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. For each domain of the Cochrane Collaboration's tool, the bias risk was scored as "low," "unclear," or "high" risk. For observational cohort studies, the Newcastle-Ottawa Scale (NOS) tool was used to assess the study quality. The NOS tool had a total of 9 points from 3 major sections: the selection of cohorts (0-4 points), the comparability of cohorts (0-2 points), and the assessment of the

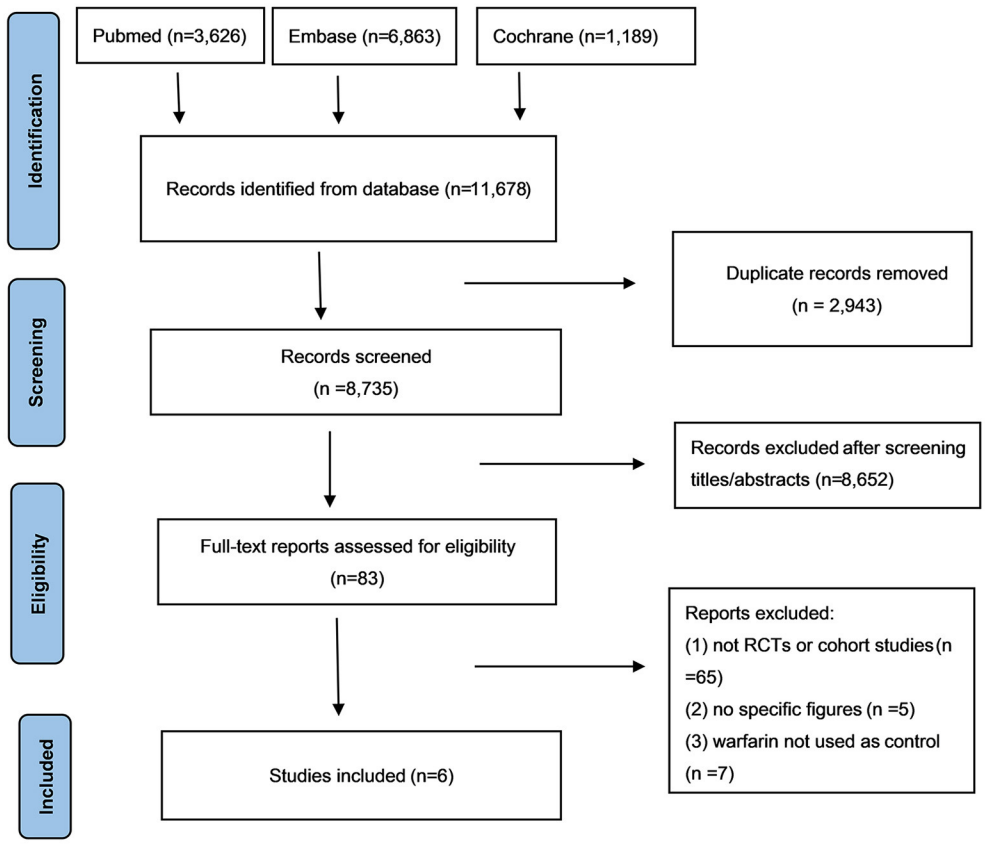

FIGURE 1 | The process of literature search of this meta-analysis. NOACs, novel oral anticoagulants; CI, confidence interval.

outcome (0–3 points). In this meta-analysis, the study with a NOS score of $\geq$ 6 points was defined as moderate to high quality, and a NOS score of $<$ 6 points was considered a low quality (19).

Data Analysis

The statistical heterogeneity across the included studies was assessed using the *P*-value in the Cochrane Q test and the I^2 statistic. A *P*-value of $<$ 0.1 or I^2 value of $>$ 50% suggested significant heterogeneity. For each included study, we collected the number of events and the sample size in the warfarin- or NOAC- groups, which were pooled by the random-effect model in consideration of the substantial heterogeneity across the included studies. The pooled results were expressed as the odds ratios (ORs) and 95% confidence intervals (CIs). In the sensitivity analysis, we re-performed the above-mentioned analysis using a fixed-effects model. Moreover, we performed the sensitivity analysis by deleting data from a single study to analyze the impact of one single study on the combined effect size. According to the Cochrane handbook, the publication bias was not formally assessed when the number of the included studies was $<$ 10.

All the statistical analyses were performed using the Review Manager version 5.4 software (the Cochrane Collaboration 2014, Nordic Cochrane Centre Copenhagen, Denmark; https://community.cochrane.org/). In this study, a *P*-value of $<$ 0.05 indicated statistical significance.

RESULTS

Study Selection

After a careful literature search, a total of 11,678 articles were initially selected from the electronic database. Among them, 2,943 articles were excluded due to the repeated selection, and 8652 were eliminated after the screenings of the titles and abstracts. Subsequently, 77 articles were precluded after the full-text screenings because (1) studies were not RCTs or observational cohorts ($n = 65$); (2) no specific data were given ($n = 5$); (3) warfarin was not used as the reference ($n = 7$). Finally, a total of 6 studies [5 RCTs (20–24) and 1 observational cohort study (16)] were selected in this meta-analysis (**Figure 1**).

Study Characteristics

The baseline characteristics of the included studies are listed in **Table 1**. The publication date of these articles ranged from 2009 to 2020, and the sample size ranged from 1,278 to 121,187. Specifically, Connolly et al. (20) included a total of 18,113 patients diagnosed with AF (6,022 patients on warfarin and 12,091 patients on NOACs). Granger et al. (21) enrolled

TABLE 1 | The baseline characteristics of the selected studies.

Included studies	Data source	Region	Study design	Type of patient	Oral anticoagulants	Average age	Male (%)	TTR (%)	No. of events	No. of patients	Follow-up time (y)	Study quality
Connolly et al. (20)	RE-LY multicenter	NA(include44 countries)	RCT	AF	Warfarin	71.6	63.3	64	17	6022	2.0	Low risk
					Dabigatran	71.5	63.7	-	26	12091		
Granger et al. (21)	ARISTOTLE multicenter	NA	RCT	AF	Warfarin	70.0	65	62.2	19	9052	1.8	Low risk
					Apixaban	70.0	64.5	-	28	9088		
Patel et al. (22)	ROCKET AF multicenter	NA(include45 countries)s	RCT	AF	Warfarin	73.0	60.3	55	24	7125	1.9	Low risk
					Rivaroxaban	73.0	60.3	-	17	7111		
Hori et al. (23)	ROCKET AF multicenter	Japanese	RCT	AF	Warfarin	71.2	78.2	65	2	639	2.5	Low risk
					Rivaroxaban	71.0	82.9	-	3	639		
Giugliano et al. (24)	ENGAGE AF-TIMI 48 multicenter	NA	RCT	AF	Warfarin	72.0	62.5	64.9	37	7012	2.8	Low risk
					Edoxaban	72.0	61.7	-	46	14,014		
Park et al. (16)	the Health Insurance Review and Assessment service of Korea	Korea	Observational cohort study	AF	Warfarin	66.4	58.2	-	402	27496	2.7	NOS=7
					NOACs (apixaban, dabigatran, edoxaban, rivaroxaban)	72.5	52.7	-	716	93691	1.2	

TTR, time in therapeutic range; RCT, randomized controlled trial; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; J-ROCKET AF, Japanese-Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; ENGAGE AF-TIMI 48, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48;AF,Atrial Fibrillation.

18,201 patients with AF, but 9,052 patients with warfarin and 9,088 patients with NOACs were included in this meta-analysis. Patel et al. (22) studied 14,264 patients with AF, including 7,111 patients treated with NOACs only and 7,125 patients treated with warfarin only. A total of 1,278 patients with AF were included in the study by Hori et al. (23), half of whom were treated with NOACs and half with warfarin. Giugliano et al. (24) studied 21,105 patients diagnosed with AF, including 7,012 patients who received warfarin and 14,014 patients who received NOACs. The study by Park et al. (16) included 121,187 patients with AF (27,496 on warfarin and 93,681 on NOACs). Among the various outcome, subretinal hemorrhage, vitreous hemorrhage, hyphema, and suprachoroidal hemorrhage were considered intraocular bleeding (18), precluding minor uncomplicated bleedings.

For the study quality assessment, all the 5 RCTs (20–24) had a low risk of bias, and the observational cohort by Park et al. (16) had an acceptable quality with a NOS of 7 points.

Incidence of Intraocular Bleeding Between NOACs vs. Warfarin

In the pooled analysis, the incidence of intraocular bleeding in AF patients treated with warfarin and NOACs was 0.87% (n = 501/57,346) and 0.61% (n = 836/136,634), respectively. Our pooled results based on the random-effects model showed that the use of NOACs was not significantly associated with the risk of intraocular bleeding (OR = 0.74, 95% CI 0.52–1.04) compared with warfarin use (**Figure 2**). Of note, there was high heterogeneity across the selected studies ($I^2 = 66\%$).

After excluding the study by Granger et al., we found that the I^2 value was reduced from 66% to 0%. The re-analysis after exclusion of the study by Granger et al. showed that NOACs distinctly diminished the rate of intraocular bleeding in patients with AF in comparison with warfarin (OR 0.54; 95% CI 0.48–0.61) (**Supplementary Figure 1**). In the sensitivity analysis with the fixed-effects model, the pooled results suggested that NOAC users had a lower incidence of intraocular bleeding compared with those patients with warfarin (OR = 0.57; 95% CI 0.51–0.63) (**Supplementary Figure 2**).

DISCUSSION

Our study was the first meta-analysis to investigate the effect of NOACs on the risk of intraocular bleeding in patients with AF compared with warfarin. According to our study based on the random-effects model, we found that there was no significant difference in the risk of intraocular bleeding in patients with AF between NOACs and warfarin. However, the pooled results changed in the sensitivity analysis when we used the fixed-effects model or excluded the study by Granger et al., and both suggested that NOAC users had a lower risk of intraocular bleeding than warfarin users.

In spite of the low incidence of intraocular bleeding in patients with AF after receiving anticoagulant therapy, it could lead to serious consequences once occurred. Massive intraocular bleeding was often associated with poor vision, and in some cases even required surgical intervention. Three previous predominant meta-analyses on this topic, conducted by Sun et al. (13), Caldeira et al. (12) and Phan et al. (14) respectively, carried out different conclusions. With an analysis involving 57,863 patients with AF or VTE from 12 studies, Sun et al. (13) found that novel oral anticoagulants could reduce the incidence of intraocular bleeding by up to 20% compared with warfarin, but Caldeira et al. (12) including 17 studies with a sample size of 117,563 patients with AF or TVE reported that NOACs couldn't diminish the incidence of intraocular bleeding in comparison with warfarin. However, although the risk estimates of Caldeira et al. cross unity, which indicated an absence of statistical significance, the wide 95% CIs and actual point estimates suggested that NOACs may still have a slight benefit (a decline by 16% in intraocular bleeding) compared with warfarin. Moreover, Phan et al. (14) conducted a network meta-analysis by including 102,617 patients with AF or VTE from 12 RCTs (11,746 of them were treated with apixaban, 18,132 with edoxaban, 11,893 with rivaroxaban, 16,074 with dabigatran, 18,389 with switched NOACs and 44,764 with warfarin). They concluded that edoxaban was associated with a significantly diminished risk of intraocular bleeding compared with warfarin, while Apixaban was the only NOAC associated with an increased risk of intraocular bleeding. Other NOACs were not different from warfarin. We believed that such a result may be caused by the small number of included studies, so we conducted an updated meta-analysis on this topic. In order to further investigate whether NOACs could reduce the incidence of intraocular bleeding in patients with AF compared with warfarin, we included data from newly published studies and then reperformed a meta-analysis on this topic. We did not include patients diagnosed with VTE because the effect of NOACs on patients with VTE and AF may be different, leading to the misestimation of the role of NOACs in the AF population. Unfortunately, it was shown that no significant difference was found between NOACs and warfarin in reducing the intraocular bleeding in patients with AF, according to the result of our meta-analysis.When in a sensitivity analysis, After excluding the study by Granger et al., we found that the I^2 value was reduced from 66% to 0%. The re-analysis after exclusion of the study by Granger et al. showed that NOACs distinctly diminished the rate of intraocular bleeding in patients with AF in comparison with warfarin.It seems to suggest that NOACS is superior to warfarin, but due to the large heterogeneity across studies, we cannot draw this conclusion and more studies are needed to confirm.

Although our study did not directly demonstrate a benefit of NOACs, the actual point estimates and 95% CI of our results still suggested a potential benefit of NOACs in reducing the risk of intraocular bleeding. These results had clinical implications for ophthalmologists to correctly manage the patients receiving anticoagulant therapy, especially those with a high probability of intraocular bleeding. Unluckily, our work cannot answer the question of whether patients with AF treated with NOACs are at a lower risk of intraocular bleeding. This meta-analysis needs to be updated in the future with new research data. Current studies support that NOACs at least do not cause more harm than warfarin (25–27), and we predict that NOACs will become more popular among patients since there is no need to

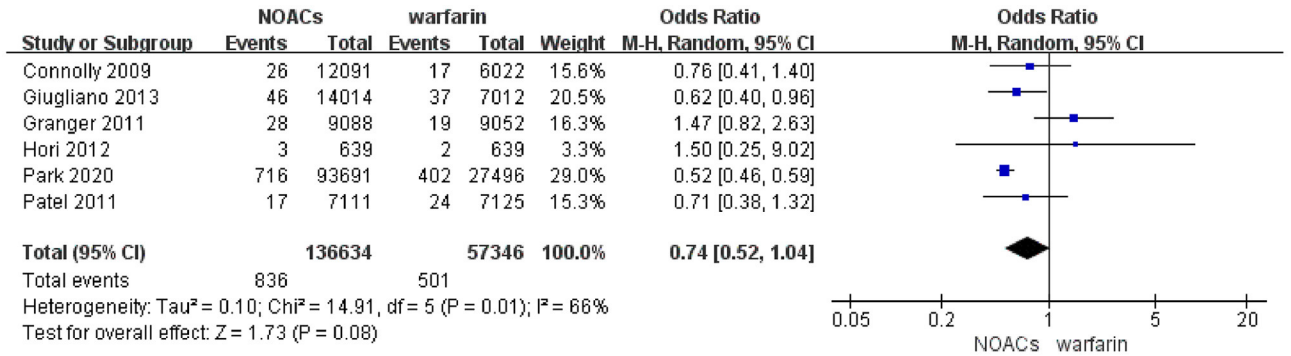

FIGURE 2 | Forest plot of intraocular bleeding events in patients with AF with NOACs vs. warfarin using the random-effects model. NOACs, novel oral anticoagulants; CI, confidence interval.

frequently draw blood to monitor the international normalized ratio. Nonetheless, clinicians still need to make sure appropriate doses of medication and always be aware of the possibility of bleeding symptoms.

Current studies did not explicitly explain the specific mechanisms of intraocular bleeding in patients receiving anticoagulation therapy. It has been speculated in the literature that NOACs only targeted one site in the coagulation, while warfarin targeted multiple sites (28). Due to the different mechanisms of action, it was also potentially suggested that the risk of intraocular bleeding may be different between NOACs and warfarin. In addition, the effects of different types (apixaban, edoxaban, dabigatran, rivaroxaban) (14, 29, 30) and doses (low, standard, high) (31–33) of NOACs may vary. Further detailed research is needed to confirm this hypothesis.

Limitations of the Study

Overall, there are still some limitations in our study. First of all, no matter what kind of antithrombotic therapy was, intraocular bleeding was uncommon. As a result, the number of studies we included was limited and small. Similarly, the number of intraocular bleeding events in each trial was quite low. Second, the long-term effect of NOACs on intraocular bleeding could not be evaluated due to the short follow-up time of the included studies. Third, our study found no significant difference between NOACs and warfarin in influencing the risk of intraocular bleeding in patients with AF, but the actual point estimates and 95% CI suggested that NOACs still have a potential benefit. Fourth, data from both RCTs and observational studies were combined simultaneously, which may reduce the reliability of the results. Last but not the least, we did not differentiate between specific NOACs, which may have contributed to our lack of statistically significant results. After all, there are pharmacokinetic and pharmacodynamic differences among them, such as bioavailability, protein binding, and metabolism.

CONCLUSIONS

Our current meta-analysis suggested that the use of NOACs had no increase in the incidence of intraocular bleeding compared with warfarin use in patients with AF. Whether the use of NOACs is superior to warfarin needs more research to confirm.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

ACKNOWLEDGMENTS

We sincerely thank Wengen Zhu (Department of Cardiology, the First Affiliated Hospital of Sun Yat-sen University, Guangzhou of Guangdong, China) for the directions in data interpretation and language polishing.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.813419/full#supplementary-material

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SYSTEMATIC REVIEW
published: 09 June 2022
doi: 10.3389/fcvm.2022.847286

Direct Oral Anticoagulants vs. Warfarin in Hemodialysis Patients With Atrial Fibrillation: A Systematic Review and Meta-Analysis

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OPEN ACCESS

Edited by:
Antonino Tuttolomondo, University of Palermo, Italy

Reviewed by:
Mettine H. A. Bos, Leiden University Medical Center, Netherlands
Iqbal Haider Jaffer, McMaster University, Canada

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Specialty section:
This article was submitted to Thrombosis, a section of the journal Frontiers in Cardiovascular Medicine

Received: 01 January 2022
Accepted: 20 May 2022
Published: 09 June 2022

Citation:
Elfar S, Elzeiny SM, Ismail H, Makkeyah Y and Ibrahim M (2022) Direct Oral Anticoagulants vs. Warfarin in Hemodialysis Patients With Atrial Fibrillation: A Systematic Review and Meta-Analysis. Front. Cardiovasc. Med. 9:847286. doi: 10.3389/fcvm.2022.847286

Background: The use of Direct Oral Anticoagulants (DOACs) in patients who have both atrial fibrillation (AF) and end-stage renal disease (ESRD) requiring hemodialysis remains controversial, with warfarin remaining the mainstay of the treatment. As hemodialysis patients were excluded from most clinical DOACs trials, the evidence of their efficacy and safety is lacking in this cohort of patients.

Aim: To review the current evidence investigating safety profile and the efficacy of DOACs in comparison with warfarin in patients with AF and end-stage renal disease (ESRD) requiring hemodialysis.

Methods and Results: We included five studies with a total of 34,516 patients in our meta-analysis. The outcomes were major bleeding, ischemic stroke, systemic embolization, hemorrhagic stroke, gastrointestinal bleeding, minor bleeding, and death. Of these patients, 31,472 (92.14%) received warfarin and 3,044 patients received DOACs (8.91%). No significant differences in the incidence of hemorrhagic stroke, major bleeding, hemodialysis access site bleeding, ischemic stroke, and GI bleeding were found between DOACs and warfarin. However, there were higher rates of systemic embolization, minor bleeding, and death events in patients who received DOACs than in the warfarin group (3.39% vs. 1.97%, P-value = 0.02), (6.78% vs. 2.2%, P-value 0.02), and (11.38% vs. 5.12%, P-value < 0.006) respectively.

Conclusion: In patients on dialysis who require anticoagulation for AF, warfarin could be associated with a significant reduction in minor bleeding, systemic embolization, and death compared to DOACs. These findings need to be validated by further prospective studies to address the best strategy to deal with the increased thrombotic and bleeding risks in such patients.

Keywords: hemodialysis, anticoagulants, atrial fibrillation, novel anticoagulation, renal failure, direct anticoagulant

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in adults and is associated with an increased risk of thromboembolic stroke; therefore, anticoagulation is the cornerstone of its management (1, 2). Patients with AF who have severe chronic kidney disease (CKD) requiring dialysis have significantly higher incidence rates of ischemic stroke. In addition, there is a higher incidence of AF among patients who have end-stage renal disease (ESRD), with an increased incidence of bleeding and complications (3–5). For decades, warfarin has been the cornerstone of anticoagulation in patients with AF. However, the safety of warfarin in patients on dialysis is questioned as it may cause a higher incidence of bleeding. Additionally, the efficacy of warfarin in stroke prevention among patients with AF who are on dialysis is debatable (2, 6). Direct oral anticoagulant agents (DOACs) have been proved to have comparative efficacy and safety profiles as warfarin in reducing the risk of thromboembolic stroke and they are currently widely used in many patient groups. DOACs have been shown to be non-inferior to warfarin in mild to moderate CKD (7). However, DOACs have varying degrees of renal clearance (80% for dabigatran, 33% for rivaroxaban, and 25% for apixaban) and there is insufficient data on the safety and efficacy of DOACs in patients with stage 5 CKD (Crcl $<$ 15 mL/min) or patients on dialysis (8). In advanced CKD (Crcl $<$ 30 mL/min) and dialysis-dependent patients, respectively, apixaban is the most commonly used DOAC (10.4 and 10.5%), followed by rivaroxaban (9.5 and 0.8%), dabigatran (3.5 and 0.3%), and edoxaban (0.1 and 0.01%) (9). This review investigates the current evidence on the efficacy and safety profile of DOACs among patients on hemodialysis in comparison to warfarin, with stroke, systemic embolism, and major bleeding being the main points of comparison.

METHODS

Information Sources and Search Strategy

The review protocol was registered with the international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO; registration number CRD42021222346).

The following databases were searched: Cochrane Library, MEDLINE, and Google scholar database in a systematic manner from 1 August to 31 December 2020. Additionally, relevant systematic reviews were manually searched. A combination of keywords or medical terms related to hemodialysis (e.g., dialysis, ESRD), AF and anticoagulation (e.g., oral anticoagulation, DOAC, NOAC, Direct oral thrombin inhibitors, factor Xa inhibitors, dabigatran, rivaroxaban, apixaban, and Edoxaban) were used. Only studies that had human participants and were written in English were included. The research strategy is presented in the **Appendix 1**.

Study Selection and Data Extraction

The search included randomized controlled trials (RCTs) and observational studies (either prospective or retrospective cohort studies). Studies with incomplete data, case reports, review articles, editorials guidelines, and duplicates were excluded.

Studies that investigated the effectiveness and safety profiles of DOACs among patients with AF and ESRD on dialysis were selected. We included the following categories of patients:

- Patients aged more than 18 years.
- Patients with ESRD on dialysis (defined as patients with a calculated glomerular filtration rate lower than 15 mL/min and requiring hemodialysis) treated with DOACs for AF.
- Patients with documented adverse outcomes (ischemic stroke, or systemic embolism, hemorrhagic stroke, major bleeding, minor bleeding, gastrointestinal bleeding, hemodialysis access site bleeding, and death).

Two authors independently performed the literature search and reviewed each title and abstract, then each of them independently reviewed the full texts of all the relevant papers. Disagreements about study eligibility were resolved via discussions among all the authors.

Study Outcome

The primary outcomes investigated were stroke, ischemic stroke, hemorrhagic stroke, systemic embolization, major bleeding, minor bleeding, gastrointestinal (GI) bleeding, hemodialysis access site bleeding, and death.

The definition of bleeding was according to International Society on Thrombosis and Haemostasis (ISTH). Major bleeding is defined as bleeding in a critical area or organ such as intracranial, intraspinal, intraocular resulting in vision changes, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome; bleeding causing a drop in hemoglobin level of 2-g/dL or more; and/or requiring transfusion of two or more units of whole blood or red cells.

Access bleeding was defined as (1) spontaneous bleeding from the arteriovenous shunt or exit site between dialysis sessions or (2) prolonged bleeding after the needles were withdrawn from the vascular access where $>$30 min of compression was required to achieve hemostasis.

