OUTCOMES OF CARDIOVASCULAR DRUG USE IN THE OLDER POPULATION

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Appropriate Dosing Regimens of Non-Vitamin K Antagonist Oral Anticoagulants for Treatment of Patients With Non-Valvular Atrial Fibrillation: An Evidence-Based Consideration

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Patients with non-valvular atrial fibrillation (NVAF) exhibit a high risk of stroke, which is associated with high mortality. Thus, stroke prevention is crucial for the overall management of NVAF. Two categories of drugs, vitamin K antagonist warfarin and non-vitamin K antagonist oral anticoagulants (NOACs), are clinically used to prevent NVAF-related stroke. In some circumstances, NOACs are superior to warfarin. However, NOACs selection for NVAF patients is affected by many factors, including individual patient characteristics, comorbidities, risk factors, or laboratory variables. This article summarizes the discrepancy in NOACs management with emphasis on the dosing regimens and influencing factors, such as stroke risk, age, body weight, renal function, gastrointestinal bleeding (GIB) risk, and combination of antiplatelet therapy, in order to identify individual groups with particular clinical characteristics who may obtain more benefit from a certain dosing regimen of NOACs. Determination of a particular subset of patient populations for the appropriate dose regimen of NOACs will help to achieve desired clinical outcomes. Furthermore, to compensate clinical evidence, we should place more emphasis on the findings of current clinical trials and supplement real-world data.

Keywords: stroke prevention, non-valvular atrial fibrillation, non-vitamin K antagonist oral anticoagulants, clinical settings, dosing regimens

INTRODUCTION

Atrial fibrillation (AF) is the most common heart arrhythmia and is linked to an elevated risk of systemic embolism (SE) and ischemic stroke (IS) (Camm et al., 2012). Oral anticoagulation has been shown to reduce IS and SE by more than 60% and decrease the mortality risk in AF patients (Potpara et al., 2019). Vitamin K antagonists (VKAs), such as warfarin, are effective in the prevention of AF-related stroke. However, clinical management of VKAs is difficult because of their narrow therapeutic index, required frequent laboratory monitoring, and drug and diet interactions (Zhao et al., 2019). Alternatively, direct oral anticoagulants (DOACs), also known as non-vitamin K antagonist oral anticoagulants (NOACs), have been developed (Zhao et al., 2019).

NOACs include dabigatran (factor IIa inhibitor), rivaroxaban, apixaban, edoxaban, and betrixaban (factor Xa inhibitors) (**Supplementary Material, Figure S1**). Phase III randomized controlled trials (RCTs) showed that NOACs are at least non-inferior to warfarin in terms of IS/SE prevention and have a low rate of intracranial hemorrhage (ICH) and major bleeding events for stroke prevention in atrial fibrillation (SPAF) (Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011; Giugliano et al., 2013). Hence, NOACs are strongly recommended by the current guidelines as a substitute for warfarin in patients with non-valvular atrial fibrillation (NVAF) (Kirchhof et al., 2016; January et al., 2019).

NOACs have been marketed extensively globally, however, the appropriate use of NOACs is a considerable issue. An observational study (Yao et al., 2017) examined the standard doses for participants with a renal indication for both potential over-dosing and under-dosing of NOACs, and showed that prescribed NOAC doses were often not in accordance with drug labeling, which may be linked to poor safety and no benefit in those patients with severe kidney disorders. Another study in Korea (Jung et al., 2018) investigated the distinction in stroke outcomes in NVAF patients based on their previous medication status, including under-dosed versus standard-dosed NOACs. Among 858 patients examined, standard-dosed NOACs or warfarin with treatment intensity was linked to a comparatively mild stroke in NVAF patients (Jung et al., 2018).

Owing to the clinical heterogeneity of AF patients, few studies have sought to uncover whether the appropriate patients are being treated and whether specific patient populations are receiving correct NOACs doses. In this article, we will outline the dosage suggestions for NVAF patients in different nations, and then provide a general outline on the NOACs performance in AF patients with particular clinical characteristics. We will reflect on how dose adjustment should be recommended based on the current knowledge, with the goal of presenting a simple and workable strategy for clinicians to choose an appropriate NOAC.

Abbreviations: NOAC, non-vitamin K antagonist oral anticoagulants; NVAF, non-valvular atrial fibrillation; GIB, gastrointestinal bleeding; AF, atrial fibrillation; SE, systemic embolism; IS, ischemic stroke; VKAs, vitamin K antagonists; DOACs, direct oral anticoagulants; ICH, intracranial hemorrhage; SPAF, stroke prevention in atrial fibrillation; RCTs, randomized controlled trials; FDA, the US Food and Drug Administration; EMA, the European Medicines Agency; NMDA, the Chinese National Medical Products Administration; ICB, intracranial bleeding; ISTH, the International Society on Thrombosis and Haemostasis; EHRA, the European Heart Rhythm Association; CKD, chronic kidney disease; CrCl, creatinine clearance; ESKD, end-stage kidney disease; CAD, coronary artery disease; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; OAC, oral anticoagulation; DAPT, dual antiplatelet therapy; CRNM, clinically relevant non-major; P-gp, P-glycoprotein; ECG, electrocardiogram.

DOSING REGIMENS PERSPECTIVES AND SUPPORTING DATA

Apart from betrixaban, other NOACs have been examined for SPAF in patients during confirmatory phase III global RCTs (e.g. ENGAGE AF-TIMI with edoxaban, ROCKET-AF with rivaroxaban, RE-LY with dabigatran, and ARISTOTLE with apixaban) and were proven to have favorable safety and efficacy (Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011; Giugliano et al., 2013). However, different doses of these agents were evaluated differently (Steffel et al., 2018). In ENGAGE AF-TIMI (edoxaban) and RE-LY (dabigatran) (Connolly et al., 2009; Giugliano et al., 2013), no pre-defined dose-decrease criteria were set; either a higher or a lower dose was verified in the fully powered cohorts (dose-reducing for edoxaban in particular patients). In contrast, in ARISTOTLE (apixaban) and ROCKET-AF (rivaroxaban) (Granger et al., 2011; Patel et al., 2011), the dose was decreased under the circumstance of pre-defined patient characteristics. For rivaroxaban and edoxaban, a standard dose was reduced in patients with one specific risk factor; however, for apixaban, data supported the dose adjustment to 2.5 mg twice daily when a patient had two of three characteristics (age ≥ 80 years, serum creatinine ≥ 1.5 mg/dL, or weight ≤ 60 kg) (**Table 1**). In addition, different countries do not adopt the same rules of NOACs prescription, and local policies, like formulary committees, regulatory approval, and cost-effectiveness, all influence NOACs availability (**Supplementary Material, Table S1**). Therefore, to reproduce the positive results from the RCTs, it is critical to use the correct dose regimen.

According to the results obtained from the RE-LY trial, two dosages of dabigatran, 150 and 110 mg, exhibited superior or non-inferior efficacy and safety compared to warfarin (Connolly et al., 2009); however, various countries have made different approvals for dabigatran dosing. Because the 150 mg dose was more effective at significantly reducing the stroke occurrence rate compared to the 110 mg dose, the US Food and Drug Administration (FDA) only approved the 150 mg dose, even though the larger dose was equal to warfarin with regards to risk of major bleeding events (Beasley et al., 2011; Cho et al., 2019). To balance the concerns about a lack of a low dose option, the FDA approved a 75 mg dose regimen of dabigatran based on pharmacokinetic simulations instead of efficacy and safety data to treat severe renal impaired patients (Steffel et al., 2018). However, the 75 mg regimen has not been tested in any clinical trial and additional RCTs are therefore necessary. By contrast, the European Medicines Agency (EMA) and the Chinese National Medical Products Administration (NMDA) focused on the bleeding risk of dabigatran and not only endorsed

TABLE 1 | NOACs and studied doses in SPAF.

NOACs	Clinical trial	Standard dose	Dose reduction
Dabigatran	RE-LY	2 × 110 mg 2 × 150 mg	No pre-specified dose-reduction criteria. 2 × 110 mg if: -age ≥80 years; -elevated risk of gastrointestinal bleeding; -concomitant verapamil;
Rivaroxaban	ROCKET-AF	1 × 20 mg	1 × 15 mg if: -CrCl ≤50 ml/min
Apixaban	ARISTOTLE	2 × 5 mg	2 × 2.5 mg if two out of three: -age ≥80 years -weight ≤60 kg; -serum creatinine ≥133 μmol/L (1.5 mg/dl) [or if CrCl 15–29 ml/min];
Edoxaban	ENGAGE AF-TIMI	1 × 60 mg	1 × 30 mg if: -CrCl ≤50 ml/min; -weight ≤60 kg; -concomitant use with strong P-gp inhibitor (verapamil, quinidine, or dronedarone);

NOAC, non-vitamin K antagonist oral anticoagulants; SPAF, stroke prevention in atrial fibrillation; CrCl, creatinine clearance; P-gp, P-glycoprotein.
The data summarized in this table are from (Steffel et al., 2018).

the 150 mg dose, but also recommended the 110 mg dose as a decreased-dose for frail patients (aging, concomitant verapamil, or other increased breeding risk) (Diener et al., 2017b; Steffel et al., 2018). It should be noted that the 75 mg regimen has not been approved for SPAF by the EMA and NMDA.

The FDA and EMA (but not the NMDA) approved the SPAF indication for apixaban. The efficacy and safety of apixaban for the above indications were instituted by the AVERROES and ARISTOTLE trials (Connolly et al., 2011; Granger et al., 2011). Since apixaban has not been studied in populations in the Chinese mainland, the NMDA did not approve the SPAF indication for apixaban, which has limited the development and application of apixaban in China.

DISCUSSION

In the real world, it is not easy to fully replace NOACs despite the challenges in particular patient cohorts. Because of the clinical heterogeneity of NVAF patients and various clinical features that can change NOACs plasma concentrations, the appraisal of bleeding and stroke rapidly goes beyond the level of detail embodied on the labels (Desmaele et al., 2016). This process may be complicated, especially when a particular clinical profile or multiple risk factors are present, and physicians should make an appropriate decision based on guidelines, evidence-based studies, and risk optimization tools.