Systemic Embolism was defined as the acute occlusion of an arterial vessel, excluding the heart, and brain.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement was used for this review.

Data Extraction and Synthesis

One author extracted data from the full text of each eligible trial, then recorded the data on a specially designed Microsoft Excel data extraction form. The author responsible for extracting data was not blinded to the journal or institution.

The data extracted included type of study, number of patients, patient data regarding age, gender, CHA2DS-Vasc Score, prior stroke or embolization, heart failure, hypertension, diabetes, smoking, type of DOACs used, DOAC doses, all events, stroke, ischemic stroke, hemorrhagic stroke, systemic embolism, major bleeding (defined as fatal bleeding, bleeding at a critical site, or bleeding that required blood transfusion), minor bleeding, gastrointestinal bleeding, hemodialysis access site bleeding, and death. One author entered the data into the Cochrane Review Manager software 5.4. An independent author compared these data to the original hardcopy of data extraction forms to correct

any data entry errors. If any data of interest were missing from the relevant studies, we contacted the main author or sponsor, and if these people were not reachable, the study was excluded. Two authors assessed the certainty of the evidence based on the following: perceived biases, limitations, and imprecision of the results.

The number of events and the number of patients were obtained for each trial, after which the data were combined using a fixed-effect model. For all outcomes, trial results were also combined using a random-effects model to test robustness to model choice. Relative risks and odds ratios with 95% CIs were used as summary estimates.

Risk of Bias in Individual Studies

Two authors assessed the quality of the included studies using the Cochrane Risk-of-Bias (ROB) Methods for RCTs. For observational studies, Newcastle-Ottawa Scale was used to judge selection, comparability, and outcomes. Any disagreements between the two authors were solved *via* group discussions.

RESULTS

Study Selection

The first search of the Cochrane Library, MEDLINE, and Google scholar databases from inception to 31 December 2020, yielded 14,350 articles. After exclusion of duplicate and irrelevant items, 6,412 titles were eliminated, and 6,285 studies were excluded for being irrelevant, or were review articles, editorials, case reports, or guidelines reports. A total of 127 studies relevant to DOAC use in patients with AF on dialysis were retrieved in full text. After careful evaluation, 122 studies were excluded as 47 studies combined patients with end stage renal disease with or without dialysis, 23 studies were related to Pharmacokinetics of anticoagulation, 5 studies were on Venous thromboembolism, 26 studies were on vascular calcification and Calcium deposition, and 21 studies were having missing outcome data. Five studies were selected based on the inclusion criteria. The study selection process is presented in **Figure 1**.

Study Characteristics

The selected studies were five articles including 34,516 participants with AF on dialysis. There were two RCTs, two retrospective cohort studies, and one observational prospective trial (10–14). Of these patients, 31,472 (92.14%) received warfarin, 2,473 (7.24%) received apixaban, 290 (0.85%) received rivaroxaban, and 281 (0.82%) received dabigatran. The type of included studies and basic characteristics of the patients are shown in **Table 1**.

Quality Assessment

The Newcastle-Ottawa Scale for Observational Studies was used to assess the quality of included studies, with three studies receiving a seven-star rating (**Table 2**). To assess both RCTs, the Cochrane ROB tool was used and indicated a low risk of bias for both trials (**Table 3**).

Baseline Characteristics

Baseline demographics can be found in **Table 4**. The mean ages of patients in the DOACs and warfarin groups were 70.55 and 70.32 years. There was no significant difference in age between the two groups. Approximately half of the patients were females. There were no significant differences in the prevalence of comorbid conditions such as hypertension (HTN), stroke or transient ischemic attack, heart failure, and diabetes mellitus (**Figure 2**).

Outcomes

The results of this study are presented in **Table 5**. There were no significant differences in the rates of stroke, ischemic stroke, hemorrhagic stroke, major bleeding, hemodialysis access site bleeding, and GI bleeding between patients on hemodialysis receiving DOACs and those receiving warfarin. There were higher rates of systemic embolism, minor bleeding and death in the DOACs group than warfarin group (3.39% vs. 1.97%), (6.78% vs. 2.2%), and (11.38% vs. 5.12%), respectively (**Figure 3**). It is important to notice that Siontis, et al. (11). described ischemic stroke and systemic emboli as one (composite) endpoint (11). It is possible that this is why the rate of systemic embolism is lower in warfarin-treated patients and why the rate of ischemic stroke does not differ significantly between treatments. We contacted the authors of the articles to obtain the respective figures; however, figures were not available. The follow up period ranged from 106 days to 540 days, two studies did not mention the follow up period (**Appendix 2**).

DISCUSSION

To the best of our knowledge, this is the first meta-analysis investigating the efficacy and safety profiles of DOACs vs. warfarin in patients with AF undergoing dialysis. In contrast to the other meta-analyses that included patients at different stages of renal impairment, we focused on patients on dialysis who have been largely under-represented in previous studies.

Our study is a comprehensive review of the current evidence from five clinical trials on the use of DOACs in patients on dialysis with AF regarding safety and efficacy. It included two RCTs and three observational trials. In this systematic review, 34,516 patients with AF who were on dialysis were enrolled, 3,044 (8.9%) were DOAC users and 31,472 (81.1%) were warfarin users. The result showed that DOACs were as effective as warfarin in the prevention of stroke, hemorrhagic stroke, major bleeding, and GI bleeding. However, DOACs were associated with higher rates of systemic embolization, minor bleeding, and death events compared to warfarin.

Stroke Risk Among Patients on Hemodialysis

In their meta-analysis, Zimmerman et al. demonstrated that 11.6% of patients on hemodialysis had AF. They also reported that the annual incidence of stroke in patients with AF on dialysis was 5.2% as opposed to 1.9% in those without AF (5). Other studies have challenged this idea and showed that AF is not an independent risk factor for stroke (15). Potential explanations are the high competing risk of mortality, a protective effect of

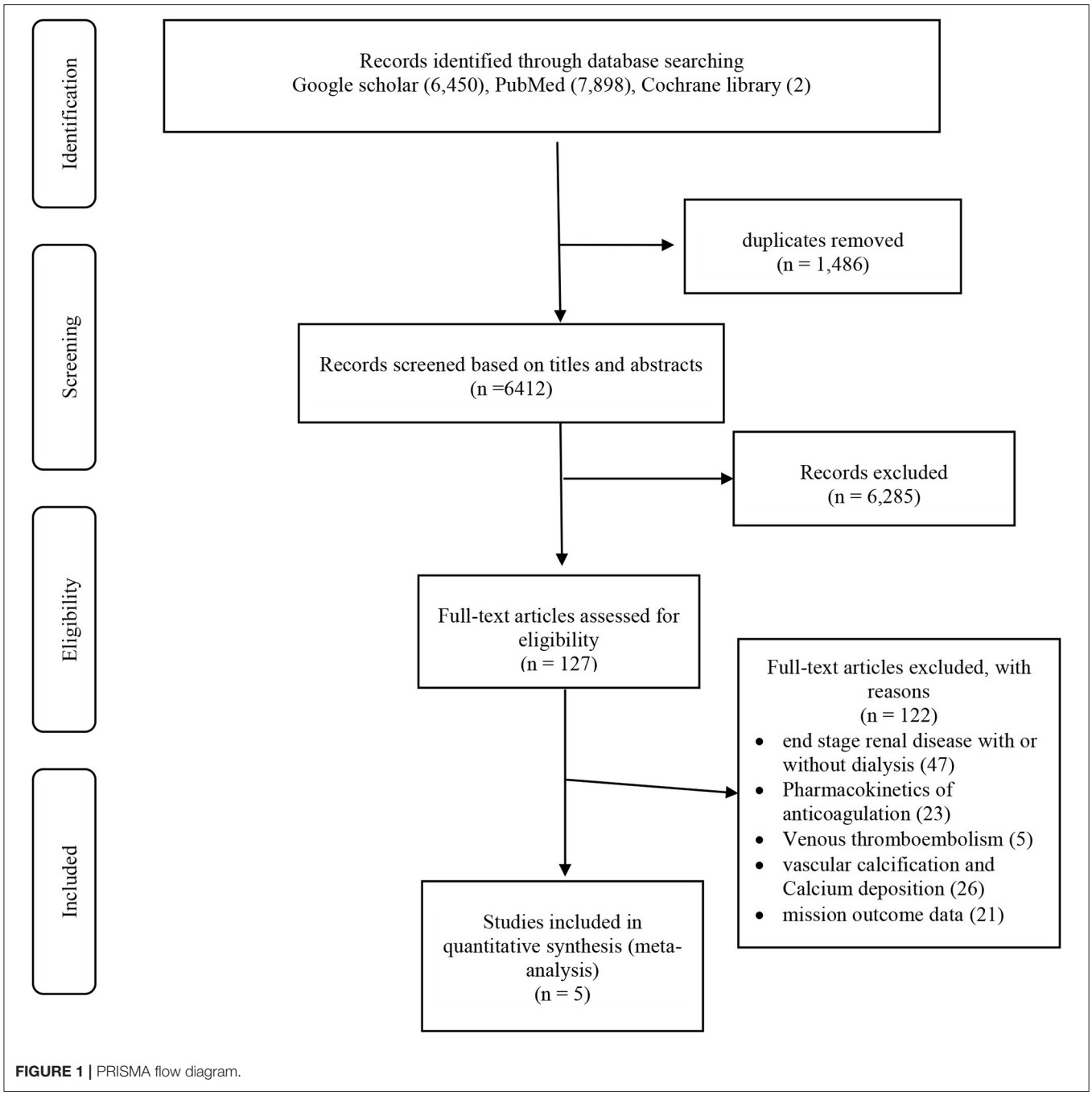

FIGURE 1 | PRISMA flow diagram.

heparin administration during dialysis, and the high prevalence of subclinical AF in patients on dialysis contaminating the "no AF" cohort in observational studies (16). Despite the paucity of studies on anticoagulation therapy in patients on dialysis, guidelines still adopt formal anticoagulation therapy for patients with high thrombotic risks. In fact, these patients were either excluded or under-represented in most of the DOAC trials (17–19).

The risk of death is higher in ESRD patients with AF than in those without AF. It is worth noting that the incidence and prevalence of AF in patients on dialysis appear to be higher because of increasing age, higher prevalence of other comorbidities, increased attention, and more people "looking for AF" with different devices e.g., 12-Lead ECG, pulse palpation, smartwatch, implantable loop recorder, ambulatory patch ECG, and multi-lead Holter monitor (5, 20–23).

TABLE 1 | Study design and baseline characteristics of the included patients.

Author name and study date	Study design	Treatment group (number of patients)	Age mean (SD)	Sex female	CHA2DS VASc score Mean (SD)	Prior stroke or embolization	Heart failure	Hypertension	DM	Smoker
Pokorney et al. (10)	RCT	Apixaban (82)	68.75 (4.3229)	34 (41.5%)	4.0 (0.6124)	17 (20.7%)	N/A	N/A	N/A	N/A
		Warfarin (72)	67.25 (3.4611)	22 (30.6%)	4.0 (0.6124)	12 (16.7%)	N/A	N/A	N/A	N/A
Siontis et al. (11)	Retrospective cohort study	Apixaban (2,351)	68.87 (11.49)	1,071	5.27 (1.77)	778 (33.1)	1,868 (79.5)	2,342 (99.6)	1,773 (75.4)	978 (41.6)
		Warfarin (23,172)	68.15 (11.93)	10,600	5.24 (1.79)	7,683 (33.2)	17,959 (77.5)	23,079 (99.6)	17,348 (74.9)	8,819 (38.1)
Chan et al. (12)	Retrospective cohort study	Rivaroxaban (244)	66.9 (12)	96	2.2 (1.0)	14.6% (36)	14.1% (34)	84.9% (207)	67.8% (165)	N/A
		Warfarin (8,064)	70.6 (11)	3,129	2.4 (1.0)	12.0% (968)	20.8% (1,677)	88.5% (7,137)	67.9% (5,475)	N/A
		Dabigatran (281)	68.4 (12)	115	2.3 (1.0)	11.2% (31)	14.6% (41)	86.9% (244)	70.4% (198)	N/A
Sarratt et al. (13)	Retrospective, cohort study	Apixaban (40)	70.9 (5.25)	20 (50.0)	4.25 (1.4361)	6 (15.0%)	19 (47.5	33 (82.5)	22 (55.0	N/A
		Warfarin (120)	66.5 (6.75)	42(51.7)	4.75 (1.4216)	29 (24.2%)	60 (50.0)	97 (80.8)	59 (49.2)	N/A
De Vriese et al. (14)	RCT	Rivaroxaban (46)	79.525 (2.731)	11 (23.9%)	4.7 (1.4)	15 (32.6 %)	17 (37%)	N/A	20 (43.5 %)	N/A
		Warfarin (44)	79.1 (3.6894)	19 (43.13%)	4.8 (1.5)	16 (36.4%)	9(20.5%)	N/A	20 (45.5 %)	N/A

SD, Standard deviation.

TABLE 2 | Risk of bias assessment using Newcastle-Ottawa Scale for observational studies.

			Chan et al. (12)	Sarratt et al. (13)	Siontis et al. (11)
Selection	Representativeness of the exposed cohort	Representative or somewhat representative of average dialysis patients in community (age/risk of stroke and bleeding)	*	*	*
	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	*	*
	Ascertainment of exposure	Secure record, structured interview	*	*	*
	Demonstration that outcome of interest was not present at start of study	Stroke or bleeding due to anticoagulant	–	–	–
Comparability	Comparability of cohorts on the basis of the design or analysis	Study controls for renal function	*	*	*
		Study controls for any additional factors (history and risk of stroke and bleeding)	*	*	-
Outcome	Assessment of outcome	independent blind assessment or record linkage	*	*	*
	Was follow-up long enough for outcomes to occur	Follow-up > 1 year	–	–	*
	Adequacy of follow up of cohorts	Complete follow up (all subjects accounted for) or subjects lost to follow up unlikely to introduce bias	*	*	*
Score			7	7	7

**Means equal to one point score.*

TABLE 3 | Cochrane risk of bias assessment for randomized trials.

Cochrane ROB tool for RCTs	Pokorney et al. (10)	De Vriese et al. (14)
1. Sequence generation	Low—randomized	Low—computer-generated, web-based, locked central randomization system
2. Allocation Concealment	Low—randomized	Low—investigators (the investigator who reviewed all CT scans and the investigator who analyzed the pulse wave analysis curves) that were blinded to the treatment allocation
3. Blinding of participants and personnel	Low- open label with blinded event adjudication	Low—the primary endpoints were objectively measured by investigators that were blinded to the treatment allocation
4. Blinding of outcome assessors	Low—blind outcome assessment	Low—adjudication committee was blinded
5. Incomplete outcome data	Low	Low
6. Selective outcome reporting	Low	Low
7. Other sources of bias	Low	Low—although industry sponsored, all primary and secondary endpoints were adjudicated by blinded clinical events committee
Overall risk of bias	Low	Low

TABLE 4 | Baseline demographics.

	DOACS ($n = 3,044$)	WARFARIN ($n = 31,472$)	RR (95% CI)	*P*-value
Age mean (SD)	70.55 (4.17)	70.32 (4.6)	0.70 [−1.13, 2.53]	$P = 0.45$
Female Sex	1,347 (44.25%)	13,812 (43.88%)	1.04 [0.92, 1.17]	$P = 0.54$
CHA2 DS2 -VASc scoremean (SD)	3.91 (1.35)	4.28 (1.15)	−0.07 [−0.20, 0.06]	$P = 0.28$
Comorbid conditions (%)				
Stroke/TIA				
N patients	3,044	31,472		
N events	883 (29%)	8708 (27.66%)	1.00 [0.94, 1.06]	$P = 1.00$
Heart failure				
N patients	2,962	31,400		
N events	1,979 (66.8%)	19,705 (62.75%)	0.96 [0.71, 1.28]	$P = 0.76$
Hypertension				
N patients	2,916	31,356		
N events	2,826 (96.9%)	30,313 (96.67%)	0.99 [0.93, 1.05]	$P = 0.75$
Diabetes mellitus				
N patients	2,962	31,400		
N events	2,177 (73.49%)	23,102 (73.57%)	1.01 [0.99, 1.03]	$P = 0.43$

DOACS, Direct oral anticoagulants; SD, Standard deviation; TIA, transient ischemic attack; RR, risk ratio; CI, confidence interval.

Use of Warfarin in Patients on Hemodialysis

Warfarin is the most frequently used drug for anticoagulation in AF. Nonetheless, the risk of bleeding in patients on dialysis is increased with warfarin, which may be caused by platelet dysfunction. Platelet dysfunction occurs both as a result of intrinsic platelet abnormalities and impaired platelet-vessel wall interaction. The classic stages of platelet response to injury (activation, recruitment, adhesion, and aggregation) are all defective in patients with renal failure. Although dialysis may partially overcome these defects, it cannot totally correct them. The dialysis process itself may, in fact, contribute to bleeding. Hemodialysis is also associated with thrombosis as a result of chronic platelet activation due to contact with artificial surfaces during dialysis (24).

In our meta-analysis, four out of the five papers reported a target INR of 2–3, and one study (14) reported a mean INR of 3.5. Lower doses of warfarin are sometimes preferred in patients on dialysis to achieve a lower INR target because of the increased risk of bleeding. However standard dosing has been shown to be superior in stroke prevention without increased bleeding risk (19, 24–26).

The use of warfarin did not bring about a significant reduction in the rates of stroke and death and was associated with an increased risk of major bleeding as reported by previous meta-analyses (27). Warfarin is thought to accelerate vascular

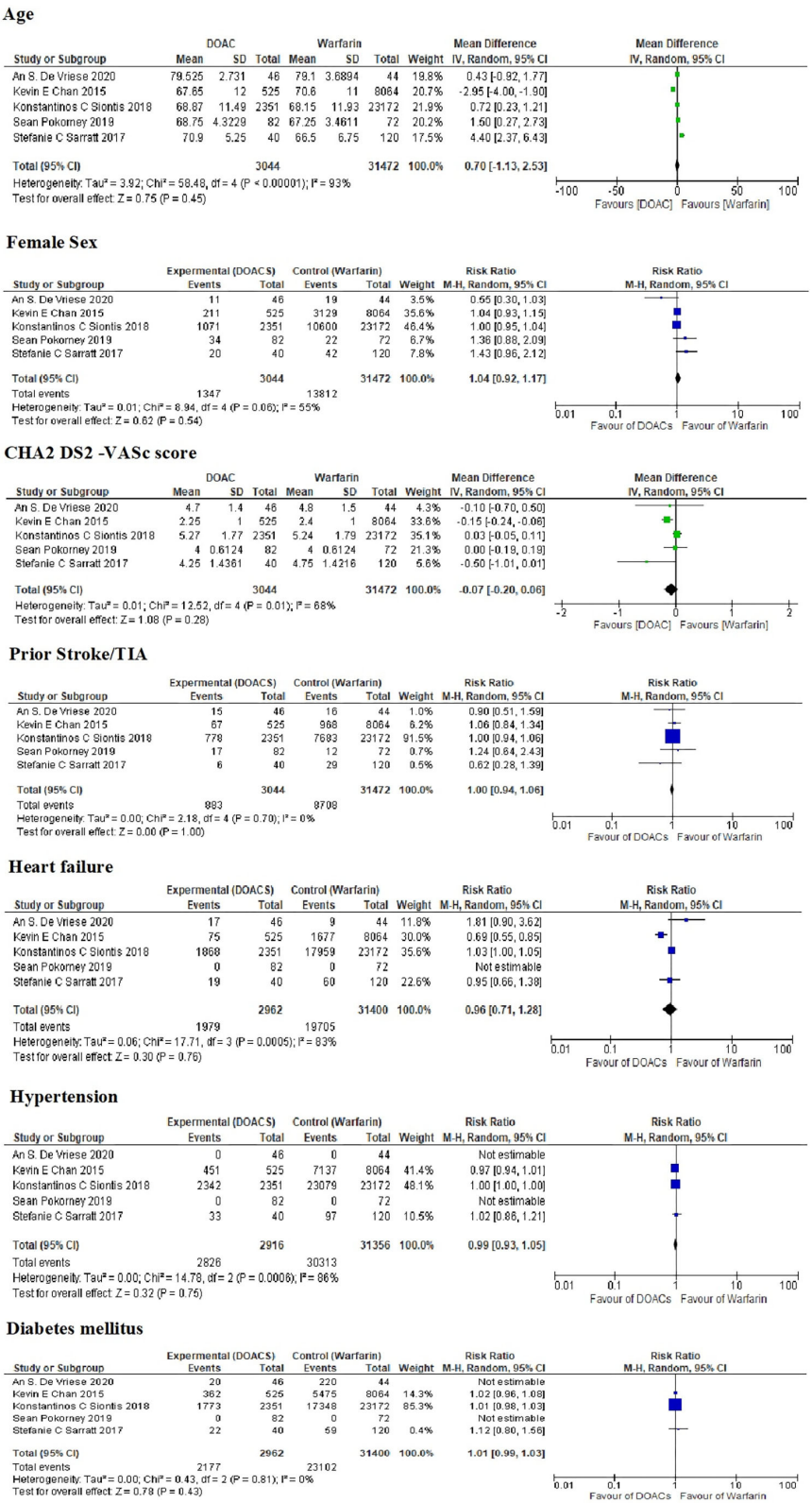

FIGURE 2 | Baseline demographics and comorbidities among different studies.

TABLE 5 | Event rates and association estimates.

	Overall ($n = 34,516$)	DOACS ($n = 3,044$)	Warfarin ($n = 31,472$)	RR (95% CI)	*p*-value
Stroke					
N patients	34,356	3,004	31,352		
N events	1,563 (4.54%)	159 (5.29%)	1,404 (4.47%)	1.27 [0.71, 2.30]	$P = 0.42$
Systemic Embolism					
N patients	34,356	3,004	31,352		
N events	721 (2.09%)	102 (3.39%)	619 (1.97%)	1.74 [1.08, 2.80]	$P = 0.02$
Ischemic stroke					
N patients	8,833	653	8,180		
N events	250 (2.8%)	22 (3.36%)	228 (2.78%)	0.91 [0.39, 2.08]	$P = 0.82$
Hemorrhagic stroke					
N patients	34,356	3,004	31,352		
N events	258 (0.75%)	23 (0.76%)	235 (0.74%)	0.53 [0.09, 3.25]	$P = 0.49$
Major bleeding					
N patients	34,516	3,044	31,472		
N events	1,167 (3.38%)	164 (5.38%)	1,002 (3.18%)	1.31 [0.90, 1.91]	$P = 0.16$
Minor bleeding					
N patients	8,993	693	8,300		
N events	230 (2.55%)	47 (6.78%)	183 (2.2%)	1.52 [1.07, 2.15]	$P = 0.02$
GI bleeding					
N patients	34,516	3,044	31,472		
N events	1,355 (3.92%)	201 (6.6%)	1,154 (3.66%)	1.26 [0.75, 2.11]	$P = 0.37$
Hemodialysis access site bleeding					
N patients	8,743	607	8136		
N events	2789 (31.89%)	187 (30.8%)	2602(31.9%)	1.05 [0.93, 1.19]	$P = 0.45$
Death					
N patients	34,352	3,004	31,352		
N events	1,607 (4.67%)	342 (11.38%)	1,607(5.12%)	1.72 [1.16, 2.55]	$P < 0.006$

DOACS, direct oral anticoagulants; GI bleeding, gastrointestinal bleeding: SE, systemic embolism; RR, risk ratio; CI, confidence interval.

calcification and aortic stenosis, which might increase the risk of ischemic stroke (2, 28). Additionally, the use of warfarin was associated with a higher risk of anticoagulant-induced renal injury than the use of DOACs (29, 30).

Use of DOACs in Patients on Dialysis

The Renal-AF trial recently investigated the use of DOACs in patients on dialysis. In this study, 154 patients with AF on dialysis were randomly assigned to either the apixaban 5 mg BID ($N = 82$) or warfarin ($N = 72$) groups, with a target INR of 2–3 and time in therapeutic range (TTR) for warfarin of 44.3%. They included patients with AF who were on hemodialysis, had CHA2DS2-VASc scores of $\geq$2, and were candidates for OAC and excluded patients with moderate to severe mitral stenosis, patients who needed aspirin at doses of >81 mg, patients who needed dual antiplatelet therapy, patients with indications for OAC other than AF, and patients with life expectancies of <3 months. The follow-up period was 1 year. The results showed that apixaban 5 mg BID caused similar rates of major bleeding (8.5%) as warfarin (9.7%) and clinically relevant non-major bleeding (31.5%) as warfarin (25.5%). Also, there was no significant difference in the incidence of stroke between the two groups (2.4% vs. 2.8%). It is important to note that the trial was stopped earlier than planned due to the lack of funding and the fact that a majority of the patients on warfarin were in the subtherapeutic range with TTR (44.3%) (10).

Similarly, Sarratt, et al. (13) compared the rates of major bleeding, clinically relevant non-major bleeding, and minor bleeding between apixaban and warfarin in patients with AF on hemodialysis. Theirs was a single-center retrospective cohort study. They found no significant differences between the two groups (13).

Siontis, et al. (11) published the results of their large, retrospective cohort study that included 25,523 patients from the United States Renal Data System (October 2010 to December 2015). According to the results of this study, standard-dose apixaban (5 mg BID) was associated with significantly lower rates of stroke, systemic embolism, and death compared to either warfarin or low-dose apixaban (2.5 mg BID). In addition, apixaban, irrespective of the dose (5 mg bd or 2.5 mg bd), was associated with lower rates of major bleeding events than warfarin. The standard dose was associated with lower rates of thromboembolic events and death. These data support the growing evidence that recommends the safety profile of apixaban in this high-risk patient group and warrants further randomized clinical trials to further confirm the results of earlier studies (11).

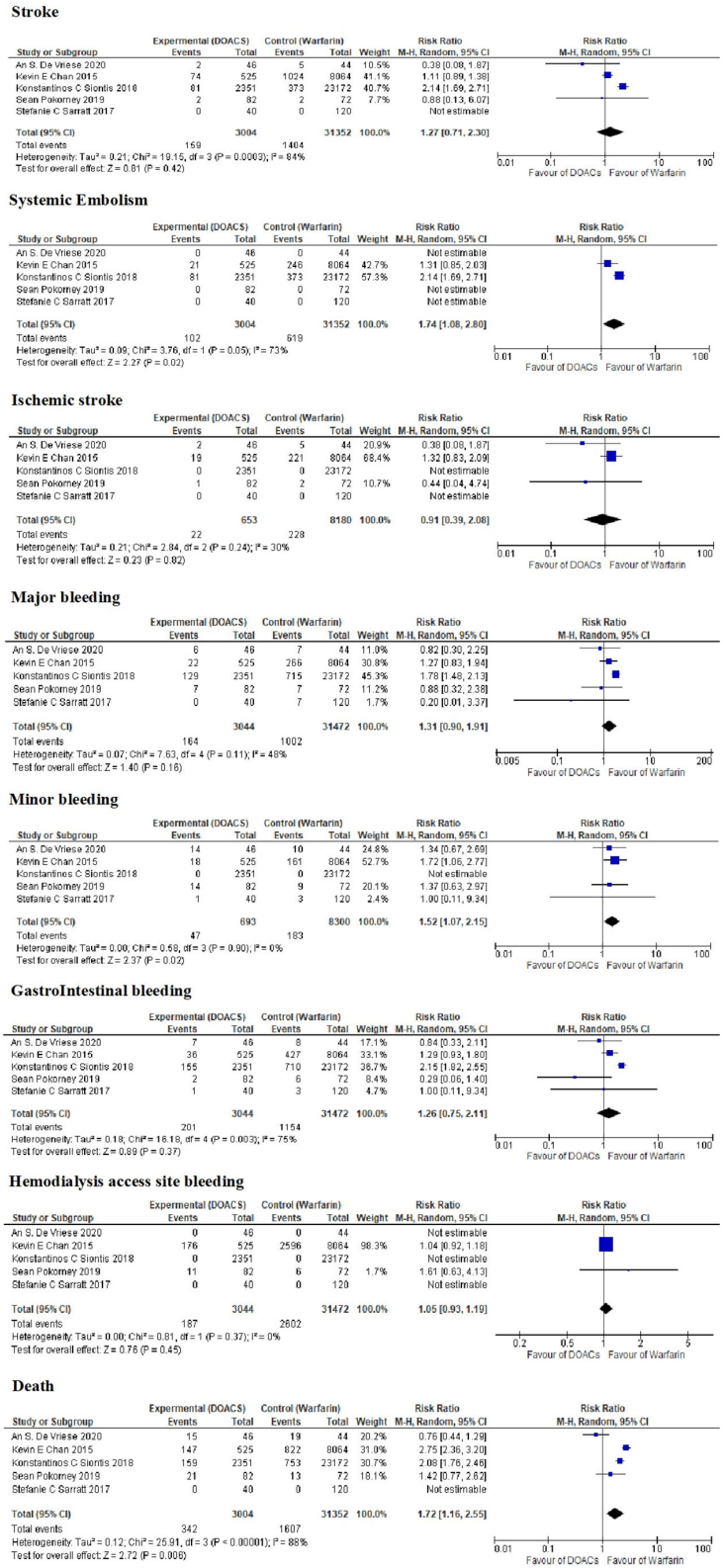

FIGURE 3 | Event rates and association estimates among different studies.

Regarding rivaroxaban and other DOACs, there was some discrepancy in results between different studies. Chan, et al. (12) used Poisson regression analysis to compare rivaroxaban and dabigatran to warfarin in patients with ESRD. Although the exact figures could not be obtained and were not included in our statistical analysis, the study concluded that dabigatran and rivaroxaban were associated with higher risks of hospitalization and hemorrhagic death compared to warfarin. On the contrary, De Vriese, et al. (14) investigated the topic from a different point of view. They assessed the relationship between vitamin K status and the risk of bleeding in patients with ESRD, with the hypothesis that warfarin could cause functional vitamin K deficiency, which might lead to more bleeding and the acceleration of vascular calcification, which was assessed by CT calcium scores in the major vessels. Patients with non-valvular AF and CHA2DS2-VASc scores of $\geq$2 were randomly divided into 3 groups: warfarin with INR 2–3, rivaroxaban 10 mg OD, and rivaroxaban 10 mg OD with a vitamin K supplement. The results showed that rivaroxaban was associated with lower rates of life-threatening and major bleeding events compared to warfarin; however, no significant differences in calcium scores were noted.

Difference in Clinical Outcome Between DOACs and Warfarin

Our data showed that DOACs are as effective as warfarin in the prevention of stroke, hemorrhagic stroke, major bleeding, and GI bleeding.

Despite the fact that each individual study did not find a significant difference in the rates of minor bleeding, systemic embolization, and mortality, the pooled data of the five studies showed a significant increase in the mortality rate among patients that took DOACs compared to patients that took warfarin [10.1% and 5.1% ($p < 0.001$)]. This difference can be attributed to several factors.

Firstly, there was a large impact of two big observational studies (more than 85% of patients) with the inherited bias to non-randomized assignments of the observational studies. Looking at the individual studies that reported this difference in mortality, Chan's study included both dabigatran and rivaroxaban at full and reduced doses (12), while Siontis, et al. (11) used both doses of apixaban. The first study included a DOAC that is clearly not suitable in ESRD–i.e., dabigatran. This drug reported renal clearance values of up to 85%, second compartment pharmacokinetics, low protein binding (thus dialyzable and prone to large variations in plasma concentrations), and a very clear-cut dose relationship with respect to thrombosis/bleeding shown in a large sub-study of RELY including more than 9,000 patients (31). Secondly, In the Siontis study, patients had high mean CHA2DS2- VASc scores of up to 5.2 $\pm$ 1.8, unlike other studies reflecting multiple comorbidities (10). Thirdly, most patients on warfarin in Chan's study were sub-therapeutic (only 13.7% of patients had $\geq$60% of their INR readings within the target of 2–3) (12).

There were also significant differences in the rates of minor bleeding and systemic embolization, with the lower rates occurring in the warfarin arm. The possible explanations for this difference include: the use of reduced DOAC doses in some patients, the inability to monitor the efficacy of anticoagulation, and the variable clearance of DOACs with hemodialysis.

The doses of DOACs varied between studies; De Vriese's group used a reduced dose of rivaroxaban 10 mg while the other studies combined reduced doses of DOACs. We contacted the authors to verify if separate data were available for both doses but unfortunately, this was not the case.

One of the major advantages of DOACs over warfarin is that there is no need for laboratory monitoring. However, in certain patient cohorts, including patients on dialysis, it might be important to ascertain either the actual DOAC concentration (quantitative) or the effect of DOACs (qualitative). None of the included studies assessed the level or the effect of DOACs, which may reflect the real-world situation with DOACs monitoring.

Unlike apixaban and edoxaban that are cleared by dialysis in 6 and 9%, respectively, dabigatran is cleared up 50%−60% within 4 h of hemodialysis. There were no published data on rivaroxaban clearance by dialysis. This reflects why apixaban was used the most in our study groups (32).

The fact that there is no need for routine laboratory monitoring of the effects of DOACs can lead to either undertreatment or overtreatment, which might be another reason for the significant differences in some parameters. Our study highlights the potential role of monitoring the level and effect of DOACs in this cohort of patients.

Ongoing Trials to Study Stroke Prevention in Patients With AF on Dialysis

There are three upcoming trials that would further depict the role of oral anticoagulation in patients with ESRD on dialysis and help establish the optimal pharmacological or interventional strategy (left atrial appendage occlusion) in this population.

The German AF network also registered an open-label RCT (AXADIA), recruiting patients since April 2017. This trial will end in July 2023. The AXADIA trial will assess the safety of apixaban vs. phenprocoumon in patients with AF on hemodialysis (33).

The AVKDIAL trial is comparing the hemorrhagic and thrombotic risks of oral anticoagulation with that of no anticoagulation in hemodialyzed patients with AF. The target INR (2–3) is monitored at least once per week (34).

The SAFE-D trial (ClinicalTrials.gov Identifier: NCT03987711) is an open-label randomized trial involving patients with ESRD and AF on dialysis to compare three arms: apixaban (both 5 mg and 2.5 mg twice daily), warfarin, and no anticoagulation, for 26 weeks (35).

LIMITATIONS

Our study has some limitations that warrant consideration. Firstly, there were only five studies that met the inclusion criteria in our meta-analysis with a relatively small number (3,044) of patients on DOACs.

Secondly, we acknowledge the heterogeneity of the five included studies. These studies have different study designs, with

two being randomized control trials while the other three were observational studies that come with an inherent selection bias. It is important to notice that the difference in mortality was attributed to two large observational studies.

Additionally, different DOAC drugs with different doses were used. Furthermore, the studies included had heterogeneous inclusion/exclusion criteria and varying definitions of each outcome and follow-up duration.

Similar to other meta-analyses, the endpoint definition may vary between studies on safety and efficacy outcomes. Some studies did not clearly define the stroke subtypes, systemic embolism, and bleeding subtypes (major or minor). Additionally, they did not clarify the etiology of bleeding endpoints, especially cerebral hemorrhage.

Finally, there were some patients receiving antiplatelet therapy who could not accurately be identified in the retrospective studies but could have possibly affected our results.

CONCLUSION

This meta-analysis has demonstrated that in patients on dialysis who need anticoagulation for AF, warfarin could be associated with a significant reduction in the rates of minor bleeding, systemic embolization, and death compared to DOACs. These findings need to be validated by further prospective studies to address the best strategy to deal with the increased thrombotic and bleeding risks in such patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.847286/full#supplementary-material

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frontiers | Frontiers in Cardiovascular Medicine

SYSTEMATIC REVIEW
published: 17 June 2022
doi: 10.3389/fcvm.2022.899906

An Updated Meta-Analysis of DOACs vs. VKAs in Atrial Fibrillation Patients With Bioprosthetic Heart Valve

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Background: Current guidelines recommend the utilization of direct-acting oral anticoagulants (DOACs) in patients with non-valvular atrial fibrillation (AF). However, the optimal anticoagulation strategy for AF patients with bioprosthetic heart valves (BPHV) remains controversial. Therefore, we conducted this meta-analysis to explore the effect of DOACs versus vitamin K antagonists (VKAs) in this population.

Methods: We systematically searched the PubMed and Embase databases until November 2021 for studies reporting the effect of DOACs versus VKAs in AF patients with BPHV. Adjusted risk ratios (RRs) and 95% confidence intervals (CIs) were pooled using the random-effects model with an inverse variance method.

Results: We selected four randomized clinical trials and seven observational studies (2236 DOAC- and 6403 VKAs-users). Regarding the effectiveness outcomes, there were no significant differences between DOACs and VKAs in stroke or systemic embolism (RR = 0.74, 95%CI: 0.50–1.08), ischemic stroke (RR = 1.08, 95%CI: 0.76–1.55), all-cause death (RR = 0.98, 95%CI: 0.86–1.12), and cardiovascular death (RR = 0.85, 95%CI: 0.40–1.80). In terms of the safety outcomes, DOACs was associated with lower risks of major bleeding (RR = 0.70, 95%CI: 0.59–0.82) and intracranial bleeding (RR = 0.42, 95%CI: 0.26–0.70), but the risks of any bleeding (RR = 0.85, 95%CI: 0.65–1.13) and gastrointestinal bleeding (RR = 0.92, 95%CI: 0.73–1.17) are not significantly different when compared with VKAs. The subgroup analysis with follow-up as a covariate revealed that the DOACs had lower risks of SSE (RR = 0.59, 95%CI: 0.37–0.94) and major bleeding (RR = 0.69, 95%CI: 0.58–0.81) in patients with a mean follow-up of more than 24 months, but no statistical differences were found in patients with the follow-up less than 24 months (SSE: RR = 1.10, 95%CI: 0.92–1.32; major bleeding: RR = 0.91, 95%CI: 0.42–2.01).

Conclusions: In AF with BPHV, patients on DOACs experienced a reduced risk of major bleeding and intracranial bleeding compared with VKAs, while the risks of stroke, cardiovascular death, and all-cause mortality were similar.

Keywords: atrial fibrillation, anticoagulants, safety, effectiveness, meta-analysis

OPEN ACCESS

Edited by:
Antonino Tuttolomondo, University of Palermo, Italy

Reviewed by:
Iqbal Haider Jaffer, McMaster University, Canada
Dana Huskens, Synapse BV, Netherlands

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Specialty section:
This article was submitted to Thrombosis, a section of the journal Frontiers in Cardiovascular Medicine

Received: *19 March 2022*
Accepted: *23 May 2022*
Published: *17 June 2022*

Citation:
Cao Y, Zheng Y, Li S, Liu F, Xue Z, Yin K and Luo J (2022) An Updated Meta-Analysis of DOACs vs. VKAs in Atrial Fibrillation Patients With Bioprosthetic Heart Valve. Front. Cardiovasc. Med. 9:899906. doi: 10.3389/fcvm.2022.899906

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia among adults, affecting an estimated 1.2 million people in the UK (1). Characterized by rhythm irregularity, AF patients are prone to forming thrombi in the left atrium/left atrial appendage due to stasis of blood and are at risk of thromboembolic events (2). Moreover, AF may be of valvular etiology or non-valvular. The presence of valvular disease further complicates the course of AF and tends to increase morbidity and mortality. Consequently, anticoagulation therapy becomes an indispensable part of preventing thromboembolic events for patients with AF and valvular heart disease (VHD).

Direct-acting oral anticoagulants (DOACs) have been considered the first-line choice for non-valvular AF patients (3). However, when it comes to patients with bioprosthetic heart valves (BPHV), the use of DOACs is contraindicated to a large extent, and warfarin is the only permitted oral anticoagulant (4). Both the American College of Cardiology (5) and major Japanese guidelines (6–8) do not endorse the use of DOACs after bioprosthetic valve replacement (BVR). Conversely, the European Society of Cardiology (9) and the European Heart Rhythm Association (10) states that DOACs should be considered in patients with AF and bioprosthetic heart valve (BPHV), but no earlier than 3 months after bioprosthetic aortic valve replacement. Nonetheless, concerning the lower PT-INR settings in Asia, the racial differences in thromboembolism or bleeding prevalence between Asian and western patients (11) and the lack of robust evidence, the results of Asian patients should not be simply generalized to the western population, and more updated researches for a clear consensus guideline are integral.

With the ever-increasing number of observational studies supporting strong evidence to the issue, we conducted the meta-analysis to better understand the effectiveness and safety of DOACs in AF patients with BPHV. It incorporated a larger patient population and considered more factors, identifing the optimal antithrombotic strategies in real-world clinical practice.

METHODS

Throughout this meta-analysis, the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for all stages of the design and implementation were followed (12). There was no need for ethical approval as only published studies were included.

Searching Strategy

We systematically searched the PubMed and Embase databases from inception to November 2021 with the following search terms: (1) *atrial fibrillation*, (2) *edoxaban* OR *dabigatran* OR *rivaroxaban* OR *apixaban* OR *non-vitamin K oral anticoagulants* OR *direct oral anticoagulants* OR *novel oral anticoagulants OR DOAC* OR *NOAC*, (3) *biologic valve* OR *bioprosthetic valve* OR *biological valve* OR *bioprosthesis*, (4) *warfarin* OR *vitamin K antagonists* OR *VKA* OR *coumadin* OR *dicoumarol* OR *acenocoumarol*. The detailed searching strategies are shown in **Supplementary Table 1**. No language restrictions were applied in this meta-analysis.

Eligibility Criteria

We included the randomized controlled trials (RCTs), *post-hoc* analyses of RCTs and observational cohort studies focusing on the effectiveness and/or safety of DOACs (dabigatran, rivaroxaban, apixaban, or edoxaban) compared with VKAs in AF patients with BPHV. We included the simultaneously reported outcomes in at least two included articles. Our effectiveness outcomes included stroke or systemic embolism (SSE), ischemic stroke, all-cause death, and cardiovascular death, whereas the safety outcomes included major bleeding, gastrointestinal bleeding, intracranial bleeding, and any bleeding. Thereinto, the primary effectiveness and safety outcomes were SSE and major bleeding, respectively. The studied outcomes and their definitions were chosen according to the originally included studies and the definitions were shown in **Supplementary Table 2**. Studies would be excluded if they had no sufficient data (e.g., comments, case reports, reviews, editorials, letters) or did not report the quantitative effect estimate. Studies involving mechanical heart valves, rheumatic valvular disease, and overlapping data were also excluded. In addition, studies that did not report stroke, systemic embolism, and major bleeding outcomes separately were also excluded.

Study Selection and Data Extraction

Two independent researchers first screened the titles and abstracts of the retrieved records and then viewed the full-texts of the potential studies for the second screening. Disagreements were resolved through discussion with each other or with the third reviewer. Data were collected as follows: the first author and publication year, study design, data source, the study characteristics, type of DOACs, number of DOAC- or VKA-users, length of follow-up, effectiveness, and safety outcomes.

Quality Assessment

The Cochrane risk of bias assessment tool evaluated the methodological quality of RCTs and *post-hoc* analysis of RCTs. The Newcastle-Ottawa Scale (NOS) tool was applied to assess the study quality for observational cohorts. The NOS tool included three major sections as follows: the selection of cohorts (0-4 points), the comparability of cohorts (0-2 points), and the assessment of the outcome (0-3 points). We regarded the NOS score of $\geq$6 points as a moderate-to-high quality, while a NOS score of $<$6 points as a low-quality (13).

Statistical Analysis

The statistical heterogeneity across the included studies was assessed using the *P*-value of the Cochrane Q-test and the I^2 value. The I^2 test was interpreted as follows: 0–40% might not be important, 30–60% may indicate moderate heterogeneity, 50–90% indicates substantial heterogeneity and over 75% indicates considerable heterogeneity.First, the number of participants and events were compiled in each group, and their corresponding crude rates of effectiveness and safety outcomes were worked out, represented by odds ratios (ORs) and 95%CIs. Second, we

reckoned the relevant outcomes using the adjusted RRs and converted the adjusted RRs and 95%CI to the natural logarithms and standard errors. All the comparison results were pooled by a random-effects model using an inverse variance method. The publication bias was evaluated for the effect estimates based on the funnel plots.

We used the Review Manager version 5.4 software (the Cochrane Collaboration 2014, Nordic Cochrane Centre Copenhagen, Denmark; https://community.cochrane.org/) to perform the meta-analysis. The statistical significance threshold was set at a *P*-value of < 0.05.

RESULTS

Study Selection

The process of the literature retrieval is presented in **Figure 1.** Through searching the electronic searches in the PubMed and EMBASE databases, our initial search yielded 176 articles. After the records screening, we selected 23 relevant articles. Subsequently, the full-text screening led to the exclusion of 12 articles based on the predefined criteria. Finally, a total of 11 studies [two *post-hoc* analyses of RCTs (14, 15), 2 RCTs (16, 17), and seven observational studies (18–24)] were included in our meta-analysis. The baseline characteristics of the included studies are illustrated in **Table 1**. All 11 included studies were published from 2016 to 2021, with the sample sizes ranging from 27 to 2,672. Participants in these studies ranged from 37 to 88.9 years old. For the quality assessment, both of the two RCTs and two *post-hoc* analyses of RCTs had a low risk of bias (**Supplementary Table 3**), whereas the seven observational studies had a moderate-to-high quality with a NOS of ≥6 points (**Supplementary Table 4**).

Crude Event Rate Between DOACs vs. VKAs

Ten included studies reported the crude rates of effectiveness or safety outcomes between DOACs vs. VKAs (14–17, 19–25). For the effectiveness outcomes shown in **Supplementary Figure 1**, compared with VKAs, no statistically difference was represented in SSE (OR = 0.70, 95%CI: 0.47–1.02), ischemic stroke (OR = 0.71, 95%CI: 0.33–1.55), all-cause death (OR = 0.81, 95%CI: 0.47–1.37) and cardiovascular death (OR = 0.89, 95%CI: 0.47–1.67).

The safety outcomes of DOACs vs. VKAs are presented in **Supplementary Figure 2**. The pooled analysis demonstrated that DOAC-users had lower event rates of major bleeding (OR = 0.60, 95%CI: 0.42–0.84) compared with VKA-users, whereas the rates of any bleeding (OR=0.83, 95%CI: 0.57–1.20), and intracranial bleeding (OR = 0.84, 95%CI: 0.26–2.66) between the two studied groups were similar.