Risk of Stroke

Large randomized prospective trials have shown that all NOACs treatments reduced ICH compared to well-controlled VKAs (Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011; Giugliano et al., 2013). A meta-analysis analyzed the findings from the pivotal phase III AF RCTs and showed that NOACs were associated with a lower risk of stroke or SE (~19%) compared to warfarin, mainly due to significant decreases in hemorrhagic stroke and intracranial bleeding (ICB) (Ruff et al., 2014). The ENGAGE AF-TIMI 48 trial illustrated the influence of under-dosing (Giugliano et al., 2013). The Edoxaban 30/15 mg group presented a higher IS rate compared to the well-controlled VKA group, which led to disapproval of this dosing regimen for clinical application. In contrast, in the RE-LY study (Connolly et al., 2009), patients receiving 150 mg dabigatran had significantly reduced IS/SE rates compared to those receiving warfarin, and this higher dose was thus recommended for related clinical application. As with 110 mg of dabigatran and rivaroxaban, apixaban, and 60 mg of edoxaban, the stroke risk was comparable to that of warfarin (Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011; Giugliano et al., 2013).

Elderly

AF incidence increases steadily during the last decades of one's lifespan (Wolff et al., 2015). Given that the stroke risk rises dramatically with age, anticoagulants provide net clinical benefit for older patients. In the phase III NVAF clinical trials (Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011; Giugliano et al., 2013), some distinctions in bleeding risk rates for patients aged ≥ 75 years using different anticoagulants were observed (**Supplementary Material, Figure S2**). For individuals aged ≥ 80 years, a reduction of dabigatran dose to 110 mg was needed. For apixaban, if two out of three risk factors existed (based on age, creatinine, or weight), a reduced dose to 2.5 mg twice daily was recommended. No age-based dose adjustments for rivaroxaban or edoxaban have been recommended (**Table 1**). The EMA recommended dabigatran at 110 mg for patients aged ≥ 75 years with stroke risk, rather than the recommended 110 mg dose from the manufacturer in all NVAF patients aged ≥ 80 years. One previous study of NOACs used in elderly patients indicated a correlation between age and higher extracranial major bleeding with two dabigatran doses (Eikelboom et al., 2011). Conversely, a similar extracranial major bleeding rate was observed with edoxaban, rivaroxaban, and apixaban, independent of age (Halperin et al., 2014; Halvorsen et al., 2014; Kato et al., 2016). The ongoing ELDERCARE-AF study (Okumura et al., 2017) compares the safety and efficacy of edoxaban 15 mg once-daily versus placebo in Japanese NVAF patients aged ≥ 80 years who are not eligible for standard treatment of oral anticoagulation.

Body Weight

Low body weight can increase NOACs exposure and risk of over-dosing (Braekkan et al., 2016). Of note, patients who have a low body weight commonly have other conditions, such as frailty, reduced muscle mass, cancer, and renal impairment, that may add to the risk of bleeding and stroke (Steffel et al., 2018). For patients with low body weight (< 50 kg), a daily dose of 300 or 220 mg dabigatran can be chosen according to the patient's circumstance; dabigatran may be a less preferable option for an under-weight older AF patient with co-existing renal impairment (Undas et al., 2020). Body weight ≤ 60 kg is a dose-decreasing criterion for edoxaban as well as apixaban (if another risk factor

is present). Since the efficacy and safety of edoxaban and apixaban are at least comparable with warfarin in underweight patients (Granger et al., 2011; Giugliano et al., 2013), either should be an appropriate choice for patients weighing < 60 kg. Body weight < 50 kg or > 120 kg only slightly affects plasma concentrations of rivaroxaban (less than 25%), and therefore dosing adjustment is not necessary.

Surprisingly, body weight was not one of the exclusion criteria in any of the NOACs trials for AF patients. Given limited data in extreme body weight, the International Society on Thrombosis and Haemostasis (ISTH) recommended that VKAs be considered for patients with a body weight > 120 kg or a body mass index (BMI) ≥ 40 kg/m^2 (Martin et al., 2016). The European Heart Rhythm Association (EHRA) recommended assessing plasma levels if a patient who is receiving NOACs has a body weight < 50 kg or > 120 kg (Steffel et al., 2018).

Renal Function

Patients with chronic kidney disease (CKD) have an elevated risk of NVAF, IS, and bleeding compared to individuals who have normal kidney function, and the risk further increases with the progression of CKD, especially among dialysis patients (Kalra et al., 2018). Four of the NOACs have varying degrees of renal clearance: 27% for apixaban, 35% for rivaroxaban, 50% for edoxaban, and 80% for dabigatran (Steffel et al., 2018). Thus, the renal function of patients on NOACs should be monitored at least annually. If the kidney functional impairment [i.e. creatinine clearance (CrCl) ≤ 60 ml/min] occurs, assessment should be more frequently executed (Steffel et al., 2018).

In the subgroup analyses of the pivotal phase III AF trials, the four NOACs presented reproducible efficacy and safety in patients who had mild to moderate CKD compared to non-CKD patients (Hijazi et al., 2014; Bohula et al., 2016; Fordyce et al., 2016; Hijazi et al., 2016). These findings suggest that NOACs can be used for patients with mild to moderate kidney dysfunction. Of note, the NOACs trials did not include patients with a CrCl of <30 ml/min (< 25 ml/min for apixaban in the ARISTOTLE trial) (Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011; Giugliano et al., 2013). Currently approved labels allowing use of some NOACs for patients with a CrCl of 15 ml/min is supported by studies from the pharmacokinetic model. Low-dose regimens of rivaroxaban, edoxaban, and apixaban are recommended for patients with severe renal insufficiency (CrCl of 15–29 ml/min) (Turakhia et al., 2018; Jain and Reilly, 2019). In Europe and China, dabigatran (110 and 150 mg) should not be administered to AF patients who have severe kidney impairment (i.e. CrCl < 30 ml/min), whereas in the US, a lower-dose of dabigatran (75 mg) has been approved for AF patients with a CrCl of 15–30 ml/min (Steffel et al., 2018).

It should be noted that rivaroxaban, edoxaban, and apixaban have not been approved for hemodialysis patients in Europe and China, as these patients were excluded from the major clinical trials. However, in the US, apixaban was approved for application in hemodialysis patients in 2014 (Undas et al., 2020). In contrast, NOACs are considered for AF patients undergoing kidney transplantation. In this subset of patients, the dose regimen should be chosen based on the assessed kidney function, and potential drug–drug interactions between the concomitant immunosuppressive agents and NOACs should be taken into account (Steffel et al., 2018). Currently, two ongoing trials, RENAL-AF (NCT 02942407) and AXADIA (NCT 02933697), aim to illustrate the advantages of apixaban over VKAs in AF patients with end-stage kidney disease (ESKD) (Turakhia et al., 2018).

After reviewing the ENGAGE AF-TIMI 48 trial, the FDA concluded that there is potential for decreased efficacy of edoxaban (60 mg QD) among patients with a high CrCl (> 95 ml/min) compared to well-managed warfarin (Bohula et al., 2016). In view of this, the FDA issued a warning: "edoxaban should not be used in patients with a CrCl > 95 ml/min because of an increased IS risk compared to warfarin", and recommended the application of other oral anticoagulation (OAC) agents in these patients[35] (SAVAYSA, 2016). The NMDA and EMA also suggested that, "edoxaban should only be used in NVAF patients with a high CrCl after a careful evaluation of the individual thromboembolic and bleeding risk" (Steffel et al., 2018). A retrospective study of the ENGAGE AF-TIMI 48 data suggested that, although there was an evident reduction in the efficacy of edoxaban 60 mg QD, its net clinical benefit and safety were comparable with those of warfarin in AF patients who had various degrees of renal impairment (Bohula et al., 2016).

Risk of Gastrointestinal Bleeding (GIB)

Several systematic reviews concluded that patients treated with NOACs had an increased GIB rate (Kovacs et al., 2015; Silverio et al., 2019). In patients at high-risk of GIB, VKA, or another NOAC other than dabigatran 150 mg, rivaroxaban 20 mg QD, or edoxaban 60 mg QD BID is preferable (**Supplementary Material, Figure S3**), as supported by the finding that the use of NOACs (especially full-dose rivaroxaban and dabigatran) was closely correlated with higher GIB events (Kirchhof et al., 2016). In RE-LY, dabigatran 110 mg BID was comparable to warfarin with regards to GIB risk, but dabigatran 150 mg BID was associated with increased GIB risk compared to warfarin (Connolly et al., 2009). In ROCKET AF, rivaroxaban 20 mg QD had a greater GIB annual risk than warfarin (Goodman et al., 2014), and administration of rivaroxaban to patients aged ≥75 years also significantly increased GIB risk compared to warfarin (Halperin et al., 2014). The ENGAGE AF-TIMI trial showed a higher GIB risk with edoxaban 60 mg QD than with warfarin (HR 1.23), and correspondingly, a low-dose edoxaban (30 mg QD) was linked to a less GIB risk (Giugliano et al., 2013). NOAC-linked GIB is potentially associated with the following considerations: 1) Anticoagulation can be local or systematic, and the existence of the active agent in the GI tract may promote bleeding from susceptible lesions. 2) NOACs may suppress GI mucosal healing. 3) Dabigatran or etexilate contains tartaric acid, which may induce direct caustic injury (Cheung and Leung, 2017). Although having a GIB history is not a contraindication for NOACs therapy, the existence of GI lesions, including GI ulceration, is contraindicated for administering NOACs.