Adjusted Data of Outcomes Between DOACs vs. VKAs

A total of eight studies reported the adjusted data of efffectiveness or safety outcomes between DOACs vs. VKAs (14–19, 21, 23). As shown in **Figure 2**, for the effectiveness outcomes, there was no significant differences between DOACand VKA groups in SSE (RR = 0.74, 95%CI: 0.50–1.08), ischemic stroke (RR = 1.08, 95%CI: 0.76–1.55), all-cause death (RR = 0.98, 95%CI: 0.86–1.12), and cardiovascular death (RR = 0.85, 95%CI: 0.40–1.80).

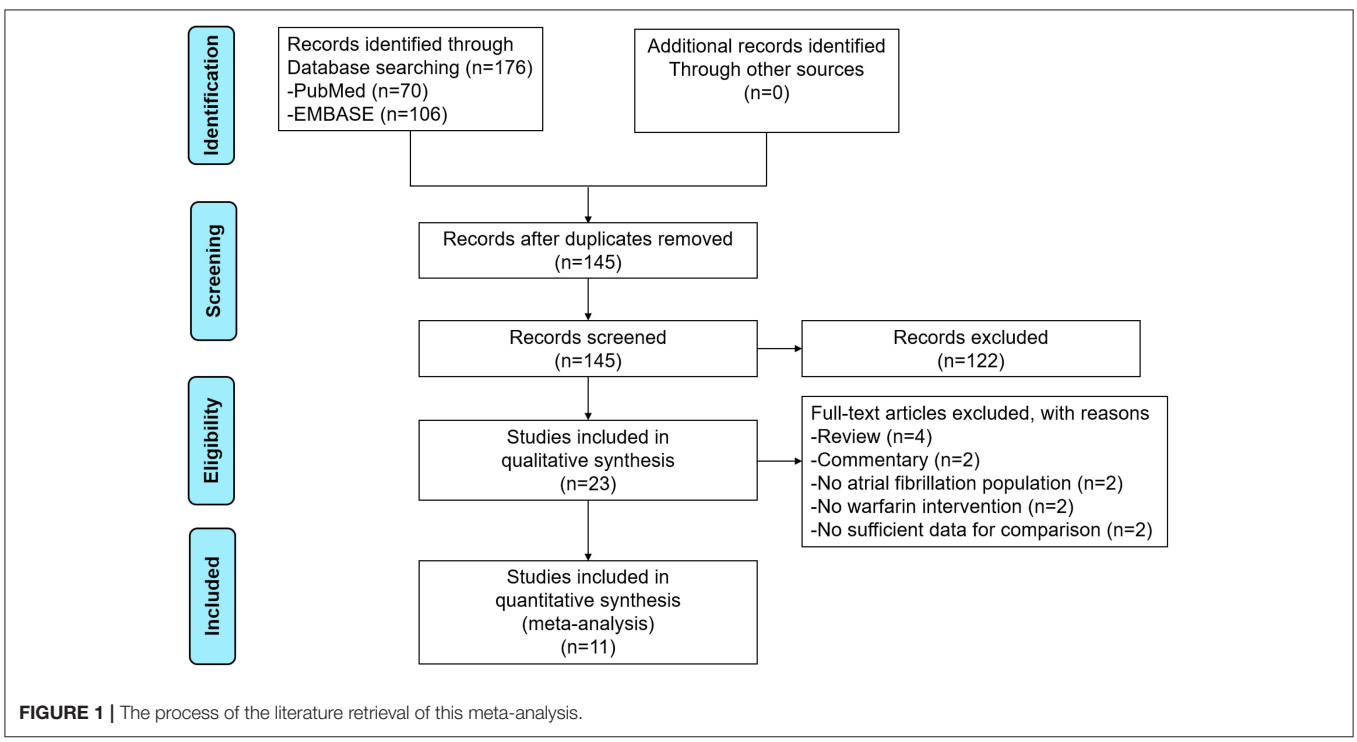

FIGURE 1 | The process of the literature retrieval of this meta-analysis.

TABLE 1 | Baseline characteristics of the included studies in this meta-analysis.

Study(author)/Study name	Region	Study design	Participants (N)	Age (years)	HAS-BLED	CHA2DS2-VASc	Male ratio(%)	DOACs regimen	Follow-up (months)	Bioprosthetic valve types
Carnicelli et al. (14)	Multi-center (America, Europe, Asia–Pacific region and South Africa)	*Post-hoc* analysis of ENGAGE AF-TIMI48	191	75.0	2.7	3.0	63.4	EDO	33.6	Mitral or aortic
Durães et al. (16) DAWA Pilot Study	Brazil	RCT	27	44.6	NA	NA	37.0	DA	3.0	Mitral and/or aortic
Guimarães et al. (15)	Multi-center (America, Europe and Asia Pacific)	*Post-hoc* analysis of ARISTOTLE	156	72.9	2.0	2.0	60.9	API	21.6	Mitral and/or aortic valve replacement or native valve repair
Guimarães et al. (17) RIVER	Brazil	RCT	1,005	59.3	1.6	2.6	39.6	RIV	39	Mitral valve
Russo et al. (23)	5 cardiologic centers in Italy	Observational study	260	65.9	1.2	3.1	56.0	EDO, DA, API, RIV	26.8	Mitral or aortic
Duan et al. (18)	America	Observational study	2,672	NA	NA	NA	NA	DA, API, RIV	34.8	Mitral and/or aortic
Mannacio et al. (21)	Italy	Observational study	642	NA	NA	NA	NA	DA, RIV, API, EDO	38.4	Aortic valve
Myllykangas et al. (22)	Finnish	Observational study	2,245*	75.4	NA	NA	57.3	DA, RIV, API, EDO	36.0	Aortic valve
Strange et al. (24)	Denmark	Observational study	397	78.6	2.6	3.6	NA	RIV, API	24.0	Mitral and/or aortic
Izumi et al. (8)	Japan	Observational study	214	76.8	3.6±1.2	4.0	46.7	NA	46.0	Mitral and/or aortic
Izumi et al. (19)	Japan	Observational study (Data from BPV-AF Registry)	752	81.3	2.5	4.3	44.7	NA	12.0	Mitral and/or aortic

RCTs, randomized controlled trials; DOACs, direct-acting oral anticoagulants; DA, dabigatran; RIV, rivaroxaban; API, apixaban; EDO, edoxaban; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol; CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 y (doubled), diabetes mellitus, stroke (doubled)-vascular disease, age 65–74 and sex category (female).

* *Patient in this study was changed into another group if the medication was changed, so 2,158 patients were in warfarin group and 168 patients were in DOACs group.*

The safety outcomes were shown in **Figure 3**. Compared with VKA-users, the use of DOACs was significant associated with reduced risks of major bleeding (RR = 0.70, 95%CI: 0.59–0.82) and intracranial bleeding (RR = 0.42, 95%CI: 0.26–0.70). There was no statistically differences in any bleeding (RR = 0.85, 95%CI: 0.65–1.13) and gastrointestinal bleeding (RR = 0.92, 95%CI: 0.73–1.17) between patients treated with DOACs compared to patients treated with VKAs.

Subgroup Analysis

As shown in **Figure 4**, SSE and major bleeding outcomes were consistent between the observational studies and RCTs (P for interaction = 0.79 for SSE; P for interaction = 0.59 for major bleeding). For patients treated with DOACs compared with VKAs, the risk of major bleeding did not show a significant difference between groups in RCTs (RR = 0.75, 95%CI: 0.51–1.11), but was statistically different in observational studies (RR = 0.67, 95%CI: 0.55–0.81).

The subgroup analysis with follow-up as a covariate revealed that the DOACs had lower risks of SSE (RR = 0.59, 95%CI: 0.37–0.94) and major bleeding (RR = 0.69, 95%CI: 0.58–0.81) in patients with a mean follow-up of more than 24 months, but no statistical differences were found in patients with the follow-up <24 months (SSE: RR = 1.10, 95%CI: 0.92–1.32; major bleeding: RR = 0.91, 95%CI: 0.42–2.01).

Publication Bias

As shown in **Supplementary Figures 3, 4**, no obvious publication biases were observed when assessed by using the funnel plots. Also, it was noted that the publication bias should not be evaluated when the included studies of the outcome were fewer than 10.

DISCUSSION

Our systematic analysis among patients with AF and BPHV indicated the following results: (1) In comparison with VKAs, DOACs were non-inferior regarding the outcomes of SSE, ischemic stroke, all-cause death and cardiovascular death. (2) As a class, DOACs were connected with decreased risk of

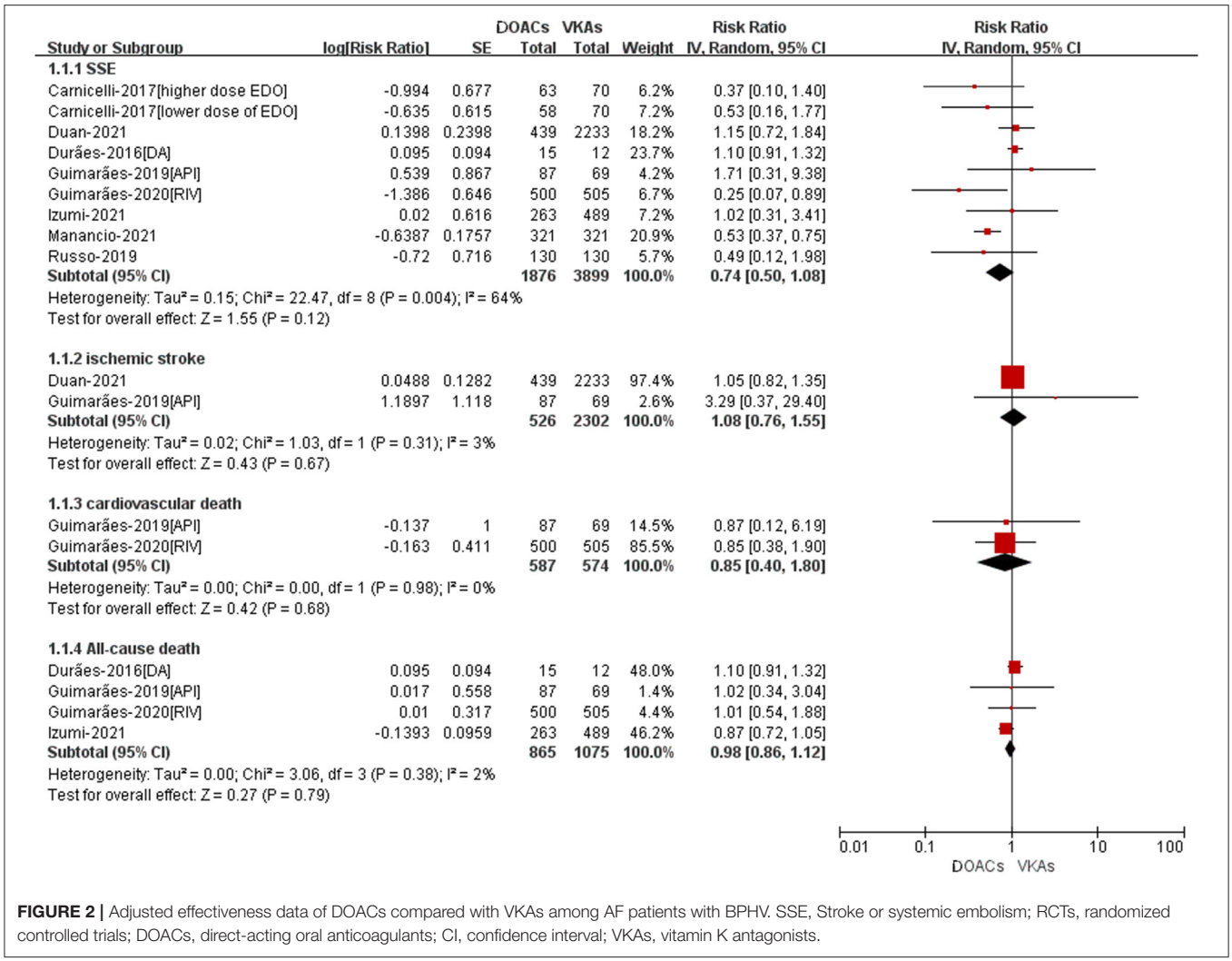

FIGURE 2 | Adjusted effectiveness data of DOACs compared with VKAs among AF patients with BPHV. SSE, Stroke or systemic embolism; RCTs, randomized controlled trials; DOACs, direct-acting oral anticoagulants; CI, confidence interval; VKAs, vitamin K antagonists.

major bleeding and intracranial bleeding as compared with VKAs. (3) DOACs were non-inferior regarding the outcomes of gastrointestinal bleeding and any bleeding.

Considering that AF patients with BPHV require long-term anticoagulation and this patient population has grown by leaps and bounds (26), finding the optimal anticoagulant treatment is critical. On the one hand, an increasing number of elderly patients undergoing BVR are affected by high cardiovascular risk factors such as hypertension, diabetes, and stroke history. They are not only susceptible to thromboembolism events, but also to bleeding events during anticoagulation therapy. On the other hand, patients with AF have an inherent risk of thromboembolic disease, which is further complicated when AF is accompanied by with BPHV (27). It has been reported that the leaflet surface is prone to microthrombi and the fabric of the sewing ring remains exposed without neointimal coverage in the 3 weeks after BVR (28, 29), all of which contribute to the higher incidence of thrombosis.

VKAs have been widely used to prevent SSE in large populations and exert an effective influence on thromboembolism, but they have a narrow therapeutic range that requires close monitoring and dose or diet adjustments in clinical practice. By the way, DOACs are still more effective and safer than VKAs in AF patients during the optimal time period in the therapeutic range. Up to date, questions remain about the most effective treatment for AF patients with BPHV. In the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF–TIMI 48) trial (14), a subgroup analysis of 131 patients with bioprosthetic mitral valves demonstrated a significantly lower rate of major bleeding in patients recieving lower-dose (30 mg) edoxaban, compared with the warfarin group. Likewise, several observational studies have reported that the use of DOACs in AF patients with BPHV appearsto be safe and effective in the treatment of thromboembolic events (30, 31). Growing evidence suggeststhat DOACs may represent a valid therapy for AF patients with BPHV. However, the current RCT conducted by Guimarães et.al stated that rivaroxaban was non-inferior to warfarin for the mean time until the occurrence of death, major cardiovascular events, or

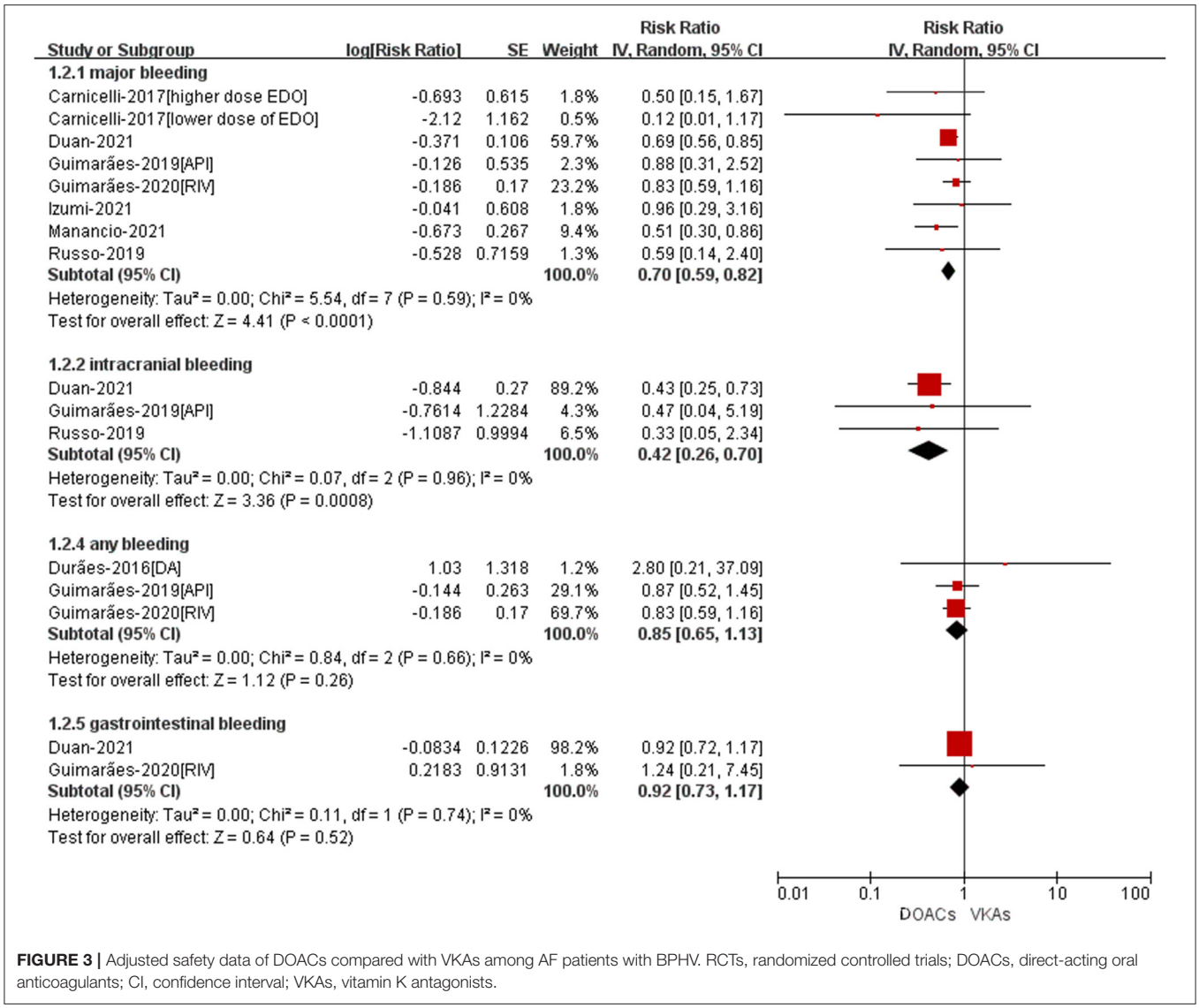

FIGURE 3 | Adjusted safety data of DOACs compared with VKAs among AF patients with BPHV. RCTs, randomized controlled trials; DOACs, direct-acting oral anticoagulants; CI, confidence interval; VKAs, vitamin K antagonists.

major bleeding at 12 months (17). Prior trials have shown that rivaroxaban was not inferior to warfarin for the prevention of SSE in ROCKET AF (32). The ARISTORLE trial also showed no significant differences between apixaban and warfarin for major bleeding or SSE for patients with BPHV and AF (15). Therefore, the large uncertainty of thromboembolic risk, concerns about bleeding complications as well as the paucity of evidence-based data limited the use of DOACs in AF patients with BPHV.

Recently, the effectiveness and safety of DOACs compared with VKAs in AF patients with BPHV have been explored in several studies (33–37) as shown in **Supplementary Table 5**. A prior systematic review by Kheiri et. al supported that SSE, mortality, and safety profiles of DOACs in AF patients with BPHV appeared to be similar to those in warfarin treatment (35). Cardoso et al. also performed a meta-analysis by including 2 *post-hoc* analyses of RCTs and two RCTs, suggesting that DOACs were associated with a reduced incidence of SSE and major bleeding as compared with warfarin in AF patients with BPHV (34). In addition to RCTs, the meta-analyses by Adhikari et al., Lacy et al., and Yokoyama et al. included a different number of observational studies (33, 36, 37). To our knowledge, this study is the largest to assess evidence in separate meta-analyses of RCTs ($n = 4$) and observational studies ($n = 7$) for DOACs compared with VKAs in AF patients with BPHV.

Our findings were largely consistent with the previous meta-analyses of RCTs and the recent meta-analyses, including a small number of observational studies. In addition, our screening criteria for patients undergoing BVR were more stringent, including only traditional biological valves. Notably, it is discovered that the results from the RCTs using DOACs for AF patients with BPHV did not find a decreased risk of major bleeding compared with VKAs as seen in the

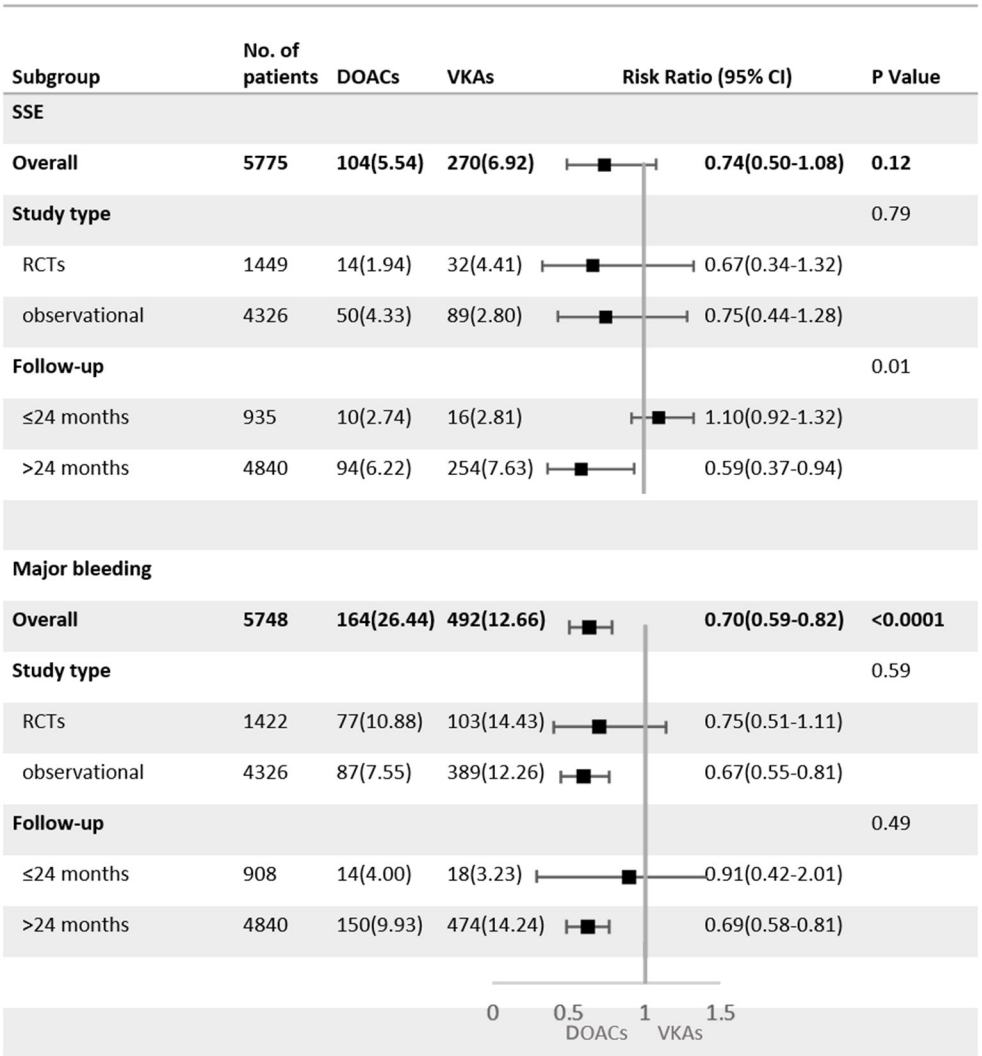

FIGURE 4 | Subgroup analysis of adjusted efficacy and safety data of DOACs compared with VKAs among AF patients with BPHV. SSE, Stroke or systemic embolism; RCTs, randomized controlled trials; DOACs, direct-acting oral anticoagulants; CI, confidence interval; VKAs, vitamin K antagonists.

observational studies. Possible explanations include different follow-up durations, diverse definitions of outcomes, different assessment tools, the interaction between former treatment and DOACs (e.g., catheter ablation), and other unmeasured confounders. For instance, the definition of major bleeding varied across the observational studies and the CHA2DS2-VASc was not adopted in all of the observational studies ($n = 5$) for predicting the risk of stroke, which may disturb the population-based risk stratification and thus lead to inconsistency. An interesting thing that we analyzed in the subgroup analysis was that the DOACs had lower risks of SSE and major bleeding in patients with a mean follow-up of more than 24 months, which may promote the long-term use of DOACs in AF patients with BPHV.