Combination of Antiplatelet Therapy

NVAF patients with stable coronary artery disease (CAD) or acute coronary syndrome (ACS) may need percutaneous coronary intervention (PCI) (Diener et al., 2017a). Since antiplatelet treatment is the key treatment for patients with ACS, CAD, or PCI, a combined therapy with anticoagulation is generally required for NVAF patients. In these patients with a high risk of complications, the risks of stent thrombosis, stroke, and bleeding (particularly intracranial hemorrhage) need to be considered. Stacking antithrombotic preparations (i.e. adding two anti-platelets to NOACs) will remarkably increase the bleeding risk, thus preventing the long-term triple therapy in daily practice (Steffel et al., 2018; January et al., 2019). To date, four prospective RCTs addressed the issue of OAC with ACS and/or undergoing PCI by comparing NOACs and warfarin in various combinations with antiplatelet agents (**Table 2**).

In the PIONEER AF-PCI trial, two different dosing regimens containing rivaroxaban [rivaroxaban 15 mg with a P2Y12 inhibitor (rivaroxaban 10 mg in patients with a CrCl of 30–50 ml/min), or a P2Y12 inhibitor with rivaroxaban 2.5 mg twice daily and aspirin] were examined with standard triple therapy [VKAs and dual antiplatelet therapy (DAPT)] (Gibson et al., 2016). This trial suggested that both rivaroxaban regimens significantly decreased the rates of severe bleeding during a 1-year follow-up period compared with the standard triple treatment, although the sample size was too small to have a significant difference statistically.

In the RE-DUAL PCI trial, the safety of clopidogrel or ticagrelor (without aspirin) and two dosages of dabigatran (150 or 110 mg BID) were compared with standard triple therapy containing aspirin, VKA, and either ticagrelor or clopidogrel in NVAF patients undergoing PCI (Cannon et al., 2017). The RE-DUAL PCI trial was not designed for individual efficacy endpoints; instead, the goal of this trial was to show whether the combined dual-treatment arms were inferior to the triple treatment arm with regard to various endpoints including thromboembolic events, death, and unplanned revascularization. It showed that both doses of dabigatran substantially lowered the major and non-major bleeding events, and were superior (150 mg) or non-inferior (110 mg) to VKA for SPAF.

The AUGUSTUS trial was an international trial with a two-by-two factorial design (Lopes et al., 2019). A total of 4,614 NVAF patients with PCI or ACS who planned to take a P2Y12 inhibitor were administered apixaban or VKA, and received aspirin or a placebo for 6 months. The primary endpoint was major or clinically relevant non-major (CRNM) bleeding, and the secondary endpoints included hospitalization or death and a composite of ischemic events. This study indicated that an antithrombotic regimen (with apixaban, without aspirin) group had fewer hospitalizations and bleeding events, but had comparable ischemic events compared with the regimen groups including aspirin, VKA, or both. AUGUSTUS also showed that dual therapy strategies (clopidogrel plus NOACs) were safer than the dual therapy of clopidogrel plus VKA with regard to bleeding risk.

The ENTRUST AF-PCI study was designed to reveal appropriate dosing regimens of antithrombotic therapy for NVAF patients with PCI. These patients received edoxaban (60 mg once daily, or reduced to 30 mg per day based on CrCl, body weight, or P-gp inhibitors) plus a P2Y12 inhibitor for 12 months, or VKA combining a P2Y12 inhibitor and aspirin for 1–12 months (Vranckx et al., 2019). This trial revealed that for NVAF patients who had PCI, the edoxaban-based regimen was not inferior to the VKA-based regimen in terms of bleeding events and was comparable in terms of ischemic events.

TABLE 2 | Trial profiles for the four NOACs with ACS or PCI in atrial fibrillation[a].

	Dabigatran (RE-DUAL PCI)	Rivaroxaban (PIONEER AF-PCI)		Apixaban (AUGUSTUS)	Edoxaban (ENTRUST AF-PCI)
Standard dose	150 mg twice daily or 110 mg twice daily	15 mg once daily	2.5 mg twice daily	5 mg twice daily	60 mg twice daily
Dose reduction in selected patients	No dose reduction	Rivaroxaban 10 mg once daily if CrCl 30–49 ml/min	No dose reduction	Apixaban 2.5 mg twice daily if at least two: age ≥80 years, body weight no more than 60 kg, serum creatinine ≥1.5 mg/dl (133 μmol/L)	Edoxaban 30 mg once daily if one or more factors were present: creatinine clearance of 15–50 ml/min, body weight ≤60 kg, concomitant use of specified potent P-glycoprotein inhibitors
P2Y12 inhibitor	P2Y12 inhibitor (clopidogrel or ticagrelor)	P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor) for 12 months	Dual antiplatelet therapy (DAPT) for 1, 6, or 12 months	Planned to use a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor) for at least 6 months	P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor) for 12 months
Study design	Randomized, open-label	Randomized, open-label		Randomized, two-by-two factorial, apixaban with VKA was open-label; aspirin with matching placebo was double-blind	Randomized, open-label
Number of patients	2,725	2,124		4,614	1,506

[a]*As outlined in detail, the four clinical trials were designed to evaluate safety, but not designed to determine non-inferiority for efficacy endpoints.*
NOAC, non-vitamin K antagonist oral anticoagulants; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; CrCl, creatinine clearance.
The data summarized in this table are from (Gibson et al., 2016; Cannon et al., 2017; Lopes et al., 2019; Vranckx et al., 2019).

According to the published RCTs, compared to the VKA regimen, the NOACs regimens (excluding edoxaban) appeared to lower the bleeding risk. Due to the fact that the above-mentioned trials were under-powered to assess the risk of thrombosis, it is still not known whether dual therapy (a NOAC plus a P2Y12 inhibitor) can sufficiently protect against myocardial infarction or stent thrombosis. Furthermore, the above-mentioned studies did not have a sufficient number of cases to obtain conclusive data regarding the safety of combined use of prasugrel or ticagrelor with P2Y12 inhibitors in dual or triple regimens. Hence, the safety of carrying out a PCI in NVAF patients on a NOAC needs to be further assessed in future prospective studies with large cohorts (Steffel et al., 2018).

CRITICAL DISCUSSIONS

It is becoming increasingly clear that AF does not always act as a source of emboli. Using cardiac pacemakers and implantable cardioverter-defibrillators that store electrocardiogram (ECG) information for months, it was shown that emboli in many patients occur without AF (Healey et al., 2012; Brambatti et al., 2014). Hence, the current thinking is that AF may just be a marker of vascular disease but not the main cause of emboli.

Ethnic differences between Asians and non-Asians may also influence the optimal dosing of anticoagulants. Due to genetic differences or various eating habits, Asian populations, at least Japanese and Taiwanese populations, have lower levels of AF compared to Americans. This leads to clinical diversity in treatment approaches. For instance, acetylsalicylic acid is not useful for preventing AF complications in Japanese populations.

In addition, drug-drug interactions require further appraisal. The pharmacokinetic properties of NOACs may be a significant factor. In contrast to earlier claims by the industry that metabolism and the renal transport system play no clinically relevant role in NOACs efficacy and safety, there is now experimental evidence in cell culture and animal models, but more importantly in humans, that CYP450 enzymes and P-glycoprotein (P-gp) can affect NOACs pharmacokinetics (**Supplementary Material, Table S2**). Some interactions with common cardiovascular drugs, such as amiodarone, dronedarone, verapamil, and diltiazem have been previously discussed (**Supplementary Material, Table S3**) (Wiggins et al., 2020). Moreover, Chinese and Japanese patients seem to have alterations in CYP expression and function. Unfortunately, how these interactions affect the efficacy and safety of NOACs remains largely unknown. In summary, physicians should pay careful attention to patient ethnicity to determine who could be poor or rapid metabolizers (CYP450 system) and who may encounter unfavorable drug interactions and increased incidence of bleeding.

CONCLUSION

NOACs have been approved to treat NVAF patients to diminish the risk of IS and SE in various countries due to their efficacy and safety profiles, which are either comparable or superior to those of the conventional treatment of warfarin, as presented in real-life registries and RCTs. First, nearly all landmark NOACs trials have excluded patients with a CrCl of <30 ml/min (with the exception of come patients on apixaban with CrCl 25–30 ml/min). However, the anticoagulant decision should be individualized, using a multidisciplinary approach based on a participant's preferences. Second, even though there has been an increase in the use of NOACs, a certain proportion of patients remains on warfarin due to the high price of NOACs. Third, NOACs prescription and availability are regulated differently across countries. This is due to differences in inclusion criteria for RCTs. Fourth, NOACs either have not been researched or have demonstrated unfavorable results in patients with mechanical prosthetic heart valves or moderate to severe mitral stenosis (usually of rheumatic origin), in which circumstances warfarin continues to be the main treatment. Finally, despite the fact that NOACs possess relatively small drug interactions, physicians should carefully appraise the pharmacokinetic influences of accompanying medications (CYP and/or P-glycoprotein inducers or inhibitors) and comorbidities when prescribing NOACs.

Thus, this article serves as a guide outlining the suggested NOACs dosages for NVAF patients, and an overview on NOACs performance in AF patients with particular clinical characteristics. Our conclusions are based on dose adjustment recommendations in the literature, with the goal of presenting a simple and workable strategy for clinicians to choose appropriate NOACs.

ETHICS STATEMENT

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SZ and PM raised the concept and design of the research. SZ wrote the manuscript. XH, JC, HC and SD revised the article for important details. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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SYSTEMATIC REVIEW
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Effectiveness and Safety of Oral Anticoagulants in Older Patients With Atrial Fibrillation: A Systematic Review and Meta-Analysis

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Background and Objective: Atrial fibrillation (AF), the most common cardiac arrhythmia, typically increases with age. Oral anticoagulants (OACs) are the cornerstone of treatment to reduce the associated risk for systemic thromboembolism. Four large randomized controlled trials (RCTs) have shown that non-vitamin K antagonist oral anticoagulants (NOACs) are non-inferior to vitamin K antagonists (VKAs) in preventing stroke and systemic embolism, as well as regarding their risk for major bleeding. However, as vulnerable geriatric patients with AF were largely underrepresented in these trials, physicians are faced with the challenge of choosing the right anticoagulant for geriatric patients in real-life clinical practice. In this vulnerable patient group, NOACs tend to be underused or underdosed due to concerns of excessive fall-related intracranial bleeding, cognitive impairment, multiple drug-drug interactions, low body weight or impaired renal function. As life expectancy continues to rise worldwide, the number of geriatric patients substantially increases. Therefore, there is an urgent need for a critical appraisal of the added value of NOACs in geriatric patients with AF at high thromboembolic and bleeding risk.

Methods and Results: This systematic review provides an overview of the literature on the impact of increased age (≥75 years), multimorbidity, polypharmacy, increased falling risk, frailty and dementia on the effectiveness and safety of NOACs as compared to VKAs, after searching the Medline database. Moreover, a meta-analysis on the impact of increased age ≥75 years old was performed after pooling results from 6 *post hoc* analyses of RCTs and 6 longitudinal observational cohort studies, highlighting the superior effectiveness (hazard ratio (HR) 0.83, 95% confidence interval (CI) [0.74–0.94] for stroke/SE; HR 0.77, 95%CI [0.65–0.92] for mortality) and non-inferior safety (HR 0.93, 95%CI [0.86–1.01] for major bleeding; HR 0.58, 95%CI [0.50–0.67] for intracranial bleeding; HR 1.17, 95%CI [0.99–1.38] for gastrointestinal bleeding) of NOACs versus VKAs in older AF patients.

Conclusion: Across geriatric subgroups, apixaban was consistently associated with the most favourable benefit-risk profile and should therefore be preferred in geriatric patients with AF. However, research gaps on the impact of increased falling risk, frailty and baseline dementia were identified, requiring careful consideration while awaiting more results.

Keywords: atrial fibrillation, oral anticoagulant, increased age, multimorbidity, polypharmacy, fall, frailty, dementia

INTRODUCTION

As life expectancy continues to rise worldwide, the number of geriatric patients substantially increases (Beard et al., 2016). In older patients ≥75 years old, multimorbidity, polypharmacy, recurring falling incidents, frailty and dementia tend to rise in prevalence and tend to coincide (Jaspers Focks et al., 2016; Piccini et al., 2016; Steffel et al., 2016; Rao et al., 2018; Martinez et al., 2018; Alexander et al., 2019). Although high age, frequently defined in studies as ≥75 years, is not a de facto criterion for a geriatric profile, it has been independently associated with higher risks of systemic thromboembolism, major bleeding, intracranial bleeding and mortality (Wolf et al., 1991; Oldgren et al., 2011; Halvorsen et al., 2014; Kato et al., 2016; Chao et al., 2020; Kirchhof et al., 2020). Moreover, the incidence and prevalence of atrial fibrillation (AF), the most frequent cardiac arrhythmia worldwide, typically increases with age (Heeringa et al., 2006; Lee et al., 2017). Oral anticoagulants (OACs) are crucial to reduce the associated risk of systemic thromboembolism in non-valvular AF (hereby referenced as AF) (Steffel et al., 2018). Four large phase III randomized controlled trials (RCTs) (RE-LY trial for dabigatran (Connolly et al., 2009), ROCKET AF trial for rivaroxaban (Patel et al., 2011), ARISTOTLE trial for apixaban (Granger et al., 2011), ENGAGE AF-TIMI 48 trial for edoxaban (Giugliano et al., 2013)) have shown that non-vitamin K antagonist oral anticoagulants (NOACs) are at least non-inferior for stroke prevention and for the risk of bleeding events as compared to vitamin K antagonists (VKAs) (Connolly et al., 2009; Patel et al., 2011; Granger et al., 2011; Giugliano et al., 2013; Ruff et al., 2014). However, concerns have risen regarding the effectiveness and safety of NOACs in real-life clinical practice in patients with multiple comorbidities and concomitant medication use, especially vulnerable geriatric patients with AF who were largely underrepresented in these trials (Lee et al., 2012). Consequently, NOACs tend to be underused or underdosed in these patients due to concerns of excessive fall-related intracranial bleeding, cognitive impairment with suboptimal therapy adherence, multiple drug-drug interactions (DDIs), low body weight or impaired renal function (Viscogliosi et al., 2017; Oqab et al., 2018; Proietti et al., 2019; Madhavan et al., 2019; Besford et al., 2020; Kapoor et al., 2020; Sanghai et al., 2020). Therefore, there is an urgent need for a critical appraisal of the added value of NOACs in geriatric patients with AF at high thromboembolic and bleeding risk.

This systematic review will provide an overview of the literature on the impact of increased age (≥75 years), multimorbidity, polypharmacy (≥5 drugs) (Masnoon et al., 2017), high falling risk, frailty and dementia on the effectiveness and safety of NOACs versus VKAs in geriatric patients with AF. Moreover, a meta-analysis on the impact of increased age ≥75 years old on NOAC versus VKA effectiveness and safety will be performed. Thereby, this overview will help guide physicians in their OAC choice for vulnerable older patients with AF.

METHODS

A thorough literature search was performed using the Medline database by one reviewer (MG) (see supplemental materials, **eTable 1**). Articles related to oral anticoagulant use for stroke prevention in adult patients with non-valvular AF and increased age (≥75 years), multimorbidity, polypharmacy (≥5 drugs), high falling risk, frailty and baseline dementia were selected. Only studies longitudinally comparing the effectiveness and safety of NOACs (dabigatran, rivaroxaban, apixaban and/or edoxaban) compared to VKAs (warfarin, phenprocoumon and/or acenocoumarol) during a mean/median follow-up of at least 3 months in these patient subgroups were included. Studies regarding OAC use for non-AF indications (e.g. venous thromboembolisms or mechanic heart valves) were excluded if no separate results of patients with AF were provided. Effectiveness and safety outcomes of interest were stroke or systemic embolism (stroke/SE), major bleeding (overall, intracranial and/or gastrointestinal) and all-cause mortality. RCTs (original trial or *post hoc* analyses), longitudinal observational cohort studies and meta-analyses written in English were included for a qualitative synthesis, while reviews, cross-sectional studies, case reports, editorials or conference proceedings were left out of consideration. For a quantitative synthesis (meta-analysis), only *post hoc* analyses of RCTs and longitudinal observational cohort studies regarding the impact of increased age ≥75 years old on NOAC versus VKA effectiveness (stroke/SE, mortality) and safety (major, intracranial and gastrointestinal bleeding) were included. Studies including even older AF patients (e.g. ≥80, 85, or 90 years old) were not included in the meta-analysis, due to concerns of channelling bias (Alcusky et al., 2020) in the introduction years and selective prescribing (of NOACs to more comorbid patients) later on, and more frequent inappropriate NOAC dosing in observational studies (Shinohara et al., 2019; Raposeiras-Roubín et al., 2020) in the oldest AF patients. However, these results were included in an additional subgroup analysis. No restriction of publication date was used.

On April 24, 2020, 4358 articles were identified. Additional articles of interest were identified by screening the reference list of studies. After screening title and abstract, 80 articles were selected by one reviewer. After reading the full-text, 50 articles were selected for the qualitative synthesis and 12 for a quantitative synthesis (i.e. 6 *post hoc* analyses of RCTs, 6

observational studies) (**Figure 1**). An overview of the included studies with study design, patient characteristics and outcome measures are displayed in tables (**eTables 2–7**).

For the impact of increased age ≥75 years old, a meta-analysis was performed using a random effects model with inverse-variance weighting with the metafor package in R (R version 3.6.1 with RStudio version 1.2.5001), by pooling results based on the logarithmic adjusted hazard ratios (HRs) and standard error. Data on the study characteristics (design, setting and duration), baseline characteristics of included patients (total number and age), intervention (e.g. NOAC versus VKA) and the abovementioned effectiveness and safety outcomes of interest were extracted from the original publications or supplemental materials. Effect sizes were presented as HR with 95% confidence interval (95%CI) for the outcome of interest of NOAC versus VKA users in forest plots using the forestplot package in R. A two-sided p-value of <0.05 was considered statistically significant. Heterogeneity was tested using the I^2-statistic and Cochran's Q-test, based on a restricted maximum-likelihood estimator. To assess the risk of bias of each study included in the meta-analysis, the quality assessment tool "QUALSYST" from the "Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields" was used (**eTable 8**) (Kmet et al., 2004). With this tool, 14 items of each quantitative study were scored on the study and outcome levels