Meanwhile, although the observational studies in our meta-analyses represented a wider range of age, CHA2DS2-VASc score, and follow-up duration than the RCTs, the overall results showed that the DOACs are comparable or superior to VKAs in terms of effectiveness and safety, providing evidence for the use of DOACs in a broader patient population than RCTs. In addition, we assessed crude event rates and adjusted data of outcomes between DOACs vs. VKAs in AF patients with BPHV. Above all, in comparison to VKAs, DOACs appeared to significantly reduce major bleeding and intracranial bleeding but showed comparable rates of SSE, ischemic stroke, all-cause death, cardiovascular death, gastrointestinal bleeding, and any bleeding.

Limitations of Study

Shortcomings still exist in our meta-analysis. A significant limitation of our study was the lack of trials with head-to-head comparisons between different DOACagents and all the comparisons made between them were indirect. Second, although we have demonstrated that DOACs reduced the incidence of major bleeding and intracranial bleeding and performed similarly in other outcomes in patients with AF and BPHV, the credibility of the research is still poor as we included seven observational studies and two subgroup analyses of RCTs. Third, it should have been more specific about the accurate adjustment of DOACdose and the position of the bioprosthetic valve, so well-adjusted and robust population-based data are pursued further clinical application.

CONCLUSION

Available data suggested that DOACs appear to reduce the risks of major bleeding and intracranial bleeding without raising the risk of SSE compared with VKAs among patients with AF and BPHV.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

FUNDING

The Clinical Research Center Project of Department of Science & Technology of Guizhou Province [grant no. (2017) 5405].

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.899906/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Cardiovascular Medicine

SYSTEMATIC REVIEW
published: 24 June 2022
doi: 10.3389/fcvm.2022.907197

Effectiveness and Safety of DOACs vs. Warfarin in Patients With Atrial Fibrillation and Frailty: A Systematic Review and Meta-Analysis

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Background: Patients with atrial fibrillation (AF) and frailty are a considerable group in clinical practice. However, existing studies provide insufficient evidence of anticoagulation strategies for these patients. Therefore, we conducted a meta-analysis to determine the effectiveness and safety outcomes of direct oral anticoagulants (DOACs) for these patients.

Methods: Randomized controlled trials or observational studies reporting the data about the DOACs and warfarin therapy among frail AF patients were included. The search was performed in the PubMed and Embase databases up to March 2022. Frailty was defined using the most widely used claims-based frailty index or the cumulative deficit model-based frailty index.

Results: A total of 4 studies involving 835,520 patients were included. Compared with warfarin, DOACs therapy reduced the risks of stroke or systemic embolism (HR = 0.79, 95%CI: 0.69–0.90), ischemic stroke (HR = 0.79, 95%CI: 0.71–0.87), hemorrhagic stroke (HR = 0.52, 95%CI: 0.35–0.76), and all-cause death (HR = 0.90, 95%CI: 0.84–0.96). In safety outcomes, DOACs was significantly associated with reduced risks of major bleeding (HR = 0.79, 95%CI: 0.64–0.97) and intracranial hemorrhage (HR = 0.58, 95%CI: 0.52–0.65) compared to warfarin, but there were no statistically differences in gastrointestinal bleeding (HR = 0.97, 95%CI: 0.73–1.29).

Conclusions: DOACs exerted superior effectiveness and safety outcome than warfarin in AF patients with frailty.

Keywords: atrial fibrillation, frailty, anticoagulation, prognosis, meta-analysis

OPEN ACCESS

Edited by:
Roberto Pola,
Università Cattolica del Sacro Cuore, Italy

Reviewed by:
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University of Padua, Italy
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Specialty section:
This article was submitted to Thrombosis, a section of the journal Frontiers in Cardiovascular Medicine

Received: *29 March 2022*
Accepted: *31 May 2022*
Published: *24 June 2022*

Citation:
Zeng S, Zheng Y, Jiang J, Ma J, Zhu W and Cai X (2022) Effectiveness and Safety of DOACs vs. Warfarin in Patients With Atrial Fibrillation and Frailty: A Systematic Review and Meta-Analysis. Front. Cardiovasc. Med. 9:907197. doi: 10.3389/fcvm.2022.907197

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia among adults affecting millions of people worldwide (1). Due to the disorganization of atrial contraction, the blood flow in AF patients is pooling and stasis, leading to a significant increase in the risk of thromboembolic events (2). Frailty is a multisystem clinical syndrome characterized by decreased physiological reserve and diminished stress capacity. The deterioration of multiple physiological systems complicates medical treatment and rehabilitation, leading to poor health outcomes (3–5). Recent investigations have demonstrated that the prevalence of AF and frailty increases with age and often occurs simultaneously (6). AF patients with frailty face difficulties in clinical treatment because of their multiple comorbidities and medications.

Although frailty is associated with increased stroke and mortality in patients with AF, there is evidence of a risk-treatment paradox, whereby frail patients with a higher risk of complications from AF are less likely to use oral anticoagulants (OACs) than non-frail patients (7, 8). Existing studies confirm that most frail AF patients should receive OACs to reduce stroke or systemic embolism (SSE) risk because the benefit outweighs the risk of bleeding (9). Clinical use of specific OACs may be based on age and/or comorbidity patterns (often in association with weight, renal function, and history of bleeding) (10). However, chronological age is an outdated concept compared to biological or functional age. In this new definition, frailty plays an indispensable role that cannot be ignored and is increasingly being used to guide the care of older adults (11). As the first-line choice for non-valvular AF patients, direct oral anticoagulants (DOACs) consist of direct thrombin (FIIa) inhibitors or direct factor Xa (FXa) inhibitors, including dabigatran, apixaban, rivaroxaban, edoxaban. Previous studies have shown that DOACs are safe and effective in patients with AF (12–16), including old patients with non-valvular atrial fibrillation (NVAF) (17). Compared with warfarin, the advantages of DOACs included a wider therapeutic window, rapid onset of action, stable and predictable anticoagulation effects, and limited drug interactions. So, it may be a better anticoagulant choice for frailty patients. Due to the poor representation of frail adults and the lack of frailty assessment in clinical trials (18), there is still no consensus on the choice of anticoagulants in frail AF patients. It is uncertain whether DOACs have an advantage over warfarin.

To fill this gap, we conducted a systematic review and meta-analysis to better understand the effectiveness and safety of DOACs in AF patients with frailty, as an increasing number of updated studies have been published.

METHODS

We conducted this meta-analysis based on the criteria of the Cochrane Handbook for Systematic Reviews of Interventions (version 6.2). The results were presented according to the preferred reporting items for systematic review and meta-analysis (PRISMA) 2020 statement. Ethical approval was not required, as this study only included articles of published data in the public domain.

Literature Search

Two reviewers performed the literature search, systematically searching the PubMed and Embase database sources until March 2022 for studies exploring the effectiveness and safety of DOACs compared with Warfarin in AF patients with frailty. The following search terms were used: (1) "atrial fibrillation," (2) "dabigatran" OR "rivaroxaban" OR "apixaban" OR "edoxaban" OR "non-vitamin K antagonist oral anticoagulant" OR "direct oral anticoagulant" OR "novel oral anticoagulant" OR "NOAC" OR "DOAC", (3) "frail" OR "frailty" OR "frailness" OR "Frailty Syndrome," (4) "Vitamin K antagonists" OR "VKA" OR "warfarin" OR "dicoumarol" OR "acenocoumarol" OR "Coumadin," The above four categories of search terms were combined using the Boolean operator "and." The detailed search strategies are shown in **Supplementary Table 1**. In addition, the reference lists of the retrieved articles and prior reviews were manually checked for additional eligible studies. We applied no linguistic restrictions in the literature search.

Inclusion and Exclusion Criteria

Criteria for inclusion were as follows: (1) The study was a randomized controlled trial (RCT), *post-hoc* analyses of RCT or observational (prospective or retrospective cohort) study; (2) The study included AF patients with frailty who received warfarin or DOACs (dabigatran, rivaroxaban, apixaban, or edoxaban); (3) Quantitative estimates of the hazard ratios (HRs) and 95% confidence intervals (CIs) reporting for safety and effectiveness outcomes among patients. Additionally, articles using claims-based frailty index or cumulative deficit model-based frailty index were included. Where frailty status was dichotomized, the threshold used by the study author was used.

We excluded studies focusing on AF patients without a clear systemic definition of frailty. Studies without adjustment or with a sample size of < 100 were excluded. In addition, we also excluded certain publication types (e.g., reviews, comments, case reports, case series, letters, editorials, and meeting abstracts) due to insufficient data or study details. If there were overlapping data among two or more studies, we included the one with the largest sample size or the longest follow-up duration.

Study Selection and Data Abstraction

Two reviewers independently screened the titles and abstracts of the retrieved studies from the electronic databases. Subsequently, we selected the eligible studies after the full-text screenings based on the pre-defined inclusion criteria. Disagreements were resolved by discussion between two reviewers or consultation with the corresponding authors. The following data of the included studies were abstracted: study characteristics (first author, year of publication, study design), study population, and baseline characteristics (age, male ratio, sample size, stroke and bleeding risk prediction scores, drugs in the DOACs group, definition of frailty, history of stroke and bleeding), effectiveness and safety outcomes, follow-up period, and outcome data

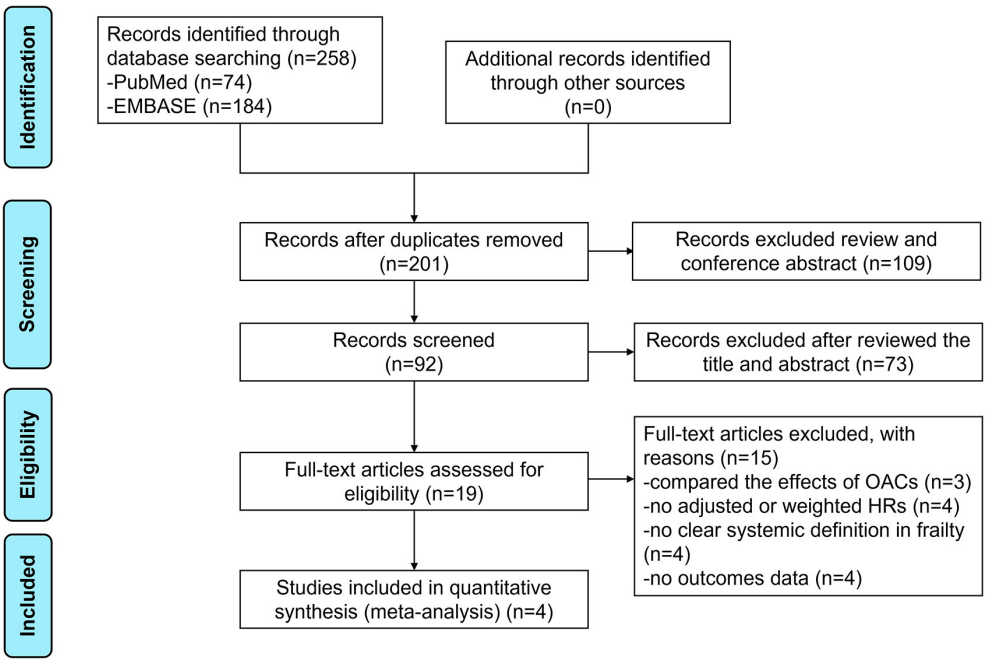

FIGURE 1 | The flow chart of literature retrieval of this meta-analysis.

(sample size and the number of events between groups, adjusted HRs).

Study Quality Assessment

We assessed the quality of *post-hoc* analysis of RCTs or observational cohorts by using the Newcastle-Ottawa Scale (NOS) tool. This tool had three domains with a total of nine points: the selection of cohorts (0–4 points), the comparability of cohorts (0–2 points), and the assessment of the outcome (0–3 points). In this meta-analysis, the NOS of $\geq$6 and $<$6 points were moderate-to-high quality and low-quality, respectively (19).

Statistical Analysis

This meta-analysis's statistical analyses were conducted using the Review Manager version 5.4 software (the Cochrane Collaboration 2014, Nordic Cochrane Center Copenhagen, Denmark; https://community.cochrane.org/). In this study, significant heterogeneity was indicated by a *P*-value of $<$0.10 in the Cochrane Q test or an I^2 value of $>$ 50%, which led to the use of random-effects models and the exploration of a potential source of heterogeneity. When these tests were negative for heterogeneity, fixed-effects models were chosen to calculate pooled HRs through the inverse-variance method. In the pooled analysis, the adjusted HRs and 95% CIs were converted to the natural logarithms [Ln [HR]] and their corresponding standard errors [Ln [upper CI]-Ln [lower CI]/3.92], which were pooled by a DerSimonian and Laird random-effects model with an inverse variance method.

RESULTS

Study Selection

The flow chart of literature retrieval is presented in **Figure 1**. Through searching the electronic searches in the PubMed and EMBASE databases, our initial search yielded 258 articles. After the records screening, we selected 92 relevant articles. By reviewing the abstract, 19 remaining studies were potentially available, and further assessed under the full-text screenings. According to the pre-defined inclusion and exclusion criteria, we subsequently excluded 15 studies because (1) studies compared the effects of OACs ($n = 3$); (2) studies did not report adjusted or weighted HRs ($n = 4$); (3) studies did not report a clear systemic definition in frailty ($n = 4$); (4) studies did not report the studied outcomes ($n = 4$). Finally, a total of 4 studies (1 *post-hoc* analyses of RCTs and 3 observational studies) were included in our meta-analysis (20–23).

Baseline Characteristics

Baseline characteristics of the included studies are illustrated in **Table 1**. Among the included studies, 3 were from the United States of America, and 1 from multiple countries (America, Europe, Asia–Pacific region, and South Africa). The mean age of patients ranged from 77.3 to 86.0 years, and the sample size was from 10,754 to 653,421. Three of the included articles used a claims-based frailty index and one article used a cumulative deficit model-based frailty index. Across studies, the study populations in the DOACs group were administrated with dabigatran, apixaban, rivaroxaban, and edoxaban. Risk of bias evaluation was performed, shown in

TABLE 1 | Baseline characteristics of the included studies in this meta-analysis.

Group	Martinez et al. (22)			Kim et al. (20)			Lip et al. (21)			Wilkinson et al. (23)	
	API/ Warfarin	DA/ Warfarin	RIV/ Warfarin	API/ Warfarin	DA/ Warfarin	RIV/ Warfarin	API/ Warfarin	DA/ Warfarin	RIV/ Warfarin	EDO (30 mg)/ Warfarin	EDO (60 mg)/ Warfarin
Participants (N)	1,392/ 1,392	1,350/ 1,350	2,635/ 2,635	109,369/ 109,369	79,365/ 79,365	137,972/ 137,972	34,594/ 34,594	9,263/ 9,263	39,898/ 39,898	5,483/ 5,478	5,447/ 5,478
Study design	Observational Study			Observational Study			Observational Study			*Post-hoc* analysis of ENGAGE AF-TIMI48	
Region	America			America			America			Multi-center (America, Europe, Asia–Pacific region, and South Africa)	
Age (mean, y)	86.0/86.0 (median)	85.0/86.0 (median)	85.0/86.0 (median)	77.3/77.3	76.4/76.4	76.8/76.8	84.2/84.2	83.3/83.4	83.7/83.7	NA	NA
Male ratio (%)	63.7/62.8	64.7/62.7	65.2/64.4	49.6/49.4	50.1/50.1	50.1/50.1	35.0/35.2	35.3/35.5	35.6/35.5	60.5/60.7	60.5/60.7
HAS-BLED	2.0/2.0	2.0/2.0	2.0/2.0	2.1/2.1	2.0/2.0	2.1/2.1	3.7/3.7	3.6/3.6	3.7/3.6	NA	NA
CHA2DS2-VASc	4.0/4.0	4.0/4.0	4.0/4.0	4.2/4.2	4.1/4.1	4.1/4.1	5.1/5.1	5.1/5.1	5.1/5.1	NA	NA
Stroke history	18.2/18.0	15.2/16.8	15.0/15.7	5.5/5.6 (inpatient)	4.6/4.6 (inpatient)	4.7/4.8 (inpatient)	22.3/22.2	21.4/22.3	21.8/22.0	NA	NA
Bleeding history	3.4/3.1	1.3/1.4	2.7/2.4	2.5/2.6 (inpatient)	1.5/1.5 (inpatient)	2.0/2.0 (inpatient)	25.7/25.9	24.5/25.2	26.0/26.3	NA	NA
Follow-up	2 years			84 days	72 days	82 days	183 days/ 233 days	226 days/ 235 days	220 days/ 234 days	2.8 years	
Definition of frailty	CFI $\geq$ 0.20			CFI $\geq$ 0.15			CFI $\geq$ 0.20			FI $\geq$ 0.12	

DA, dabigatran; RIV, rivaroxaban; API, apixaban; EDO, edoxaban; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol; CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 y (doubled), diabetes mellitus, stroke (doubled)-vascular disease, age 65–74 and sex category (female); CFI, claims-based frailty index; FI, frailty index.

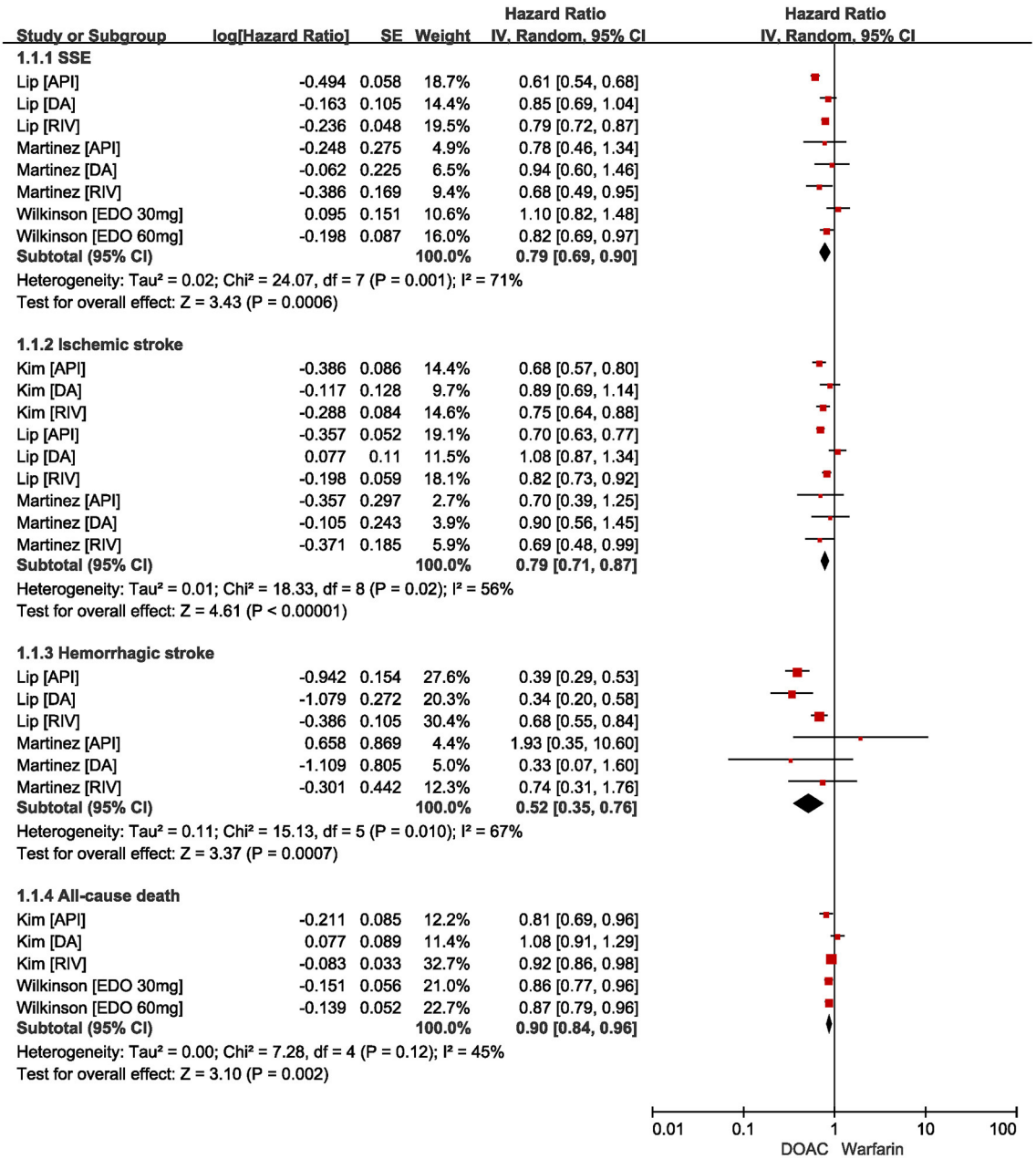

FIGURE 2 | Comparing effectiveness of DOACs with warfarin in AF patients with frailty. AF, atrial fibrillation; SSE, stroke and systemic embolism; DOACs, direct oral anticoagulants; CI, confidence interval; IV, inverse of the variance; SE, standard error.

Supplementary Table 2. All the studies had a NOS of ≥6 points suggesting moderate-to-high quality.

SYNTHESIS OF RESULTS

Outcomes Between DOACs vs. Warfarin in Frail AF Patients

As shown in **Figure 2**, our pooled results based on the random-effects model showed that compared with warfarin, the use of DOACs was significantly associated with reduced risks of effectiveness outcomes, including SSE (HR = 0.79, 95%CI: 0.69–0.90), ischemic stroke (HR=0.79, 95%CI: 0.71–0.87), hemorrhagic stroke (HR = 0.52, 95%CI: 0.35–0.76), and all-cause death (HR = 0.90, 95%CI: 0.84–0.96).