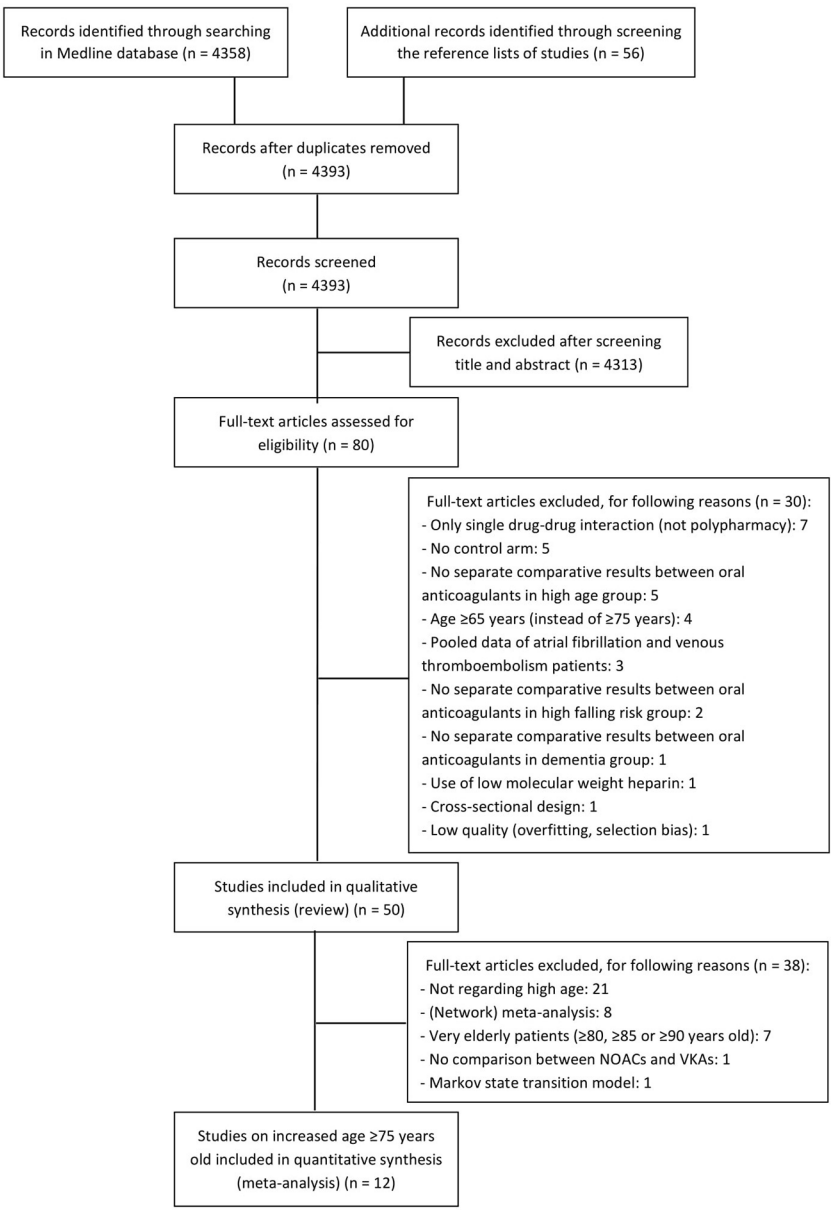

FIGURE 1 | PRISMA flow diagram.

depending on the degree to which the specific criteria were met or reported ("yes" = 2, "partial" = 1, "no" = 0). Items not applicable to a particular study design were marked "n/a" and were excluded from the calculation of the summary score. A percentage was calculated for each paper by dividing the total sum score obtained across rated items by the total possible score. Studies were included if scoring at least 80% on the quality assessment tool. The risk of publication bias at the outcome level for the studies included in the meta-analysis was assessed through funnel plot asymmetry and Egger's regression test. This work has been performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (PRISMA checklist included in supplemental materials, **eTable 9**).

RESULTS

Increased Age

Randomized Studies

Several *post hoc* analyses and meta-analyses of the pivotal phase III RCTs have been performed, illustrating similar stroke/SE and mortality risks with reduced dose NOACs in AF patients ≥75 years old as compared to warfarin, whereas significantly lower stroke/SE and mortality risks with standard dose NOACs were observed (**eTable 2**) (Ruff et al., 2014; Sadlon and Tsakiris, 2016; Kim et al., 2018; Caldeira et al., 2019; Malik et al., 2019). Furthermore, besides a significantly lower intracranial bleeding risk and a similar major bleeding risk for both standard and reduced dose NOACs (Ruff et al., 2014; Sadlon and Tsakiris, 2016; Kim et al., 2018; Caldeira et al., 2019; Malik et al., 2019), a similar to significantly higher gastrointestinal bleeding risk for reduced and standard dose NOACs respectively has been illustrated (Kim et al., 2018; Malik et al., 2019). However, substantial heterogeneity was detected in these meta-analyses for the bleeding risk assessment in older patients (I^2-value ranging from 84% (Malik et al., 2019) to 94%) (Kim et al., 2018), potentially attributed to differences in the safety profile of individual NOACs (Sadlon and Tsakiris, 2016; Kim et al., 2018; Caldeira et al., 2019; Malik et al., 2019). Indeed, in the individual *post hoc* analyses of RCTs, an increased bleeding risk for dabigatran and rivaroxaban was observed in older AF patients, as opposed to lower risks for apixaban and edoxaban.

In a subgroup analysis of the RE-LY trial, a significant interaction between age and treatment for major and gastrointestinal bleeding was seen for dabigatran (Eikelboom et al., 2011). In AF patients ≥75 years old, similar major bleeding and significantly higher gastrointestinal bleeding risks were seen for both dabigatran doses (Eikelboom et al., 2011). In AF patients 80–84 years old, significantly higher major bleeding and major extracranial bleeding risks, and a similar intracranial bleeding risk was observed for standard dose dabigatran (150 mg), whereas a significantly lower intracranial bleeding, similar major bleeding and significantly higher extracranial bleeding risk was noted for reduced dose dabigatran (110 mg) as compared to warfarin (Lauw et al., 2017). The point of reversal from lower to higher major bleeding rates along the age spectrum was estimated to be >77 years for dabigatran 150 mg and >80 years for dabigatran 110 mg. For extracranial major bleeding, this reversal point was >74 years and >76 years respectively. Based on these results, an age of 75–80 years was implemented as a criterion to consider dose reduction and ≥80 years of age was implemented as a dose reduction criterion for dabigatran (Boehringer Ingelheim, 2010; Eikelboom et al., 2011). Nonetheless, these results illustrate the potentially worse safety outcomes for dabigatran in older patients, especially regarding the gastrointestinal bleeding risk. Moreover, worse safety outcomes have been observed for rivaroxaban in AF patients ≥75 years old, as a *post hoc* analysis of the ROCKET AF trial documented significantly higher gastrointestinal bleeding risks, whereas similar major bleeding and intracranial bleeding risks for rivaroxaban as compared to warfarin were noted (Halperin et al., 2014). Similarly, in the Japanese J-ROCKET AF trial, rivaroxaban use in older AF patients was associated with a similar major bleeding risk (Hori et al., 2014). On the contrary, apixaban use has been associated with a significantly lower major bleeding, intracranial bleeding and major bleeding risk as compared to warfarin in AF patients ≥75 years old in a subgroup analysis of the ARISTOTLE trial (no report of gastrointestinal bleeding risk) (Halvorsen et al., 2014). Even in an exploratory analysis among AF patients ≥80 years old, superior safety results were observed. Likewise, edoxaban use in AF patients ≥75 years old was associated with a similar (standard dose edoxaban) to significantly lower (reduced dose edoxaban) major bleeding risk and a significantly lower intracranial bleeding risk as compared to warfarin in a *post hoc* analysis of the ENGAGE AF-TIMI 48 trial, although a significantly higher gastrointestinal bleeding risk was observed (Kato et al., 2016). Results were consistent in patients ≥80 and ≥85 years old.

Based on the abovementioned results, network meta-analyses have specifically compared the efficacy and safety of NOACs in AF patients ≥75 years old (Lin et al., 2015; Sadlon and Tsakiris, 2016; Malik et al., 2019; Deng et al., 2020). Despite a similar stroke/SE risk (Lin et al., 2015; Sadlon and Tsakiris, 2016; Malik et al., 2019), these indirect head-to-head comparisons between NOACs have highlighted significantly lower major bleeding risks for apixaban and edoxaban as compared to dabigatran (both doses) and rivaroxaban, except for a similar risk between edoxaban and dabigatran 110 mg (Lin et al., 2015; Sadlon and Tsakiris, 2016; Malik et al., 2019). No significant differences in major bleeding were observed when indirectly comparing apixaban to edoxaban, and dabigatran to rivaroxaban (Lin et al., 2015; Malik et al., 2019). Importantly, rivaroxaban was associated with a significantly higher risk for intracranial bleeding as compared to other NOACs (Lin et al., 2015; Malik et al., 2019). Moreover, a network meta-analysis that estimated the rank probability of OACs in AF patients ≥75 years old, which reflects the hierarchy of drugs on efficacy and safety, showed that apixaban ranked best on both stroke/SE prophylaxis (followed by rivaroxaban, edoxaban, dabigatran 110 mg and warfarin) and major bleeding risk (followed by edoxaban, dabigatran 110 mg, warfarin, and rivaroxaban) (Deng et al., 2020). In another network meta-analysis, although dabigatran 150 mg ranked best on efficacy outcomes followed by apixaban, apixaban also

ranked best on safety measures while dabigatran 150 mg the worst (Malik et al., 2019).

In conclusion, these *post hoc* analyses and meta-analyses of RCTs have shown that apixaban is associated with the best efficacy and safety profile of all OACs in older AF patients, followed by edoxaban (Lin et al., 2015; Sadlon and Tsakiris, 2016; Malik et al., 2019; Deng et al., 2020).

Observational Studies

As older AF patients included in RCTs may have been relatively less comorbid and more compliant, there are concerns regarding the extrapolation of these results to real-life clinical practice. Moreover, the number of very old patients (≥85 years old) was limited in these RCTs. Therefore, post-surveillance observational studies are equally important in the evaluation of the effectiveness and safety of NOACs in older AF patients. Several have been performed in different age strata, however, mostly without edoxaban data, and have described comparable results as the randomized studies, illustrating the non-inferior to superior effectiveness and safety of NOACs over VKAs, the benefit of OAC continuation over discontinuation and the superior safety profile of apixaban (**eTable 2**).

In terms of effectiveness, NOACs had an equal stroke/SE risk as compared to VKAs in AF patients ≥75, ≥80, ≥85, and ≥90 years old (Avgil-Tsadok et al., 2016; Lai et al., 2018; Giustozzi et al., 2019; Hohmann et al., 2019; Nishida et al., 2019; Mitchell et al., 2019; Russo et al., 2019; Shinohara et al., 2019; Alcusky et al., 2020). Some studies even described a significantly lower stroke/SE (Deitelzweig et al., 2019; Kim et al., 2019) and ischemic stroke risk (Mitchell et al., 2019; Deitelzweig et al., 2019; Chao et al., 2020), as opposed to a higher stroke/transient ischemic attack (TIA) risk in one small Italian study (Poli et al., 2019) and a borderline increased ischemic stroke/TIA risk for apixaban in another study due to off-label underdosing (Alcusky et al., 2020). Mortality rates in NOAC users were similar (Nishida et al., 2019; Mitchell et al., 2019) to even significantly lower (Deitelzweig et al., 2019; Kim et al., 2019; Poli et al., 2019; Russo et al., 2019; Alcusky et al., 2020; Chao et al., 2020) as compared to warfarin. In terms of safety, NOACs were associated with a similar (Giustozzi et al., 2019; Mitchell et al., 2019; Nishida et al., 2019; Poli et al., 2019; Russo et al., 2019; Chao et al., 2020) to lower (Kim et al., 2019; Shinohara et al., 2019; Nishida et al., 2019; Chao et al., 2020; Wong et al., 2020) major bleeding, a similar (Hohmann et al., 2019; Kim et al., 2019) to significantly higher (Mitchell et al., 2019; Wong et al., 2020) gastrointestinal bleeding and a lower (Hohmann et al., 2019; Kim et al., 2019; Mitchell et al., 2019; Chao et al., 2020; Wong et al., 2020) intracranial bleeding risk (except for a similar risk in one study) (Russo et al., 2019) as compared to VKAs in AF patients ≥75, ≥80, ≥85 and ≥90 years old (Shinohara et al., 2019; Hohmann et al., 2019; Nishida et al., 2019; Mitchell et al., 2019; Giustozzi et al., 2019; Russo et al., 2019; Kim et al., 2019; Poli et al., 2019; Chao et al., 2020). Interestingly, in AF patients ≥90 years old, the use of NOACs as compared to no anticoagulation was associated with a significantly lower risk for the composite effectiveness endpoint (stroke/SE, pulmonary embolism and death), and a borderline similar risk for major bleeding and intracranial bleeding (Raposeiras-Roubín et al., 2020). On the contrary, VKAs as compared to no anticoagulation were associated with a similar risk for the composite effectiveness endpoint, but a significantly higher risk for major bleeding and intracranial bleeding (Raposeiras-Roubín et al., 2020). This differential safety profile was also illustrated in a Markov state transition model, demonstrating a lack of net clinical benefit for warfarin as compared to no anticoagulation after the age of 87, whereas only after the age of 92 for apixaban (Shah et al., 2019). In other words, even the oldest AF patients appear to still benefit from NOACs instead of discontinuing anticoagulation.

Moreover, in line with randomized studies, differences in safety outcomes between NOACs were seen. Apixaban was associated with a significantly lower major bleeding and intracranial bleeding risk as compared to VKAs in ≥75 and ≥80 year old AF patients (Deitelzweig et al., 2019; Hohmann et al., 2019; Alcusky et al., 2020; Wong et al., 2020). Importantly, as the ARISTOTLE trial did not provide data on the gastrointestinal bleeding risk of apixaban in older AF patients, observational studies were reassuring, illustrating a similar (Wong et al., 2020). to significantly lower (Deitelzweig et al., 2019; Hohmann et al., 2019) gastro-intestinal bleeding risk of apixaban as compared to VKAs in older AF patients. Dabigatran was associated with a similar (Avgil-Tsadok et al., 2016; Deitelzweig et al., 2019; Alcusky et al., 2020) to significantly lower (Wong et al., 2020) major bleeding risk, a similar (Lai et al., 2018; Deitelzweig et al., 2019; Hohmann et al., 2019; Wong et al., 2020) to a significantly higher (Avgil-Tsadok et al., 2016) gastrointestinal bleeding risk, and a significantly lower (Avgil-Tsadok et al., 2016; Lai et al., 2018; Deitelzweig et al., 2019; Wong et al., 2020) intracranial bleeding risk as compared to warfarin in ≥75 in ≥75, ≥80 and ≥85 year old, ≥80 in ≥75, ≥80 and ≥85 year old, and ≥85-year-old AF patients (Avgil-Tsadok et al., 2016; Lai et al., 2018; Deitelzweig et al., 2019; Hohmann et al., 2019; Alcusky et al., 2020; Wong et al., 2020). On the contrary, rivaroxaban was associated with a similar (Alcusky et al., 2020) to significantly higher (Deitelzweig et al., 2019; Wong et al., 2020) major bleeding risk, a similar (Lai et al., 2018) to significantly higher (Deitelzweig et al., 2019; Hohmann et al., 2019; Wong et al., 2020) gastrointestinal bleeding risk, and a similar (Lai et al., 2018) to significantly lower (Deitelzweig et al., 2019; Wong et al., 2020) intracranial bleeding risk as compared to warfarin in ≥75 in ≤75, ≤80 and ≤85 year old, ≥80 in ≤75, ≤80 and ≤85 year old, and ≥85 in ≤75, ≤80 and ≤85 year old year-old AF patients (Lai et al., 2018; Deitelzweig et al., 2019; Hohmann et al., 2019; Alcusky et al., 2020; Wong et al., 2020). In a head-to-head comparison between NOACs in AF patients ≥80 years, apixaban was associated with a significantly lower risk of stroke/SE, major bleeding, gastrointestinal bleeding and mortality as compared to dabigatran and rivaroxaban, and even a significantly lower risk of intracranial bleeding as compared to rivaroxaban (Deitelzweig et al., 2019).

In conclusion, observational studies have illustrated the non-inferior to superior effectiveness and safety profile of NOACs as compared to VKAs in older AF patients, with most reassuring data on apixaban. Importantly, even in the oldest AF patients

≥90 years old, NOAC use was still beneficial over OAC discontinuation (Raposeiras-Roubín et al., 2020).

Meta-Analysis

After pooling the results of 6 *post hoc* analyses of RCTs and 6 observational studies in a meta-analysis, a significantly lower stroke/SE and all-cause mortality risk of NOACs versus VKAs in AF patients ≥75 years old was observed (HR 0.83, 95%CI [0.74-0.94], I^2 26.1% for stroke/SE; HR 0.77, 95%CI [0.65-0.92], I^2 91.7% for mortality) (**Figures 2** and **3**). The considerable heterogeneity noted for mortality outcomes may be due to heterogeneous mortality results in two observational studies (Nishida et al., 2019; Chao et al., 2020). When performing a sensitivity analysis excluding these two studies, a significantly lower all-cause mortality risk was still present and heterogeneity was low (HR 0.79, 95%CI [0.73-0.86], I^2 34.7%, **eFigure 1**).

Major bleeding risks were similar between NOACs and VKAs (HR 0.93, 95%CI [0.86–1.01]), although substantial heterogeneity was present (I^2 84.6%), probably due to differential safety profiles of the different types of NOACs used in older AF patients as discussed above (**Figure 4**). Indeed, when performing a sensitivity analysis specifically comparing dabigatran and rivaroxaban to VKAs, major bleeding risks were similar (HR 1.00, 95%CI [0.92–1.09]) with lower but still substantial heterogeneity detected (I^2 76.8%) (**eFigure 2A**), although driven by heterogeneous results from observational studies (I^2 0.00% for results from RCTs, I^2 82.6% for results from observational studies) (**eFigures 2B, C**). When specifically comparing apixaban and edoxaban to VKAs, major bleeding risks were significantly lower (HR 0.77, 95%CI [0.65–0.91], I^2 70.9%) (**eFigure 2D**).

Furthermore, a significantly lower intracranial bleeding (HR 0.58, 95%CI [0.50–0.67], I^2 63.1%) and a borderline similar gastrointestinal bleeding risk (HR 1.17, 95%CI [0.99–1.38], I^2 91.5%) were observed for NOACs as compared to VKAs (**Figures 5** and **6**). In a sensitivity analysis specifically comparing results from dabigatran, rivaroxaban, and edoxaban to VKAs, a significantly higher gastrointestinal bleeding risk (HR 1.28, 95% CI [1.13–1.46], I^2 82.6%) was demonstrated (**eFigure 3A**), with substantial heterogeneity driven by dabigatran results (I^2 81.9% for dabigatran, I^2 0.00% for rivaroxaban, not performed for edoxaban as only one study was available) (**eFigures 3B, C**). However, when

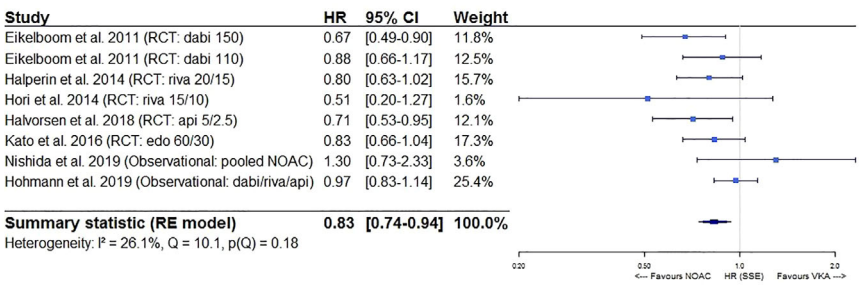

FIGURE 2 | Forest plot of the risk of stroke or systemic embolism of NOACs versus VKAs in elderly atrial fibrillation patients ≥75 years old. Api 5/2.5, apixaban 5 mg (standard dose) and 2.5 mg (reduced dose); CI, confidence interval; Dabi 150, dabigatran 150 mg (standard dose); Dabi 110, dabigatran 110 mg (reduced dose); Edo 60/30, edoxaban 60 mg (standard dose) and 30 mg (reduced dose); HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant; RCT, randomized controlled trial (*post hoc* analysis); RE model, random effects model; Riva, rivaroxaban; Riva 20/15, rivaroxaban 20 mg (standard dose) and 15 mg (reduced dose); Riva 15/10, rivaroxaban 15 mg (standard dose) and 10 mg (reduced dose); Stroke/SE, stroke/systemic embolism; VKA, vitamin K antagonist.