The safety outcomes are shown in **Figure 3**. Compared with warfarin users, DOACs were significantly associated with reduced risks of major bleeding (HR = 0.79, 95%CI: 0.64–0.97) and intracranial hemorrhage (HR = 0.58, 95%CI: 0.52–0.65). There were no statistical differences in

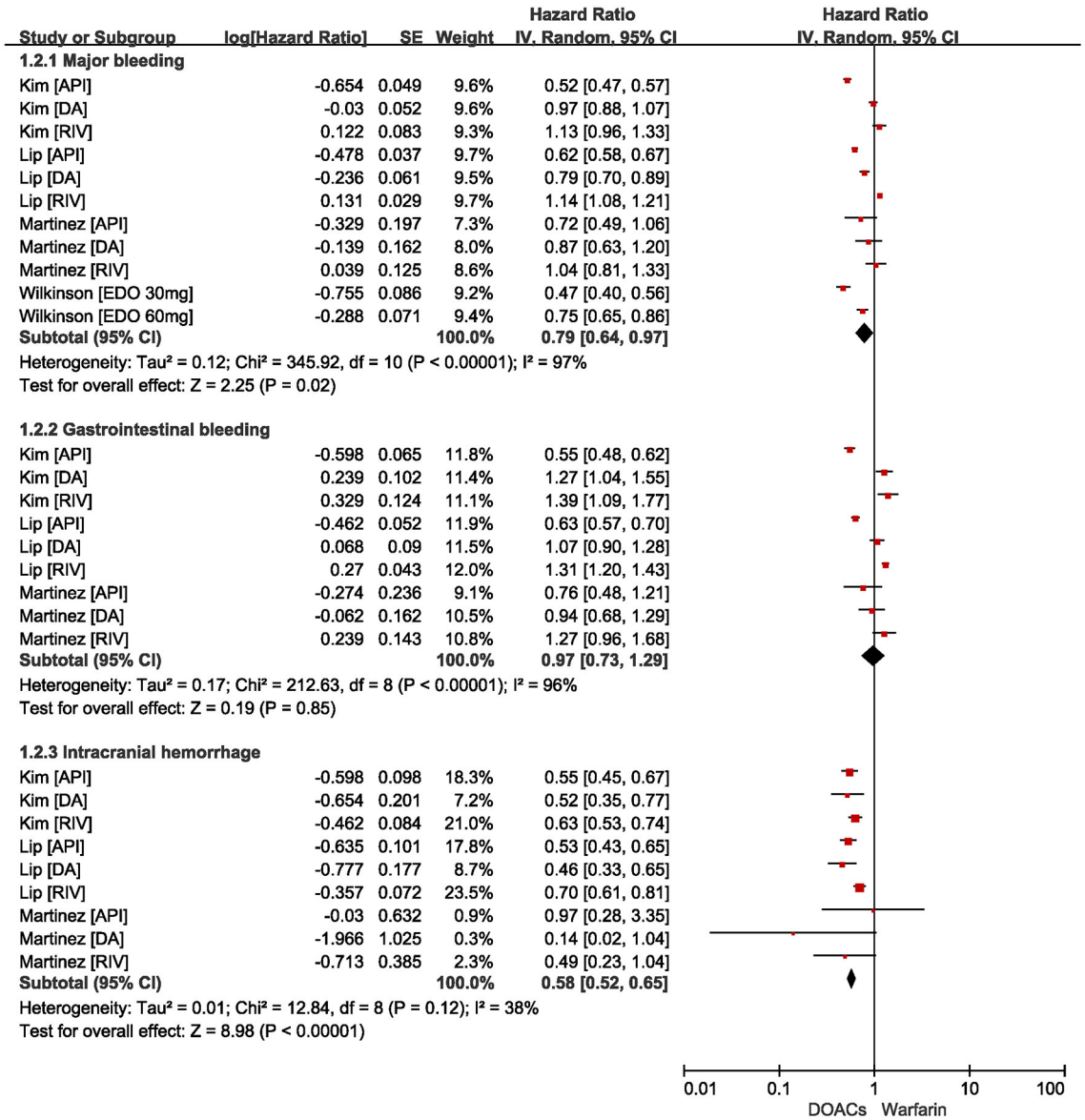

FIGURE 3 | Comparing safety of DOACs with warfarin in AF patients with frailty. AF, atrial fibrillation; DOACs, direct oral anticoagulants; CI, confidence interval; IV, inverse of the variance; SE, standard error.

gastrointestinal bleeding (HR = 0.97, 95%CI: 0.73–1.29) between patients treated with DOACs compared to patients treated with warfarin.

DISCUSSION

The main findings of our meta-analysis can be summarized as follows: (1) DOACs were associated with lower risks of SSE, ischemic stroke, hemorrhagic stroke, and all-cause death compared with warfarin. (2) In safety outcomes, DOACs therapy was associated with a significant reduction in major bleeding and intracranial hemorrhage but with no significant difference in the risk of gastrointestinal bleeding compared with warfarin.

Patients with AF and frailty have reduced physiological reserve and stress capacity, resulting in a substantially increased risk of thrombotic events, bleeding, and death than non-frail AF patients, making their management challenging. Frailty status was positively correlated with CHA2DS2-VASc and HAS-BLED scores, suggesting that frail patients may more urgently need OAC treatment to prevent stroke. Still, anticoagulant use often comes at the expense of a potential risk of bleeding (24). Balancing the benefits and risks of anticoagulation in such patients is a significant challenge for clinicians. Available studies confirmed that most frail patients, whether formally assessed or not, should receive OAC because the benefit outweighs the absolute risk of bleeding (25). However, guidelines do not give clear recommendations on the dosage and specific types of

OAC to prescribe, and there is a paucity of relevant studies on frail patients.

Current AF guidelines recommend the use of DOACs as first-line drugs for stroke prevention based on four published remark DOAC trials. This means that the advantages of DOACs over warfarin in the general population have been well-proved. However, the anticoagulation strategies for stroke prevention in AF patients with co-morbidities (e.g., frailty, anemia, cancer) are incomplete, and further studies should confirm the advantages of DOACs in these special populations. In our meta-analysis, we synthesize evidence on treatment strategies in frail AF patients and provide some insights into the advantages of DOACs over warfarin. Due to the poor representation of frail patients and the lack of assessment of frailty, there were no relevant RCTs, so our meta-analysis selected relatively high-quality retrospective studies that covered a larger number of frail AF populations. There was considerable heterogeneity in the pooled estimates, and the heterogeneity of outcomes was not reduced by excluding one study at a time, indicating that the results were stable. Many reasons contribute to differences among studies, such as different thresholds for defining frail status, insufficient follow-up time, possible misclassification and selection bias in claims database-based studies, and exclusion of severely frail patients.

Perera et al. have shown that in geriatric medicine, general medicine, and cardiology services, frail AF patients were significantly less likely to use warfarin upon hospital admission and discharge than non-frail patients and appeared more vulnerable to adverse clinical outcomes, with and without antithrombotic therapy (8). In the meantime, high rates of morbidity and polypharmacy and the risk of falls are often common reasons for not using oral anticoagulants (OACs) in these patients (26). However, our study shows that DOACs are more effective and safer than conventional VKA-warfarin. This evidence will provide clinicians with firm support for anticoagulation in patients with AF and frailty, making it a promising candidate for the first choice of antithrombotic drugs in this population. We know that DOACs are directed against a single active coagulation factor. Its anticoagulant effect is independent of antithrombin, its pharmacokinetics are stable, and there are few interactions with food and drugs (27). This feature may make it more suitable for patients with AF and frailty who have deteriorated multiple physiological systems and require multiple medications. Because frail older patients are prone to decrease renal function, dabigatran has the highest renal clearance, which may lead to higher plasma concentrations of the drug, thereby increasing the risk of bleeding. In contrast, apixaban, which has lower renal clearance, appears to be safer. However, due to the absence of head-to-head clinical trials between DOCAs, our article cannot prove which DOACs are more effective and safer. Future research will help to provide robust evidence for this issue.

An interesting finding is that the studies we included reported the effects of different doses of DOACs. Research by Lip et al. showed that there was no statistically significant difference in the incidence of the primary effectiveness and safety outcome between patients taking standard-dose DOACs and the reduced-dose compared with warfarin (21). In contrast, Okumura et al. demonstrated in a randomized clinical trial that, in old Japanese patients (≥80 years of age) with NVAF, a once-daily 15-mg dose of edoxaban significantly reduced the risk of SSE and did not result in a significantly higher incidence of major bleeding (28). Subjects in this trial have the poor renal function, low body weight, a history of severe bleeding, ongoing use of non-steroidal anti-inflammatory drugs (NSAIDs), or current use of antiplatelet drugs, all of which present a dilemma for oral anticoagulation in these patients (29). However, edoxaban 15-mg daily provided them with strong oral anticoagulation support. It is reassuring that more and more research is beginning to focus on oral anticoagulation in old frail patients, further research will help to provide robust evidence for this issue.

LIMITATION

Our study had several limitations. First, we included a limited number of observational studies, reducing the reliability of our findings. Second, the thresholds for defining frail status differed in each study, and subjects with different baseline characteristics may have significant bias despite statistical adjustments. At the same time, since most of the studies were based on claims databases, misclassification and selection bias may be responsible for the high heterogeneity of outcomes. Third, the different definitions of frailty cannot perform a detailed comparative analysis. Due to the small number of included studies, we were also unable to obtain sufficient data to perform a subgroup analysis of the results with high heterogeneity.

CONCLUSION

In conclusion, for patients with AF and frailty, DOACs exerted superior effectiveness and safety outcome than warfarin in reducing the risk of SSE, ischemic stroke, hemorrhagic stroke, all-cause death, major bleeding, and intracranial hemorrhage. Still, there is no difference in gastrointestinal bleeding.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

FUNDING

This study was funded by National Natural Science Foundation of China (21866019).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.907197/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 08 September 2022
DOI 10.3389/fcvm.2022.944687

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Thrombosis,
a section of the journal
Frontiers in Cardiovascular Medicine

RECEIVED 15 May 2022
ACCEPTED 03 August 2022
PUBLISHED 08 September 2022

CITATION
Li C, Lau W, Qian N, Song L, Jin C, Zhou D, Yu Y, Pan X and Zhou Q (2022) Clinical characteristics and prognosis of patients with left ventricular thrombus in East China.
Front. Cardiovasc. Med. 9:944687.
doi: 10.3389/fcvm.2022.944687

Clinical characteristics and prognosis of patients with left ventricular thrombus in East China

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Background: Left ventricular thrombus (LVT) is a serious complication in patients with left ventricular dysfunction. However, there is still a paucity of data on treatments and prognosis of patients with LVT. This study aims to evaluate the clinical characteristics of patients with LVT and to determine the impact of LVT on the incidence of major adverse cardiovascular events (MACEs) and all-cause mortality.

Methods: From January 2010 to January 2020, 237 patients diagnosed with LVT at The Second Affiliated Hospital Zhejiang University School of Medicine in East China were retrospectively included. Clinical characteristics, treatments, MACEs, and bleeding events [thrombolysis in myocardial infarction (TIMI) I and II] were collected. MACE is determined as the composite of all-cause mortality, ischemic stroke, acute myocardial infarction (MI), and acute peripheral artery emboli.

Results: The all-cause mortality rate was 28.3% (89.6% due to cardiovascular death), ischemic stroke 8.4%, MI 3%, peripheral artery emboli 1.7%, and bleeding events (TIMI I and II) 7.6% were found during a median follow-up of 736 days. Total LVT regression occurred in 152 patients (64.1%). Atrial fibrillation [hazard ratio (HR), 3.049; 95% confidence interval (95% CI) 1.264–7.355; $p = 0.013$], moderate and severe renal function injuries (HR, 2.097; 95% CI, 1.027–4.281; $p = 0.042$), and left ventricular ejection fraction (LVEF) $\leq$ 50% (HR, 2.243; 95% CI 1.090–4.615; $p = 0.028$) were independent risk factors for MACE, whereas the use of β-blocker (HR, 0.397; 95% CI 0.210–0.753; $p = 0.005$) was its protective factor. Age (HR, 1.021; 95% CI 1.002–1.040; $p = 0.031$), previous caronary artery bypass grafting (CABG; HR, 4.634; 95% CI 2.042–10.517; $p < 0.001$), LVEF $\leq$ 50% (HR, 3.714; 95% CI 1.664–8.290; $p = 0.001$), and large thrombus area (HR, 1.071; 95% CI 1.019–1.126; $p = 0.007$) were independent risk factors for increasing all-cause mortality, whereas the use of β-blocker (HR, 0.410; 95% CI 0.237–0.708; $p = 0.001$) was protective factor.

Conclusion: This study showed that atrial fibrillation, moderate and severe renal dysfunction, and LVEF $\leq$ 50% were independent risk factors for MACE; age, previous CABG, LVEF $\leq$ 50%, and large thrombus area were independent risk factors for all-cause mortality. It was found that the use of β-blockers could improve the prognosis of patient with LVT for the first time. It is recommended that clinicians could be more active in applying patient with LVT with anticoagulants.

KEYWORDS

left ventricular thrombus, clinical characteristics, treatment, prognosis, MACE, bleeding

Introduction

Left ventricular thrombus (LVT) is a serious complication in patients with left ventricular dysfunction and is associated with poor outcomes. Despite adequate interventional and medical therapy, LVT remains to be an important source of cerebral and peripheral arterial embolism with a subsequent increased mortality (1, 2). Heart diseases, such as acute myocardial infarction (MI), cardiomyopathy, valvular heart disease, myocarditis, and myocardial insufficiency, are common causes of LVT. According to a single-center retrospective study from May 2003 to November 2011, the population incidence rate of LVT was 0.72‰. Coronary heart disease is the main cause (80.6%). Other causes of LVT include dilated cardiomyopathy (DCM) 8.1%, hypertrophic cardiomyopathy 3.2%, stress cardiomyopathy 4.8%, aortic valve stenosis 1.6%, and Brugada syndrome 1.6% (3). To date, clinical features, treatments, and the prognosis of acute MI-related LVT have been well studied, but the follow-up time was relatively short. Besides that, the prognosis of other disease-related LVT, such as cardiomyopathy, valvular disease, and myocarditis, is still rarely reported, nationally and internationally. In this study, we retrospectively analyzed the clinical characteristics, treatments, and the prognosis of LVT from a comprehensive spectrum of diseases during a 1- to 10-year follow-up from The Second Affiliated Hospital Zhejiang University School of Medicine (SAHZU) in East China, which will provide more clinical evidence on the management of LVT.

Materials and methods

Research design and population

Between January 2010 and January 2020, 542,844 echo studies were screened from the echocardiography reporting system of the SAHZU. All patients with a reported LVT confirmed by 2 independent experts, regardless of the underlying disease, were included. One patient with right ventricular thrombus, 3 patients with atrial thrombus, and 9 patients lost to follow-up were excluded. All the included patients were followed up by phone call or at the outpatient clinic. This study has been approved by the Ethics Committee of SAHZU. The patients' informed consent were exempted due to the nature of the study.

Thrombus evaluation

Echocardiography analyses were performed for this study by an independent cardiologist in accordance with the published guidelines. Contrast transthoracic echocardiography (TTE) was performed to confirm the diagnosis of LVT if the initial TTE was inconclusive. To be distinguishable from the underlying myocardium, a clear thrombus–blood interface was required and the LVT had to be visible on at least 2 orthogonal views. The number, size (the largest two-dimensional area available on the index echocardiogram), location, and echogenicity of each thrombus were evaluated. All thrombus data were evaluated using the Philips EPIQ7 Ultrasound System (Philips Ultrasound, Inc.).

Definition of end points

The primary endpoints were major adverse cardiovascular events (MACEs) and all-cause mortality. MACE was defined as all-cause mortality, ischemic stroke, acute MI, and acute peripheral artery emboli (4–6). The secondary end points were ischemic stroke, acute MI, and acute peripheral artery emboli. The primary safety end point were bleeding events defined as any clinically relevant moderate and severe bleeding events according to thrombolysis in myocardial infarction (TIMI)

classification: TIMI I—intracranial hemorrhage or clinically visible hemorrhage (including imaging), with a decrease of hemoglobin concentration ≥ 5 g/dL and TIMI II—clinically visible hemorrhage with decreased hemoglobin concentration by 3–5 g/dL (7). Total LVT regression was defined by a complete disappearance of LVT on all echocardiography views at the last available follow-up (8).

Data collection

We constructed a local database termed LVT database and used uniform standards by training to collect the data on socioeconomic status, previous and current medical histories, laboratory investigations, echocardiography, coronary angiography, and medication of the patients with LVT from the electronic medical record (EMR) system and ultrasonography system. Individual case report form was created to collect outpatient and phone call follow-up data. MACE and bleeding events (TIMI I and II) during the period of observation were recorded.

Statistical analysis

All data were shown as mean ± standard deviation or median (interquartile range) for continuous variables and as the number (%) of patients for categorical variables. In order to identify independent correlates, the variables with a p-value < 0.05 in univariate analysis were entered into multivariate regression analysis using a forward likelihood-ratio method for MACE and all-cause mortality. The number of the other end points is small, resulting in a low incidence, which is not enough for the corresponding regression analysis, and no further analysis was performed. The 95% CI for HR was presented. A two-sided p < 0.05 was considered statistically significant. All statistical analyses were conducted using Statistical Package for the Social Sciences version 25.0 (SPSS Inc., Chicago, IL, United States) (9).

Results

Baseline clinical characteristics

A total of 237 patients diagnosed with LVT were definitively included, 26 patients further received left ventricular contrast TTE for the confirmation of LVT. The mean age was 59.9 ± 15.2 years, 84% were men. The baseline characteristics of patients are described in Table 1. In total, 168 patients (70.9%) had coronary heart disease, 28 patients (11.8%) had atrial fibrillation, 65 patients (27.4%) had heart failure (HF), and 23 patients (9.7%) had a history of stoke. Almost half of the population (48.9%) had a history of anterior wall MI, and 49 patients (20.7%) had a history of DCM.

The detailed baseline echocardiographic parameters are shown in Table 1. In brief, the mean ejection fraction (EF) was 40.05 ± 14.67%, and the median value of the thrombus area was 2.76 (1.76–4.47) cm^2. In total, 27 cases (11.4%) were complicated with more than two thrombi, 31 cases (13.08%) were with mobile thrombi, 157 cases (66.2%) were with moderate and high echogenicity thrombi; 46 (19.4%) thrombi were inside the aneurysm, 219 (92.4%) were located in heart apex (Table 1).

Medication treatments

Most of the study population (82.3%) was treated with anticoagulation therapy, including vitamin K antagonists (VKA) (65.8%; n = 156), direct oral anticoagulants (DOACs) (12.7%; n = 30), and low molecular weight heparin (LMWH) (3.8%; n = 9). Anticoagulation + antiplatelet therapy was prescribed in 49.8% (n = 118) of patients. In total, 42 patients did not take any anticoagulants; of which, 38 cases (90.5%) took 1–2 kinds of antiplatelet drugs and 1 patient with subarachnoid hemorrhage, 1 patient with heart transplantation, and 2 patients refused to take anticoagulants (Table 2).

TABLE 1 Baseline clinical characteristics and transthoracic echocardiography (TTE) findings.

Variable	All patients (n = 237)
Age(years)	59.89 ± 15.55
Male	199 (84%)
BMI (kg/m^2)	23.76 ± 3.74
Smoking	110 (46.4%)
Hypertension	116 (48.9%)
Diabetes	42 (17.7%)
Hyperlipidemia	11 (4.6%)
Stroke	23 (9.7%)
Atrial fibrillation	28 (11.81%)
Coronary heart disease	168 (70.89%)
Previous PCI	133 (56.12%)
Previous CABG	9 (3.80%)
Anterior myocardial infarction	116 (48.9%)
Cardiomyopathy	55 (23.2%)
LA size (cm)	4.15 ± 0.70
LVIDd (cm)	5.70 ± 0.98
LVIDs (cm)	4.47 ± 1.20
LVEF (%)	40.05 ± 14.67
LVEF ≤ 50%	168 (70.89%)
Apex location	219 (92.4%)
Ventricular aneurysm	66 (27.85%)
Thrombus area (cm^2)	2.76 (1.76-4.47)
Number of thrombus>1	27 (11.4%)

BMI, body mass index; PCI, percutaneous coronary intervention; CABG, caronary artery bypass grafting; LA, left atrium; LVIDd, left ventricular end-diastalic diameter; LVIDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction.

TABLE 2 Medication treatment following left ventricular thrombus diagnosis.

Variable	All patients (n = 237)
Antiplatelet therapy only	38 (16%)
Anticoagulation only	77 (32.5%)
Anticoagulation + antiplatelet therapy	118 (49.8%)
Aspirin + anticoagulant	28 (11.8%)
Clopidogrel/ticagrelor + anticoagulant	24 (10.1%)
Aspirin + clopidogrel/ticagrelor + anticoagulant	66 (27.8%)
Anticoagulation type	195 (82.3%)
Warfarin	156 (65.8%)
DOACs	30 (12.7%)
LMWH	9 (3.8%)
RASI	121(51.1%)
Aldosterone antagonist	115 (48.5%)
β-blocker	173 (73%)
Digoxin	46 (19.4%)

DOACs, direct oral anticoagulants; LMWH, low molecular weight heparin; RASI, renin angiotensin inhibitor.

Follow-up results

Outcomes of the thrombus

Among 237 patients with LVT, 182 patients underwent follow-up TTE. Thrombus resolution was achieved in 152 cases (64.1%) with a median time of 57 days from the baseline echocardiography to the final echocardiography, and residual LVT was observed in 30 cases (12.7%). Among 55 patients who did not undergo follow-up TTE, death events were reported in 42 cases.

Outcomes of the events

Within a median follow-up period of 736 days, the rate of MACE occurred in 36.7% (n = 87): all-cause mortality 28.3%, ischemic stroke 8.4%, MI 3%, and peripheral artery emboli 1.7%. Of all-cause mortality, 61 cases (91%) were cardiovascular deaths and 6 patients (9%) died of non-cardiovascular origin, including pneumonia, cancers, bleeding, and multiple injuries. The median duration from diagnosis of LVT to death was 318 days. All emboli complications included 20 cases with stroke, 7 cases with MI, and 4 cases with peripheral artery emboli. Bleeding events of varying degrees occurred in 16.9% (n = 40) patients: TIMI I bleeding 4.2% (n = 10), TIMI II bleeding 3.4% (n = 8), and TIMI III bleeding 9.3% (n = 22) of patients, respectively. Bleeding events included 6 cases of cerebral hemorrhage, 14 cases of the gastrointestinal tract, 2 cases of hemoptysis, 2 cases of the urinary system, 1 case of the abdominal cavity, 2 cases of postoperative wound bleeding, and 17 cases of skin and mucous membranes (4 of them had bleeding in 2 sites). In addition, we also collected the following clinical outcomes during the period of observation: 5 cases had heart transplantation, 1 case underwent ventricular tumor resection, 1 case underwent ventricular aneurysm closure, 2 patients had a new left atrial thrombus, 4 cases had venous emboli, and 20 patients were observed to have recurrent LVT.

Outcomes of statistical analysis

Logistic regression analysis for major adverse cardiovascular event

Univariate analysis showed that coronary heart disease (p = 0.017), atrial fibrillation (p = 0.020), left ventricular end-systolic diameter (LVIDs; p = 0.011), moderate and severe renal function injury (p = 0.009), left ventricular ejection fraction (LVEF) $\leq$ 50% (p = 0.006), and β-blocker use (p = 0.004) were significantly correlated to MACE. These variables were entered in multivariate logistic regression analysis using a forward likelihood-ratio method. Finally, atrial fibrillation (HR, 3.049; 95% CI 1.264–7.355; p = 0.013), moderate and severe renal function injury (HR, 2.097; 95% CI, 1.027–4.281; p = 0.042), and LVEF $\leq$ 50% (HR, 2.243; 95% CI 1.090–4.615; p = 0.028) were independent risk factors for MACE, whereas the use of β-blocker (HR, 0.397; 95% CI 0.210–0.753; p = 0.005) was a protective factor (Table 3).