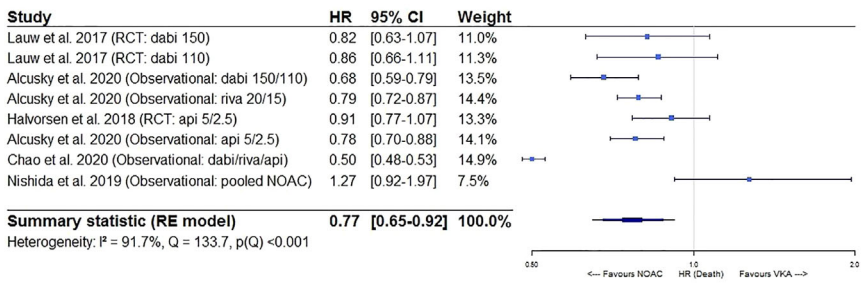

FIGURE 3 | Forest plot of the risk of all-cause mortality of NOACs versus VKAs in elderly atrial fibrillation patients ≥75 years old. Api 5/2.5, apixaban 5 mg (standard dose) and 2.5 mg (reduced dose); CI, confidence interval; Dabi 150, dabigatran 150 mg (standard dose); Dabi 110, dabigatran 110 mg (reduced dose); Death, all-cause mortality; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant; RCT, randomized controlled trial (*post hoc* analysis); RE model, random effects model; Riva, rivaroxaban; Riva 20/15, rivaroxaban 20 mg (standard dose) and 15 mg (reduced dose); VKA, vitamin K antagonist.

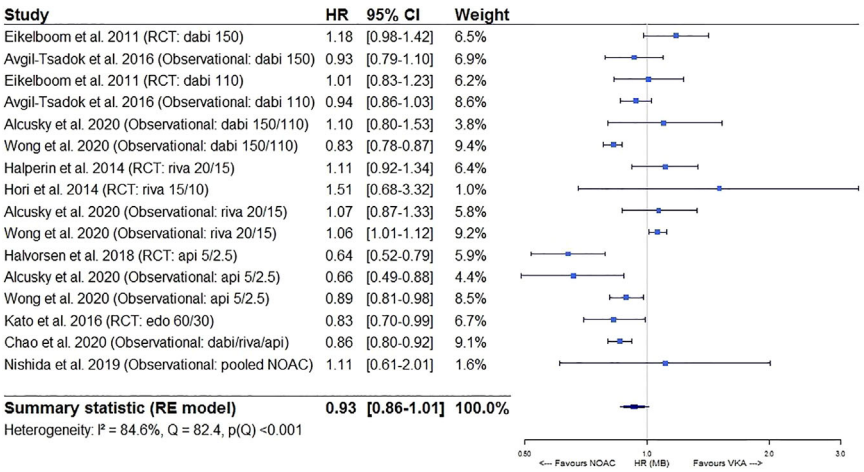

FIGURE 4 | Forest plot of the risk of major bleeding of NOACs versus VKAs in elderly atrial fibrillation patients ≥75 years old. Api 5/2.5, apixaban 5 mg (standard dose) and 2.5 mg (reduced dose); CI, confidence interval; Dabi 150, dabigatran 150 mg (standard dose); Dabi 110, dabigatran 110 mg (reduced dose); Edo 60/30, edoxaban 60 mg (standard dose) and 30 mg (reduced dose); HR, hazard ratio; MB, major bleeding; NOAC, non-vitamin K antagonist oral anticoagulant; RCT, randomized controlled trial (*post hoc* analysis); RE model, random effects model; Riva, rivaroxaban; Riva 20/15, rivaroxaban 20 mg (standard dose) and 15 mg (reduced dose); Riva 15/10, rivaroxaban 15 mg (standard dose) and 10 mg (reduced dose); VKA, vitamin K antagonist.

comparing apixaban to VKAs, a similar gastrointestinal bleeding risk (HR 0.78, 95%CI [0.54–1.13], I^2 86.0%) was observed (**eFigure 3D**).

Moreover, in a subgroup analysis, results from observational studies investigating very old AF patients (≥80, ≥85, or ≥90 years old) were additionally included in the meta-analyses on the effectiveness and safety outcomes of interest. Seven additional observational cohort studies were included (four including AF patients ≥80 years old (Deitelzweig et al., 2019; Kim et al., 2019; Russo et al., 2019; Shinohara et al., 2019), two including AF patients ≥85 years old (Lai et al., 2018; Poli et al., 2019), and one including AF patients ≥90 years old) (Giustozzi et al., 2019). Similar trends were observed, although the major bleeding risk was significantly lower for NOACs as compared to VKAs in AF patients ≥75, ≥80, ≥85, or ≥90 years old (HR 0.92, 95%CI [0.84-0.998], I^2 89.1%) (**eFigures 4A–E**).

No publication bias was suspected based on visual inspection of funnel plots (**eFigures 5A–E**), except for mortality outcomes, but this was probably due to considerable heterogeneity in study results. Indeed, after excluding the two most heterogeneous observational studies (Nishida et al., 2019; Chao et al., 2020) in the abovementioned sensitivity analysis, publication bias was no longer suspected (**eFigure 5F**).

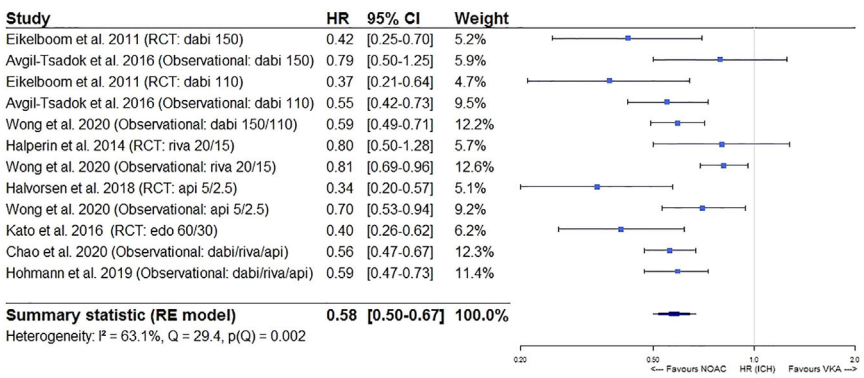

FIGURE 5 | Forest plot of the risk of intracranial bleeding of NOACs versus VKAs in elderly atrial fibrillation patients ≥75 years old. Api 5/2.5, apixaban 5 mg (standard dose) and 2.5 mg (reduced dose); CI, confidence interval; Dabi 150, dabigatran 150 mg (standard dose); Dabi 110, dabigatran 110 mg (reduced dose); Edo 60/30, edoxaban 60 mg (standard dose) and 30 mg (reduced dose); HR, hazard ratio; ICH, intracranial bleeding; NOAC, non-vitamin K antagonist oral anticoagulant; RCT, randomized controlled trial (*post hoc* analysis); RE model, random effects model; Riva, rivaroxaban; Riva 20/15, rivaroxaban 20 mg (standard dose) and 15 mg (reduced dose); VKA, vitamin K antagonist.

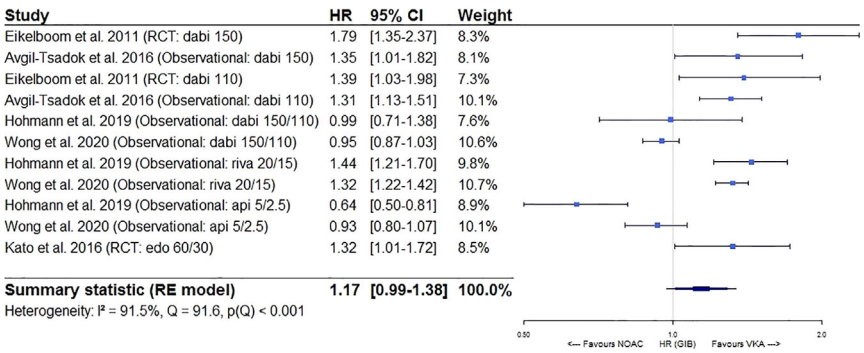

FIGURE 6 | Forest plot of the risk of gastrointestinal bleeding of NOACs versus VKAs in elderly atrial fibrillation patients ≥75 years old. Api 5/2.5, apixaban 5 mg (standard dose) and 2.5 mg (reduced dose); CI, confidence interval; Dabi 150, dabigatran 150 mg (standard dose); Dabi 110, dabigatran 110 mg (reduced dose); Edo 60/30, edoxaban 60 mg (standard dose) and 30 mg (reduced dose); GIB, gastrointestinal bleeding; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant; RCT, randomized controlled trial (*post hoc* analysis); RE model, random effects model; Riva, rivaroxaban; Riva 20/15, rivaroxaban 20 mg (standard dose) and 15 mg (reduced dose); VKA, vitamin K antagonist.

In conclusion, NOAC use in AF patients ≥75 years old was associated with a superior effectiveness and a non-inferior safety profile as compared to VKAs in our meta-analysis based on randomized and observational studies, which is in line with the abovementioned RCT-based meta-analyses in older AF patients.

Multimorbidity

Unfortunately, studies investigating the impact of multimorbidity based on the number of baseline comorbidities, are limited, as only one study has been published so far (**eTable 3**). In this *post hoc* analysis of the ARISTOTLE trial, apixaban use in AF patients with moderate multimorbidity (3–5 comorbidities) was associated with a significantly lower stroke/SE and major bleeding risk, and a similar mortality risk as compared to warfarin, whereas in highly multimorbid AF patients (≥6 comorbidities), all outcome risks were similar (Alexander et al., 2019). More studies investigating the impact of multimorbidity based on the absolute number of baseline comorbidities are needed, although these preliminary results illustrate the preserved efficacy and safety of apixaban, even in patients with high multimorbidity.