Cox regression analysis for all-cause mortality

Univariate analysis showed that age (p = 0.018), male (p = 0.035), previous caronary artery bypass grafting (CABG; p = 0.006), previous percutaneous coronary intervention (PCI; p = 0.007), LVIDs (p = 0.001), LVEF $\leq$ 50% (p < 0.001), thrombus area (p = 0.029), and β-blocker use (p = 0.001) were significantly correlated to all-cause mortality. These variables were entered in multivariate cox regression analysis using a forward likelihood-ratio method. Finally, age (HR, 1.021; 95% CI 1.002–1.040; p = 0.031), previous CABG (HR, 4.634; 95% CI, 2.042–10.517; p < 0.001), LVEF $\leq$ 50% (HR, 3.714; 95% CI 1.664–8.290; p = 0.001), and thrombus area (HR, 1.071; 95%CI, 1.019–1.126; p = 0.007) were independent risk factors for all-cause mortality, whereas the use of β-blocker (HR, 0.410; 95% CI 0.237–0.708; p = 0.001) was a protective factor (Table 4 and Figure 1).

Discussion

Clinical characteristics

Despite adequate interventional and medical therapy, the incidence of LVT is still high in both ischemic and non-ischemic cardiomyopathies currently. LVT remains to be an

TABLE 3 Logistic regression analysis for the association between major adverse cardiovascular events (MACEs) and clinical findings.

Variable	Univariate regression			Multivariate regression		
	P-value	HR	95% CI	*P*-value	HR	95% CI
Age	0.100	1.015	0.997–1.033	–	–	–
Male	0.985	0.993	0.484–2.039	–	–	–
BMI(kg/m^2)	0.285	0.989	0.970–1.092	–	–	–
Smoking	0.622	1.143	0.672–1.943	–	–	–
Alcohol	0.875	0.947	0.479–1.870	–	–	–
Hypertension	0.989	1.004	0.592–1.702	–	–	–
Diabetes	0.617	0.836	0.413–1.690	–	–	–
Hyperlipidemia	0.086	0.163	0.200–1.294	–	–	–
Stoke	0.480	1.369	0.573–3.268	–	–	–
Cardiomyopathy	0.675	1.111	0.679–1.819	–	–	–
Coronary heart disease	**0.017**	0.521	0.305–0.890	–	–	–
Atrial fibrillation	**0.020**	2.592	1.163–5.775	**0.013**	3.049	1.264–7.355
Previous CABG	0.074	3.630	0.884–14.899	–	–	–
Previous PCI	0.065	0.605	0.355–1.031	–	–	–
Moderate and severe renal dysfunction	**0.009**	2.462	1.258–4.818	**0.042**	2.097	1.027–4.281
LA size	0.573	1.114	0.765–1.621	–	–	–
LVIDd	0.200	1.194	0.910–1.567	–	–	–
LVIDs	**0.011**	1.340	1.071–1.677	–	–	–
LVEF $\leq$ 50%	**0.006**	2.425	1.282–4.586	**0.028**	2.243	1.090–4.615
Ventricular aneurysm	0.063	0.554	0.298–1.032	–	–	–
Thrombus Area(cm^2)	0.100	1.054	0.990–1.122	–	–	–
Number of thrombus >1	0.419	0.698	0.292–1.670	–	–	–
Antiplatelet therapy only	0.940	0.979	0.561–1.707	–	–	–
Anticoagulation only	0.617	1.197	0.592–2.142	–	–	–
Anticoagulation + antiplatelet therapy	0.854	1.051	0.620–1.782	–	–	–
RASI	0.084	0.626	0.368–1.066	–	–	–
Aldosterone antagonist	0.806	1.936	0.550–1.591	–	–	–
β-blocker	**0.004**	0.426	0.237–0.766	**0.005**	0.397	0.210–0.753
Digoxin	0.955	1.019	0.523–1.988	–	–	–

BMI, body mass index; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; LA, left atrium; LVIDd, left ventricular end-diastalic diameter; LVIDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; RASI, renin angiotensin inhibitor. Bold values are statistical differences more eye-catching.

important cause for cerebral and peripheral arterial embolism and subsequent mortality. Patients with LVT are with poor clinical prognosis and high risks of MACE. This study provides new insights into the clinical characteristics and prognosis from a relatively large cohort of patients with LVT in the Chinese population.

The average age of 237 patients enrolled in this study is 59.9 ± 15.2 years, which is similar to the age reported abroad. The incidence of women is significantly lower compared with men, the proportion of women in our hospital (16%) is similar to the proportion of women reported abroad (15–30.4%) (10, 11). Coronary heart disease is still the main disease complicated by LVT in this study, but when compared with the study by Lee et al. (3), the rate of coronary heart disease-related LVT was decreased (70.9% vs. 80.6%). This may be due to the progress of PCI technology and the normalization of various medication treatments, such as anti-platelet aggregation and anti-arteriosclerosis for coronary heart disease.

In this study, DCM, valvular heart disease, and other concurrent LVT diseases increased by 9.7% when compared with the study by Lee et al. (3), which may be related to the advance in thrombus detection technology, the prolongation of the population's average life-span, and the better healthcare nowadays.

Transthoracic echocardiography remains the main method for detecting LVT due to its convenience, non-invasiveness, strong reproducibility, and high specificity. The advances in ultrasound technology and the use of contrast agents potentially help clinicians to identify LVT (12). In this study, the thrombus was mostly located in the apex of the left ventricle where blood flow was the slowest or most stagnant due to abnormal ventricular wall movement, and thrombus was found in 52% of ventricular aneurysms. Thrombus echogenicity was dominated by medium-to-high echogenicity (66.2%), indicating the high degree of thrombus calcification.

Anticoagulation therapy

At present, due to the lack of clinical evidence and considering the bleeding risk of combined application of antiplatelet and anticoagulant medication, there are certain

TABLE 4 Cox regression analysis for the association between all-cause mortality and clinical findings.

Variable	Univariate regression			Multivariate regression		
	P-value	HR	95% CI	*P*-value	HR	95% CI
Age	**0.018**	1.02	1.003–1.037	**0.031**	1.021	1.002–1.040
Male	**0.035**	0.755	0.418–1.361	–	–	–
BMI	0.975	0.898	0.970–1.060	–	–	–
Smoking	0.957	1.013	0.623–1.649	–	–	–
Hypertension	0.861	0.958	0.593–1.548	–	–	–
Diabetes	0.981	1.008	0.54–1.882	–	–	–
Hyperlipidemia	0.916	0.272	0.38–1.958	–	–	–
Stoke	0.689	0.842	0.364–1.950	–	–	–
Alcohol	0.868	0.947	0.495–1.808	–	–	–
Cardiomyopathy	0.210	1.308	0.859–1.991	–	–	–
Coronary heart disease	0.055	2.516	0.981–6.452	–	–	–
Atrial fibrillation	0.105	1.676	0.898–3.131	–	–	–
Previous CABG	**0.006**	2.981	1.360–6.536	< **0.001**	4.634	2.042–10.517
Previous PCI	**0.007**	0.528	0.311–0.831	–	–	–
Moderate and severe renal function injury	0.984	1.006	0.579–1.748	–	–	–
LA size	0.347	1.175	0.839–1.646	–	–	–
LVIDd	0.060	1.261	0.99–1.606	–	–	–
LVIDs	**0.001**	1.354	1.125–1.629	–	–	–
LVEF ≤ 50%	<**0.001**	4.753	2.169–10.418	**0.001**	3.714	1.664–8.290
Ventricular aneurysm	0.061	0.559	0.305–1.027	–	–	–
Thrombus area (cm^2)	**0.029**	0.52	1.005–1.101	**0.007**	1.071	1.019–1.126
Number of thrombus >1	0.263	0.619	0.267–1.435	–	–	–
Antiplatelet therapy only	0.495	0.797	0.416–1.529	–	–	–
Anticoagulation only	0.865	1.045	0.627–1.744	–	–	–
Anticoagulation + antiplatelet therapy	0.702	1.098	0.680–1.774	–	–	–
RASI	0.953	1.015	0.621–1.660	–	–	–
Aldosterone antagonist	0.656	1.116	0.688–1.809	–	–	–
β-blocker	**0.001**	0.464	0.285–0.754	**0.001**	0.410	0.237–0.708
Digoxin	0.595	1.174	0.65–2.119	–	–	–

BMI, body mass index; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; LA, left atrium; LVIDd, left ventricular end-diastalic diameter; LVIDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; RASI, renin angiotensin inhibitor. Bold values are statistical differences more eye-catching.

controversies about the treatment strategy for LVT caused by ischemic heart disease. STEMI guidelines recommend additional anticoagulation on the basis of antiplatelet treatment in patients developing LVT, with VKA as the standard anticoagulant agent. The 2013 ACC/AHA guideline for STEMI management suggested adding VKA to dual antiplatelet therapy (DAPT) in patients with LVT for at least 3 months (13). Similarly, the 2014 ASA guideline for primary prevention of stroke gives an IIa recommendation for using VKA adjunctive to DAPT in STEMI patients with LVT (14). The 2017 ESC guidelines for STEMI recommend treatment of LVT with oral anticoagulation for up to 6 months guided by repeated imaging, but no agent preference is given (15). In 2018, CCS issued guidelines for antiplatelet therapy: for the treatment of patients with LVT after PCI, it is recommended to use aspirin, clopidogrel, and oral anticoagulants for initial treatment, but stop aspirin within 6 months (16). A total of 168 patients with ischemic heart disease complicated with LVT were enrolled, 37 of whom did not take anticoagulants, accounting for 22%. During the first half of the decade, 36.4% of patients did not take anticoagulants. While from February 2015 to January 2020, 15% of patients did not take anticoagulants, so clinicians are more active in the anticoagulation treatment of LVT caused by ischemic heart disease.

The anticoagulant treatment plan for LVT caused by non-ischemic heart disease has been relatively clear. Patients with DCM with LVEF < 30% or a history of embolism or echocardiography found mural thrombosis is recommended to add treatment with anticoagulants. In this study, a total of 38 patients with DCM with LVEF < 30%, 2 of whom did not take anticoagulants due to waiting for heart transplantation. Therefore, patients with DCM in this study nearly meet the guideline-directed anticoagulation treatment plan.

However, the total rate of anticoagulant treatment was 82.3% in this study, which was a little low compared with 98.7% in a similar study by Lattuca et al. (8) in the United States (8). Therefore, the treatment of LVT in China is still more conservative. In a study of 244 patients with MI complicated with LVT, the median follow-up time was 807 days, and the thrombus disappearance rate was 63.96% (12). In another study, 156 patients with all diseases complicated with LVT were followed up for a median of 632 days, and the thrombus

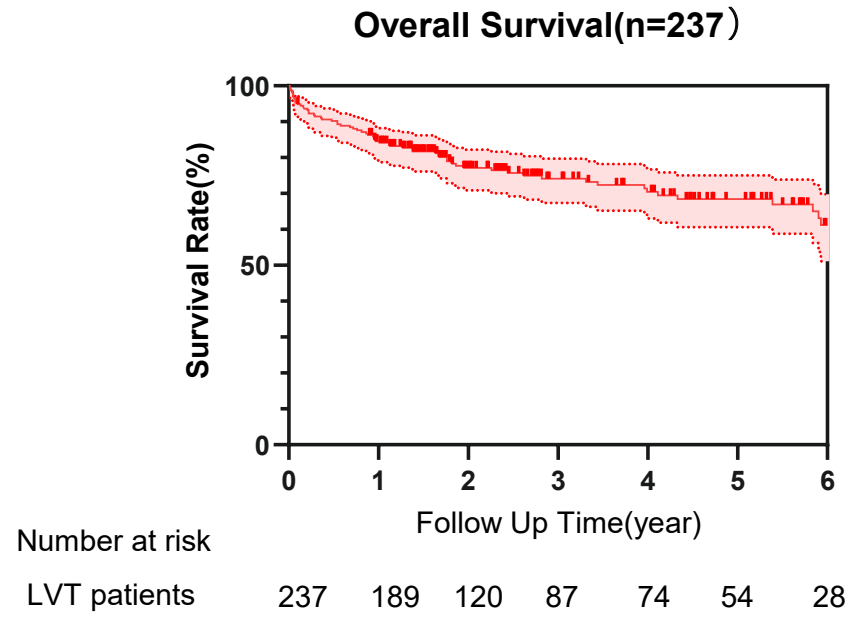

FIGURE 1
Survival curve of patients with left ventricular thrombus (LVT) during the follow-up time.

disappeared by 66.7%, compared with 64.1% in our study (8). These studies highlight that the current antithrombotic regimen needs to be improved because nearly one-third of patients did not achieve total LVT regression and remained exposed to a high risk of clinical complications even when combined with antiplatelet agents.

Fortunately, since 2020, there is an increasing number of studies done to explore more reasonable anticoagulation schemes in the treatment of LVT. Lots of articles discussed the comparison of the effects of DOACs and VKA, which showed no significant difference in the incidence of new thromboembolic events, bleeding, the rate of resolution of thrombus, and even the all-cause mortality. DOACs and VKA have similar efficacy and safety in treating LVT, prompting the inference that DOACs are the possible alternatives to VKA in LVT therapy. Most recently, the breakthrough of 2 novel randomized controlled trials have shown DOACs to be a promising treatment for LV thrombus. They also appealed that the optimal timing and type of anticoagulation for LV thrombus, and the role of screening for high-risk patients, should be tested in more prospective, randomized trials (17–25). We analyzed the relationship between baseline medication and mortality within 1 month and found aspirin/clopidogrel/ticagrelor + anticoagulant (HR, 0.066; 95% CI 0.011–0.403; p = 0.003) and aspirin + clopidogrel/ticagrelor + anticoagulant (HR, 0.059; 95% CI 0.004–0.804; p = 0.034) had protective effect on mortality. It indicated that the baseline medication has an impact on mortality within 1 month.

Clinical outcomes

The main result of this study showed a high rate of MACE in patients with LVT, as 28.3% of patients died and 13% of patients had embolic complications during follow-up. A study by Lattuca et al. (8) from Europe reported that the mortality and embolic complications occurred in 18.9% (n = 30) and 22.2% (n = 35) of 156 patients, respectively (8). A study from Singapore showed that the all-cause mortality rate was 21.7% (n = 53) of 244 patients with post-AMI LVT (12). Meanwhile, a study from Xinqiao Hospital in China showed that the mortality and the embolic complications rate of 92 patients were 30.4 and 10.9%, respectively, within a median follow-up period of 702 days (10). Another study from Shanghai East Hospital showed that after following up for 1 year, the frequency of mortality and embolic complications was 12 and 28%, respectively, for 25 patients with post-MI LVT (26). Based on these studies, the MACE of patients with LVT is especially high nationally and internationally. The mortality of our patients is higher than other studies. It may be due to the availability of NOACs, alertness, inertia of clinician, and longer follow-up time. Cox regression analysis in this study showed that those who underwent CABG surgery before the formation of thrombus had a 4.634 times higher risk of death than those who did not. Meanwhile, it also showed the risk of death for patients with LVEF $\leq$ 50% was 3.714 times higher than the patients with LVEF $>$ 50%, and the risk of death increased 1.071 times for every 1 cm^2 increase in thrombus area. These results had also been confirmed by other studies. In this way, we supposed that relatively aggressive treatment could

be considered for patients with severe coronary heart disease or lower LVEF or bigger LVT area in order to improve the prognosis of these patients (9–12, 26, 27).

In addition, according to the 2017 AHA/ACC/HRS Guideline for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death, β-blockers are generally safe agents that effectively suppress ventricular ectopic beats and arrhythmia and prevent sudden cardiac death in a wide array of cardiac diseases. According to the guidelines, β-blockers are indicated in all patients, except those with AV block, bradycardia, or asthma and are recommended in all patients with HF, regardless of baseline rhythm, and β-blockers are also used for the control of ventricular rates to avoid rapid irregular ventricular activation (28, 29). In this study, the risk of MACE for patients taking the medication of β-blocker was reduced to nearly one-third compared to that who did not take it, which was consistent with the above guidelines.

Study limitations

This study is a retrospective study from a single center. The research was conducted based on a retrospective observation and analysis of data collected in a tertiary hospital located in East China. We could not exclude the influence of geographical, economic, and cultural differences. Most patients only underwent TTE examinations. Due to its limited sensitivity in detecting LVT, the detection rate of LVT in this study may be underestimated. Due to the nature of the retrospective study, the study was not conducted regularly with continuous TTE to determine more accurate LVT resolution time and the possibility of LVT recurrence after stopping treatment; there may be unmeasured variables in the study, which may be important predictors of LVT. In addition, the information, especially for the medication data, that is provided by the phone call follow-up recipients by memories maybe not completely accurate, which leaves room for uncertainty in our research results (30). Despite these limitations, this study provides valuable data for the clinical characteristics, treatment, and prognosis of LVT in China.

Conclusion

Most studies discuss the risk factors for LVT formation, whereas our study focuses on the risk factors of MACE and all-cause mortality after LVT formation. This study showed that atrial fibrillation, moderate and severe renal function injury, and LVEF $\leq$ 50% were independent risk factors for MACE; age, previous CABG, LVEF $\leq$ 50%, and large thrombus area were independent risk factors for all-cause mortality. It was found that the use of β-blockers could improve prognosis for the first time. LVT is an uncommon complication of ischemic and non-ischemic cardiomyopathy, which is associated with a high risk of adverse events and mortality. It is recommended that doctors could be more active in applying patients with LVT with anticoagulants. More randomized controlled studies with a large sample size should be performed to assess the efficacy and safety of target-specific treatment for patients with LVT.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

This study has been approved by the Ethics Committee of SAHZU. Due to the nature of the study, written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

CL involved in data collection, collation, follow-up, and statistical analysis and wrote the original draft. WL involved in data collection, collation, and follow-up and helped in the drafting of the manuscript. NQ involved in statistical analysis, contributed to the interpretation of data, and revised the manuscript. LS involved in data collection and follow-up. CJ involved in revising manuscript. DZ and YY involved in statistical analysis. XP involved in the conception, research design, and revision of manuscript and helped in the acquisition of data. QZ involved in the study design and final revision of manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 01 November 2022
DOI 10.3389/fcvm.2022.966649

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Thrombosis, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 11 June 2022
ACCEPTED 29 September 2022
PUBLISHED 01 November 2022

CITATION
Gao W, Wang H, Liu Y, Tang Q, Wu P, Lin T, Li T and Sun D (2022) Sodium alginate-hydrogel coatings on extracorporeal membrane oxygenation for anticoagulation. *Front. Cardiovasc. Med.* 9:966649. doi: 10.3389/fcvm.2022.966649

Sodium alginate-hydrogel coatings on extracorporeal membrane oxygenation for anticoagulation

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Thromboembolism caused by the use of extracorporeal membrane oxygenation (ECMO) remains common among patients with existing heart diseases and contributes to significant morbidity and mortality during the COVID-19 pandemic. Various surface modification strategies have been proposed, showing that the methacrylated alginate (MA-SA) hydrogel layer is transparent, which aids the observation of the thromboembolism from the inner wall of the tubing. In the combined dynamic and static blood of ECMO tubing inner surface *in vitro* experiments, it was also demonstrated that the adhesion of blood clots to the surface of vessels was remarkably reduced, and the MA-SA-based hydrogel coating could significantly prolong the activated partial thrombin time and block the endogenous coagulation. The favorable properties of natural polysaccharides of hydrogel coatings make them the best surface material choices to be applied for blood-contacting medical devices and significantly improve anticoagulant performance.

KEYWORDS

hydrogel coating, ECMO tube, natural polysaccharide, sodium alginate, anticoagulation

Introduction

Extracorporeal membrane oxygenation (ECMO) plays an important role during the COVID-19 pandemic. It is an extracorporeal lung assist technology used to partially or completely replace the patient's cardiopulmonary function and extends the patient's life while waiting for the primary disease to be treated. Membrane lungs, blood pumps, and blood pipelines are the core compositions of ECMO, they act as the artificial lung, heart, and blood vessels, respectively. Polyvinyl chloride (PVC) is among the raw materials

of the blood pipeline, it ranked third among the widely produced plastic polymers worldwide (1).

For the cardiopulmonary bypass, the PVC circuit which can initiate the activation of platelets and the coagulation cascade after blood cell contact is a possible detrimental effect (2). The heparin-coated artificial anticoagulant is commonly used on the inner wall of the ECMO tubing to prevent blood clotting. The development of antithrombotic surfaces will be a major advancement in medical applications. The PVC surface activation was prepared on ammonia plasma-treated PVC (3).

Heparin was widely used as an anticoagulation coating because red blood cells (RBC) are negatively charged and RBC is repelling heparin (glycosaminoglycan with negative charge, Hep). Heparin is an animal-derived polysaccharide, which brings out animal sensitization. Natural polysaccharides exhibit anticoagulation mechanisms similar to heparin. It can be potentially developed into a natural anticoagulant and can be used as an alternative to heparin. Among polysaccharides, sodium alginate was selected as a non-toxic natural plant polysaccharide material, combined with calcium (coagulation factor IV) as an important component of anticoagulation function (4). Sodium alginate is a heparin-like polysaccharide, its sulfated polysaccharide site can bind to antithrombin III (AT-III), catalyze AT-III, antagonize coagulation factors IIa, Xa, IXa, XIa, and XIIa, thereby blocking the intrinsic coagulation pathway, inhibits the conversion of prothrombin to thrombin (IIa), inhibits thrombin activity, and hinders the conversion of fibrinogen to fibrin monomers.

Functional hydrogel coatings (5) play an essential role as structural components in the emerging field of medical devices by tailoring the molecular interactions between the hydrogel polymer network and drugs (i.e., covalent linkage, electrostatic interaction, and hydrophobic interaction) the drug release rate can be efficiently tuned (6–9). The materials used for the coating of sodium alginate are mainly PVC (10) and polyelectrolyte (PE) (11). At the same time, the latest hydrogel coating is also applied to the PVC tubing (12).

Thus, we synthesized the methacrylated alginate (MA-SA)-based hydrogel coating PVC tubing for anticoagulation with UV cross-link reaction, as illustrated in **Figure 1**.

Materials

Alginate was purchased from Aladdin, Shanghai, China. Dimethyl sulfoxide was obtained from Beijing Chemical Reagent Company, Beijing, China. N-(3-aminopropyl) methacrylamide hydrochloride dimethyl sulfoxide and 1-hydroxybenzotriazole monohydrate were supplied by Sigma, USA. Phosphate buffer solution (PBS) was purchased from Biotopped, Beijing, China. Chloroform, isopropyl alcohol, and ethanol were obtained from Tianjin Chemical Reagent Wholesale Company, Tianjin, China. TRIzol Reagent was obtained from Ambion company, Austin, USA. DNase/RNase-Free Water was obtained from Soleibo Technology Co., Ltd., Beijing, China. IL-1β, IL-6, and TNF-α were obtained from General Biological Co., Ltd., Chuzhou, China.

Preparation of the methacrylated alginate-based hydrogel coatings on extracorporeal membrane oxygenation surfaces

The synthesis of MA-SA-based hydrogel coating was carried out using the following procedure. After dissolving a total of 0.25 g of alginate in 75 ml of deionized water, a sufficient amount of N-(3-aminopropyl) methacrylamide hydrochloride was added to the alginate solution. Subsequently, a total of 20 ml of a 1:1 mixture of dimethyl sulfoxide and water containing 0.291 g of 1-ethyl-3-(3-dimethyl aminopropyl) carbodiimide hydrochloride and 0.205 g of 1-hydroxybenzotriazole monohydrate was added to the first solution. The resulting mixture was allowed to react at room temperature for 48 h. Then, the solutions were rinsed using a saturated soda solution and dialyzed against deionized water for 3 days (13).

The alginate and gelatin methacryloyl are chemically anchored on the ECMO tubing surfaces [Product Category: Disposable Extracorporeal Circulation Tube (Adult); Manufacturer: Dongguan Kewei Medical Equipment Co., Ltd.; Production batch number: 20190618]. ECMO tubing inner surfaces were cleaned using an ammonia plasma (3), washed with ethanol, and then completely dried. The aminosilane, a coupling agent for a silica-based material, functionalized the ECMO tubing and was further incubated in 1, 2, and 5 wt% MA-SA solution with 0.1% (w/v) Irgacure 2,959 under 365 nm ultraviolet light. The inner parts of the ECMO tubing were finally washed with deionized water and were completely dried before use (14).

Properties of the methacrylated alginate-based hydrogel coatings on extracorporeal membrane oxygenation surfaces

The internal surface morphologies of the MA-SA-based hydrogel coatings were detected using a scanning electron microscope (SEM, HITACHI, Japan) after being completely lyophilized for 12 h. The static water contact angle measurement was performed at room temperature using a contact angle goniometer (DSA100, KRUSS, German). Using a microsyringe, a droplet (3 μL) of distilled water was dropped on the surface and the value of the water contact angle was recorded after 30 s.

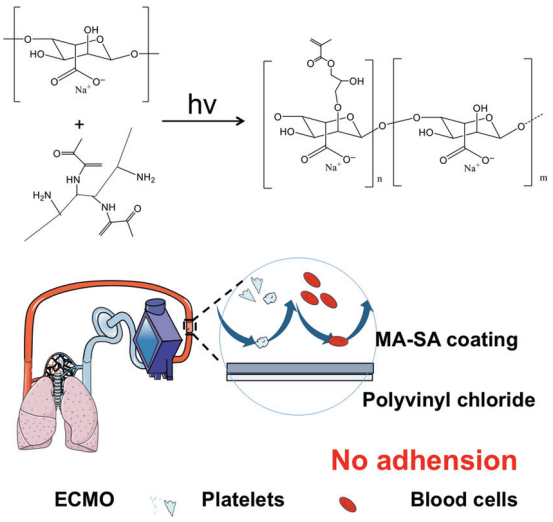

FIGURE 1
Methacrylated alginate (MA-SA)-based hydrogel coatings on extracorporeal membrane oxygenation (ECMO) surfaces. The medical device used in this study is polyvinyl chloride (PVC) tubing with MA-SA hydrogel-coated ECMO surfaces.

Compatibility of the methacrylated alginate-based hydrogel coatings on extracorporeal membrane oxygenation surfaces

Cell lines and cell culture

Human umbilical vein endothelial cells (HUVECs) were obtained from the American Type Culture Collection (ATCC). HUVECs were cultured in DMEM medium (Gibco, USA) supplemented with 10% of fetal bovine serum (FBS) (Gibco, USA) and 1% penicillin-streptomycin (HyClone, USA) in a humidified incubator (Thermo Fisher Scientific, USA) at 37°C and 5% CO_2. The cultured medium was replaced in about 2∼3 days, and the cells grew to 80∼90% density for passage.

Cytotoxicity

Human umbilical vein endothelial cells (HUVECs) cells were cultured in DMEM medium (Gibco, USA) supplemented with 10% FBS (Gibco, USA) and 1% penicillin-streptomycin (HyClone, USA) in a humidified incubator (Thermo Fisher Scientific, USA) at 37°C and 5% CO_2. The cytocompatibility of the MA-SA-based hydrogel coatings for ECMO was determined by a direct contact method between the MA-SA-based hydrogel and HUVECs. HUVECs were seeded on the inner tube surface of 1, 2, and 5 of the MA-SA-based hydrogel coatings ECMO at a density of 5×10^4 cells/cm^2 in 24-well plates and incubated for a day (10, 15).

Flow cytometry

Flow cytometry was used to test cell apoptosis. HUVECs cells were counted and then inoculated to 6-well plates. The same amount of medium was added to the NC group, meanwhile, the MA-SA-based hydrogel coating was added to the experimental group. After 24 h of treatment, cells were digested and collected with trypsin without EDTA (Solarbio, USA), and then washed twice with PBS (Gibco, USA). The collected samples were suspended in the binding buffer following the Annexin V-FITC/PI Apoptosis Detection Kit (KeyGEN BioTECH, China). After staining with Annexin V-FITC and PI in the dark at room temperature for 10 min, apoptotic cells were examined by flow cytometric analysis (BD Biosciences, USA) (Excitation wavelength Ex = 488 nm; Emission wavelength Em = 530 nm). The experimental results were analyzed with FlowJo version 10.6.2, and the average value was obtained from three independent experiments performed on each group.

Human blood hemocompatibility assessment

Fresh whole blood was obtained from the Third Central Hospital of Tianjin, China using a standard vacuum blood collection tube. This procedure was approved by the Human Ethics Committee of the hospital (IRB-2020-025-01). The blood was then centrifuged at 3000 r/min for 10 min. The lower supernatant platelet-poor plasma (PPP) is used to assess clotting time. Wash the 0.5 mm × 0.5 cm MA-SA-based hydrogel coatings tubing in a 24-well plate thrice with distilled water. Subsequently, equilibrate the tube with PBS at 37°C for 30 min, and then add a total of 200 μl PPP and incubate at 37°C for 1 h. After incubation, the activated partial thrombin time (APTT), thrombin time (TT), prothrombin time (PT), and fibrinogen amount (FIB) of PPP were measured thrice using the automatic coagulation analyzer (Diagnostica Stago, STA-R Evolution, France).

Investigation of the effects on anti-inflammatory gene expression of RAW cells

Total RNA was isolated with TRIzol reagent (Invitrogen) after 8 h induction with PVC and coating material. RNA was reverse transcribed by PrimeScript RT kit (TaKaRa). Quantitative RT-PCR was performed with SYBR Premix Ex Taq (TaKaRa) and QuantStudio 3 and 5 Real-time PCR (Thermo Fisher). Using the housekeeping gene β-actin as the baseline, the gene expression of PVC and coating material groups was quantitatively analyzed (16).

Result and discussion

The properties of the methacrylated alginate-hydrogel coatings

The surface of the MA-SA-hydrogel coatings was irradiated with UV light to polymerize the hydrogel layer. The MA-SA-hydrogel was shown in **Supplementary Figure 1**. **Figures 2A,B** demonstrated that the MA-SA hydrogel coating was uniform, illustrating macro images of pristine and the MA-SA-coated hydrogel tubing. The MA-SA-hydrogel coating is transparent and observing thrombosis through the tubing is easier than the N,N-dimethylacrylamide on the activated surfaces (17). The morphology of the MA-SA-hydrogel-coated ECMO surface is porous about 5 μm, however, the diameter of RBC observed in an optical microscope is less than 8 μm (18). The contact angle is 112° in **Figure 2C**, proving the MA-SA-hydrogel coating is hydrophobic, hence, a more favorable proof that the MA-SA-hydrogel coating is less prone to thrombosis.

Anticoagulation properties of the methacrylated alginate-hydrogel-coated extracorporeal membrane oxygenation tubing to human blood

When blood passes through the inner surface of the MA-SA-hydrogel-coated tubing, the sodium alginate coating with a heparin-like structure binds with the antithrombin (AT) through a special pentose sequence, catalytically activates and amplifies AT activity. Activated AT binds to coagulation factors involved in the intrinsic coagulation pathway, and plays an anticoagulant effect by antagonizing the activated factor II (IIa) and factor X (Xa), including antagonizing IXa, XIa, and XIIa, thereby prolonging the APTT and TT. After tightly combining the AT-coagulation factor complex, it is separated from the surface of the sodium alginate coating and continues to play an anticoagulant effect in the blood while the fixed sodium alginate coating continues to bind and catalyze the activation of AT as shown in **Figure 3A**. **Supplementary Figure 2** shows the good biocompatibility of the MA-SA-hydrogel coating.

The anticoagulant activity of the MA-SA-hydrogel-coated tubings was examined using the hemostasis indices, APTT, TT, PT, and FIB. Standard vacuum blood collection tubings were used to obtain patients' wasted blood samples from healthy blood coagulation at Tianjin Third Central Hospital. Blood clots were formed when blood samples contact foreign surfaces following platelet activation. This can be catastrophic in clinical settings involving extracorporeal circulation, particularly during heart-lung bypass surgery where blood is circulated in PVC tubing (19). The hydrogel coating can significantly prolong the APTT and TT and block the intrinsic coagulation pathway, thereby significantly improving the anticoagulation performance of the inner surface of the ECMO tube in static blood *in vitro*. The APTT and TT in the 1 wt% MA-SA-hydrogel-coated tubings group were significantly increased (**Figures 3B,C**) as compared with those of the control ECMO

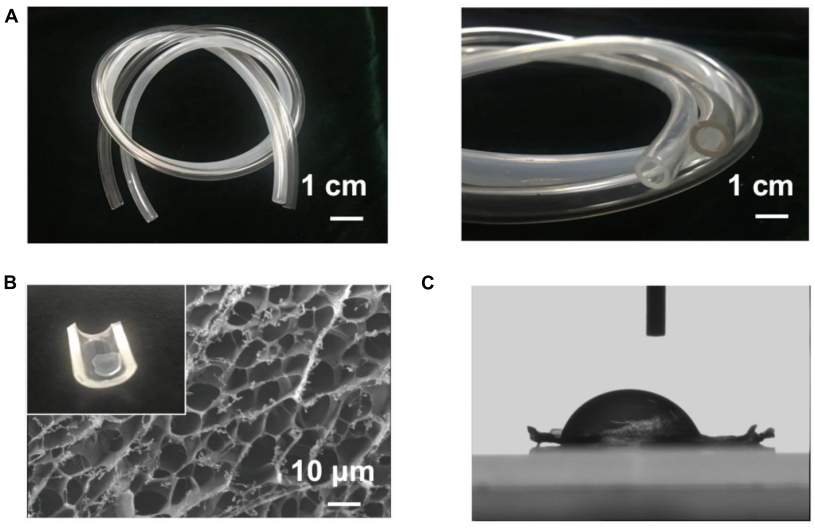

FIGURE 2
The image of methacrylated alginate (MA-SA)-hydrogel coatings on polyvinyl chloride (PVC) surfaces. **(A)** Macro images of the coating and the pristine tubing demonstrate that the method used here can produce a transparent and uniform hydrogel coating. **(B)** The scanning electron microscope (SEM) image of the methacrylated alginate (MA-SA)-hydrogel and the inset in the upper left corner of the hydrogel drop on the surface of the PVC tube. **(C)** The contact angle of MA-SA-hydrogel.

tubing, indicating improved anticoagulation abilities with static blood inside the MA-SA-hydrogel-coated hydrogel tubing. No significant differences were observed in the PT (9.4–15.4 s) and FIB (2–4 g/l) (Figures 3D,E). The dexamethasone and oxidated sodium alginate mainly formed the composite coatings through ionic and covalent bond methods (20). SA/heparin

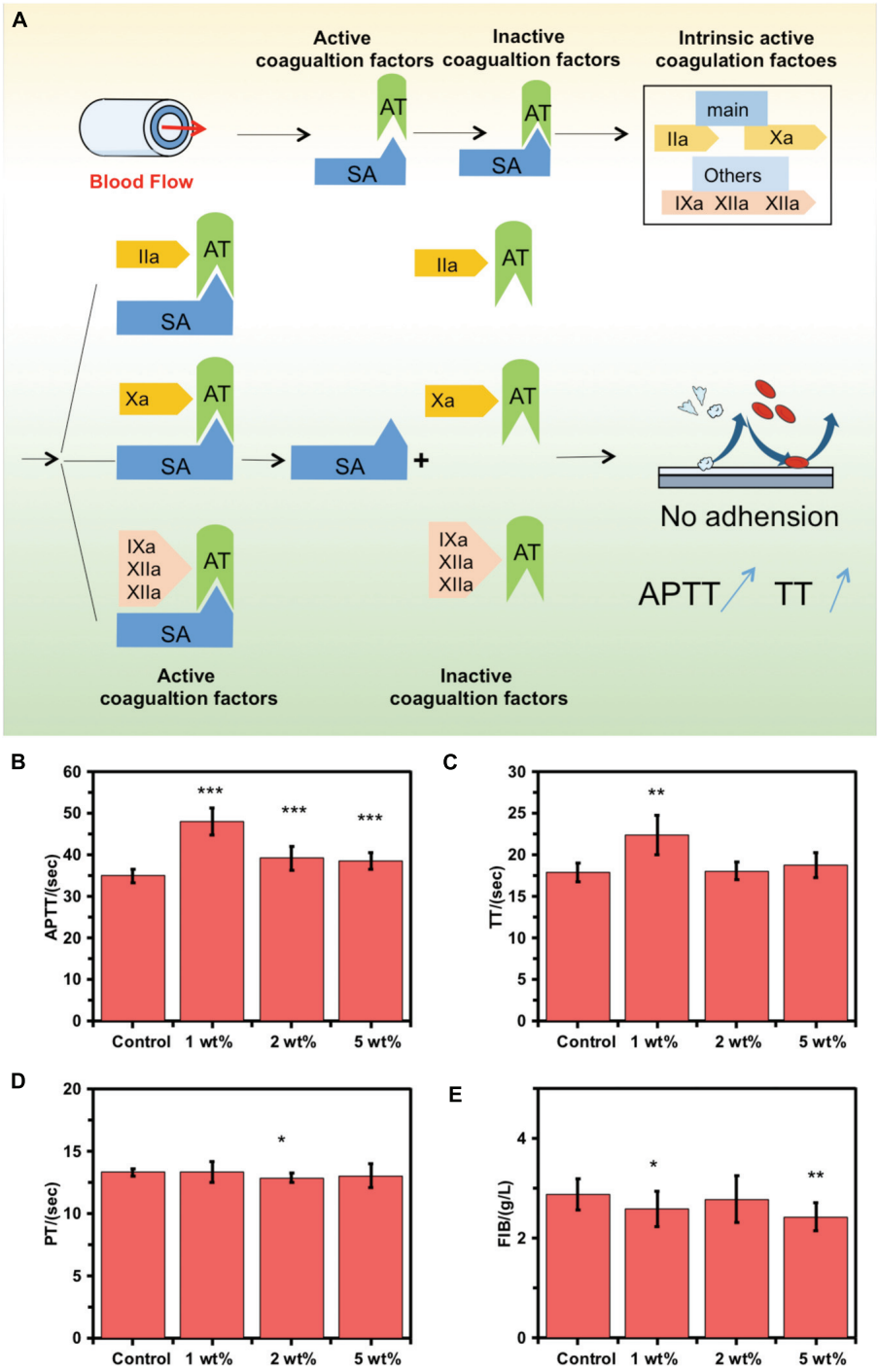

FIGURE 3
Coagulation function on the inner surface of control extracorporeal membrane oxygenation (ECMO) and MA-SA-Hydrogel coating tubings. **(A)** Schematic diagram of anticoagulation mechanism. **(B)** The activated partial thrombin time (APTT), **(C)** thrombin time (TT), **(D)** prothrombin time activity, and **(E)** fibrinogen amount (FIB) were measured using an automated blood coagulation analyzer and exposed to human blood (***$p < 0.001$; **$p < 0.01$; *$p < 0.05$; NS, not significant).

composites were covalently immobilized onto the surface of the PVC pipeline (10). SA hydrogel sample with 1 wt% also has the best anticoagulant effect in our previous research (4). The same MA-SA-hydrogel-coated hydrogel coating treatment to the other component materials of the ECMO kit, polycarbonate (joint) and polymethylpentene (oxygenator membrane filament), and the anticoagulant properties of the two materials improved after coating in **Supplementary Figure 3**. Compared to protein-coated tubing (BioLine coating, MAQUET Inc.) and heparin coated tubing (Carmeda Bioactive Surface, Medtronic Inc.), sodium alginate-hydrogel coated PVC tubing also has anticoagulant properties and anticoagulant performance is slightly lower than commercial products. But, it is most important that sodium alginate comes from marine plants, which are more abundant and do not introduce animal-derived (heparin from animal intestinal mucosa) and human-derived (albumin from human blood) components, reducing the risk of allergy in patients in **Supplementary Figure 4**. Uncoated PVC tubing can activate the inflammatory response, thereby increasing the release of pro-inflammatory cytokines IL-6 and TNF-α from macrophages, and coated PVC tubing can reduce the release of IL-6 and TNF-α from macrophages, thereby reducing inflammation reaction in **Supplementary Figure 5**.

Anticoagulation properties of the methacrylated alginate-hydrogel-coated extracorporeal membrane oxygenation tubing to simulated blood

The control blood sample in closed circular tubing loops was circulated until it is fully coagulated, as shown in **Figure 4A**. Simulated blood that was circulated through pristine tubing formed larger amounts of wall-adhering clots than blood in contact with coated tubing. The clotted blood samples were subsequently poured into a petri dish, blood clots were removed and weighed. Then, the tubing was gently rinsed twice and then weighed. The average pristine tubing weight gain is 5.3%, whereas that of the coated tubing is 0.8% in static blood, as shown in **Figure 4B**.

Whole blood was circulated through the circuit using a cardiopulmonary bypass circuit machine roller pump at a flow rate of 2.5–3.5 L/min, as shown in **Figure 4C**. In dynamic blood, the average tubing weight gain for the pristine tubing was 10.5% as compared to the coated tubing in **Figure 4D** which has a 3.6% weight gain. This indicates that blood clots adhered more readily to the pristine than to the MA-SA-coated tubing. These two

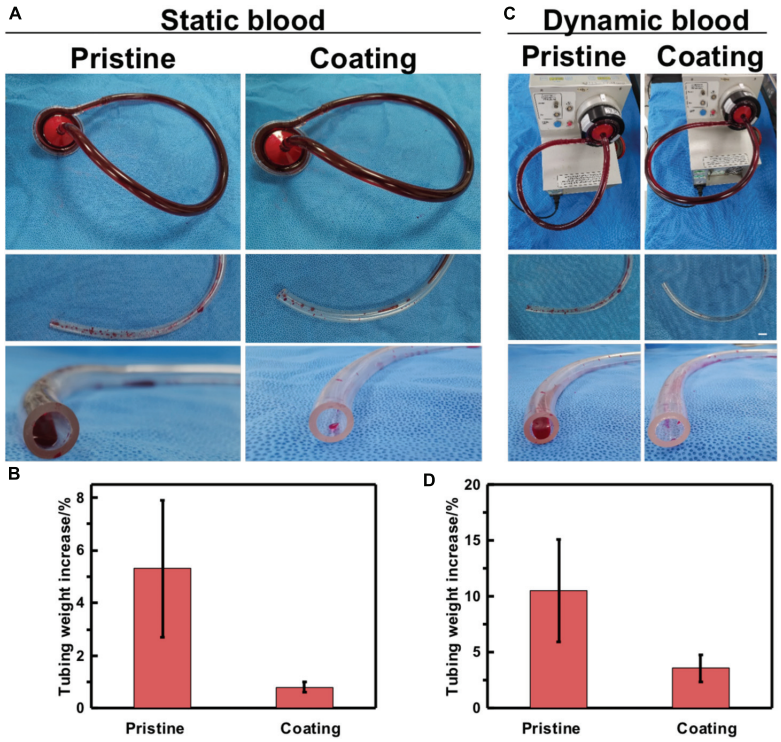

FIGURE 4
In vitro blood loop tests of static blood and dynamic blood. **(A)** Image of apparatus used for continuous flow testing of pristine and coated tubing. Testing was done in parallel to accurately control the end time point of flow. **(B)** Quantification of blood clotting adhesion to the tubing walls in static blood. **(C)** Image of pristine and coated tubing after flow testing and gentle rinsing with saline. **(D)** Quantification of blood clotting adhesion to the tubing walls in dynamic blood. Error bars represent SD for three repeated experiments.

pieces of evidence indicate that the MA-SA-hydrogel coatings on the PVC tubing show potential benefits in medical applications to address thrombosis-related complications.

Conclusion

These experiments show evidence that surface modification of the PVC with SA hydrogel coating leads to platelet activation, thrombosis, and blood incompatibility. The MA-SA-hydrogel coatings decreased the adhesion and activation of platelets thus improving their anticoagulation performance. It is believed that hydrophobic materials and natural polysaccharide surfaces of the coated tubing prolong the APTT and TT thereby blocking the intrinsic coagulation pathway. The MA-SA-hydrogel-coating technology is a design strategy that may mitigate the thromboembolism caused by the use of blood-contacting medical devices.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Third Central Hospital of Tianjin, China IRB-2020-025-01. The patients/participants provided their written informed consent to participate in this study.

Author contributions

WG and DS: conceptualization, investigation, and writing – original draft preparation. WG, DS, HW, YL, QT, PW, and TiL: methodology. YL, TiL, and DS: validation. QT and DS: data curation. WG, DS, and ToL: writing – review and editing and funding acquisition. All authors have read and agreed to the published version of the manuscript.

Funding

This work was financially supported by the Beijing Natural Science Foundation Youth Project (2224106) and the Tianjin Key Medical Discipline (Specialty) Construction Project, the Tianjin "Project + Team" Key Training Special Project (XC202040), the Tianjin "131" Innovative Talent Team Project (201939), and Key Project of Tianjin Natural Science Foundation (21JCZDJC00240).

Acknowledgments

We are grateful to Xiaodong Wang from Beijing Haoyujiahe Technology Co., Ltd., for his help and Shilin Li from the National Center for Nanoscience and Technology of China for drawing a part of **Figure 1**.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.966649/full#supplementary-material

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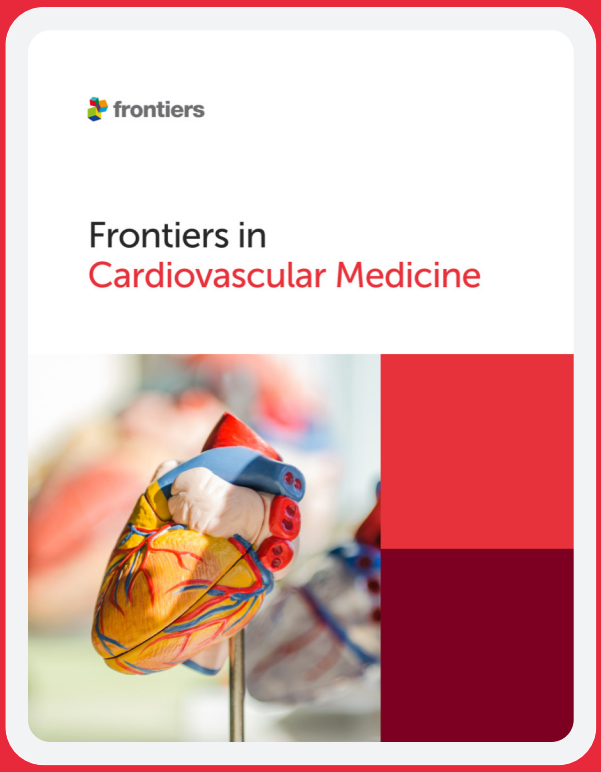

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