A high clinical risk score, such as a high CHADS2, CHA_2DS_2-VASc, or HAS-BLED score, can also be used as a proxy to identify patients with multimorbidity, although comorbidities not included in these risk scores are not acknowledged. Several randomized and observational studies have reported outcome rates of NOACs versus VKAs in AF patients with a high clinical risk score, illustrating comparable results as seen in the overall pivotal phase III RCTs (Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011; Giugliano et al., 2013) and studies on increased age, namely the superior efficacy of apixaban and standard dose dabigatran, the (mostly) superior safety of apixaban, non-inferior safety of dabigatran and edoxaban, and non-inferior (in randomized studies) to inferior (in observational studies) safety of rivaroxaban as compared to warfarin (**eTable 3**). Indeed, significantly lower stroke/SE, major bleeding and intracranial bleeding risks, and a similar mortality risk were observed for apixaban-treated patients with a CHADS2 or CHA_2DS_2-VASc score of ≥3 as compared to warfarin in a *post hoc* analysis of the ARISTOTLE trial (Granger et al., 2011; Lopes et al., 2012). In the RE-LY trial, dabigatran use in AF patients with a CHADS2 score of ≥3 was associated with a similar (110 mg) to significantly lower (150 mg) stroke/SE risk, a similar major bleeding risk (both doses), a significantly lower intracranial bleeding risk (both doses) and a similar mortality risk (both doses) as compared to warfarin (Connolly et al., 2009; Oldgren et al., 2011). Likewise, non-inferior stroke/SE and major bleeding risks in AF patients with a CHADS2 score of ≥3 were observed in the ROCKET AF trial (Patel et al., 2011) and J-ROCKET AF trial (Hori et al., 2014) for rivaroxaban, and in the ENGAGE AF-TIMI 48 trial (Giugliano et al., 2013) for edoxaban.

In line with these randomized studies, four observational cohort studies also examined the impact of multimorbidity based on high CHA_2DS_2-VASc (4–5, ≥6) (Mentias et al., 2018; Hernandez et al., 2018), HAS-BLED (≥4) (Wong et al., 2020), Gagne comorbidity (3–4, ≥5) (Mentias et al., 2018), and/or Charlson Comorbidity Index scores (≥4) (Hohmann et al., 2019). In AF patients with multimorbidity, NOAC use was associated with similar (Mentias et al., 2018; Hohmann et al., 2019) to significantly lower (Hernandez et al., 2018) stroke/SE and mortality risks, and significantly lower (Hohmann et al., 2019; Wong et al., 2020) intracranial bleeding risks as compared to warfarin (Hernandez et al., 2018; Mentias et al., 2018; Hohmann et al., 2019; Wong et al., 2020). On safety outcomes, both apixaban and dabigatran were associated with similar to significantly lower major bleeding and gastrointestinal bleeding risks compared to warfarin, as opposed to similar to significantly higher major bleeding and gastrointestinal bleeding risks for rivaroxaban across studies (Mentias et al., 2018; Hernandez et al., 2018; Hohmann et al., 2019; Wong et al., 2020).

In conclusion, despite at least non-inferior effectiveness outcomes, these observational studies highlight the potential worse safety profile of rivaroxaban as opposed to non-inferior

to superior safety profiles of apixaban and dabigatran in AF patients with multimorbidity. These results are in line with the abovementioned results in older AF patients, although safety results of dabigatran appeared to be better in AF patients with multimorbidity due to similar to significantly lower gastrointestinal bleeding risks in observational studies.

Polypharmacy

Post hoc analyses of two phase III RCTs (the ARISTOTLE (Jaspers Focks et al., 2016) and ROCKET AF trial (Piccini et al., 2016)) have been performed on the impact of polypharmacy, illustrating the at least equal efficacy of apixaban and rivaroxaban, non-inferior to superior safety of apixaban, and non-inferior to inferior safety of rivaroxaban as compared to warfarin (**eTable 4**). Indeed, similar stroke/SE and mortality risks were observed for apixaban- and rivaroxaban- versus warfarin-treated AF patients with polypharmacy (Jaspers Focks et al., 2016; Piccini et al., 2016). Apixaban use in patients with 6–8 and ≥9 drugs was associated with a significantly lower intracranial bleeding and similar gastrointestinal bleeding risk as compared to warfarin (Jaspers Focks et al., 2016), whereas rivaroxaban use in patients with 5–9 and ≥10 drugs was associated with a similar intracranial bleeding risk (no report on gastrointestinal bleeding) (Piccini et al., 2016). Intriguingly, a significant interaction between the number of comedication use and both apixaban and rivaroxaban was present for major bleeding (Jaspers Focks et al., 2016; Piccini et al., 2016). For apixaban, the safety benefit was attenuated in AF patients with the highest number of concomitant medications, as a significantly lower major bleeding risk was observed in patients with 6–8 drugs, whereas an equal risk in patients with ≥9 drugs (Jaspers Focks et al., 2016). For rivaroxaban, a significantly higher major bleeding risk was observed in patients with 5–9 drugs as compared to warfarin, whereas a similar risk in patients with ≥10 drugs (Piccini et al., 2016).

Pooling the results of both RCTs, two meta-analyses illustrated that NOACs were associated with a superior efficacy (significantly lower stroke/SE and all-cause mortality risk) and non-inferior safety (similar major bleeding risk) in AF patients with polypharmacy (≥5 drugs) as compared to warfarin, which is in line with results of our meta-analysis on increased age (Harskamp et al., 2019; Kim et al., 2019).

Furthermore, two observational cohort studies on polypharmacy (≥7 drugs (Hohmann et al., 2019) and ≥5 to ≥10 drugs (Martinez et al., 2019)) illustrated results in line with the abovementioned randomized studies and provided limited reassuring data on dabigatran use in patients with polypharmacy. Similar (Hohmann et al., 2019) to significantly lower (Martinez et al., 2019) stroke/SE and significantly lower (Hohmann et al., 2019) intracranial bleeding risks were observed for NOACs as compared to VKAs in these studies. In one observational study, apixaban was associated with a significantly lower gastrointestinal bleeding and similar other major bleeding risk, dabigatran with a similar gastrointestinal bleeding and lower other major bleeding risk, whereas rivaroxaban with a significantly higher gastrointestinal bleeding and similar other major bleeding risk as compared to phenprocoumon (Hohmann et al., 2019). However, the other observational study, though industry-sponsored, observed similar major bleeding risks with rivaroxaban as compared to warfarin in patients with ≥5 and ≥10 drug used (Martinez et al., 2019).

Overall, results on the impact of polypharmacy were consistent as observed in AF patients with multimorbidity, highlighting the preserved effectiveness of NOACs, the non-inferior to superior safety of apixaban and dabigatran, and the opposing non-inferior to inferior safety of rivaroxaban. However, as both randomized and observational data on apixaban use in patients with polypharmacy was most reassuring, apixaban use also appears to be the first choice in patients with polypharmacy, as seen in older AF patients. Nonetheless, the attenuated safety benefit of apixaban in patients with the highest number of concomitant medications should warrant caution and close monitoring.

High Falling Risk

A high falling risk or recent fall does not automatically contraindicate OAC use. In a Markov decision analytic model using data on stroke and major bleeding rates in both non-anticoagulated and VKA-treated AF patients ≥65 years old with or without falls, the role for continuing instead of omitting OACs was examined (Man-Son-Hing et al., 1999). Weighing the increased risk for fall-related intracranial haemorrhage against the substantial reduction in ischemic stroke risk among warfarin-treated AF patients as compared to non-anticoagulated patients, a person would have to fall about 295 times in 1 year for warfarin not to be the preferred therapy (Man-Son-Hing et al., 1999). In other words, AF patients at high risk of falling still appear to benefit from anticoagulation despite the associated risk for intracranial haemorrhage. Therefore, it is of importance to evaluate potential differences in outcomes between individual OACs, especially regarding intracranial haemorrhage as the most feared fall-related outcome. However, only two secondary analyses of phase III RCTs studies specifically assessed the impact of high falling risk on NOAC efficacy and safety, namely the ARISTOTLE (Rao et al., 2018) and ENGAGE AF-TIMI 48 trial (Steffel et al., 2016), though these were largely underpowered (**eTable 5**). In apixaban-treated AF patients with ≥1 prior fall in the last year, the risk of intracranial bleeding was significantly lower as compared to warfarin, whereas the risks of stroke/SE, major bleeding and mortality were similar (Rao et al., 2018). Likewise, a significantly lower intracranial bleeding risk, and similar stroke/SE, major bleeding, gastrointestinal bleeding and mortality risks were observed for edoxaban users at high risk of falling as compared to warfarin (Steffel et al., 2016). Besides lack of subgroup analyses of the RE-LY (Connolly et al., 2009) and ROCKET AF trial (Patel et al., 2011), to the best of our knowledge, no large observational studies have been performed so far specifically comparing the effectiveness and safety of individual NOACs in AF patients at high falling risk. This emphasizes an urgent need for more research on the topic to help guide physicians in their OAC choice for AF patients at high falling risk.

While awaiting more results, the preserved efficacy and safety outcomes of apixaban and edoxaban may warrant their use in AF patients prone to fall, especially because of the significantly lower intracranial bleeding risk.

Frailty

Unfortunately, as the four pivotal phase III RCTs did not specifically include or investigate frail AF patients, especially since patients with an estimated life expectancy of <1–2 years or less than the expected trial duration were excluded (Connolly et al., 2009; Lopes et al., 2010; Ruff et al., 2010; Granger et al., 2011; Patel et al., 2011; Giugliano et al., 2013), randomized data is lacking on the impact of frailty on the efficacy and safety of NOACs in AF. Luckily, limited yet useful observational data is emerging on this clinically relevant topic, highlighting comparable results as seen in studies on increased age, namely the similar effectiveness of all NOACs and the most favourable safety profile of apixaban in contrast to the least favourable profile of rivaroxaban (**eTable 6**).

Indeed, in a retrospective cohort study including frail AF patients using the Johns Hopkins Claims-based Frailty Indicator (Segal et al., 2017), NOAC use was associated with a similar stroke/SE and gastrointestinal bleeding risk, and a significantly lower intracranial and other major bleeding risk as compared to phenprocoumon (Hohmann et al., 2019). Importantly, as seen in studies investigating older AF patients, differential safety outcomes between individual NOACs were noted in frail patients. Apixaban was associated with a significantly lower gastro-intestinal bleeding risk, dabigatran with a similar risk, whereas rivaroxaban with a significantly higher risk as compared to phenprocoumon. Moreover, another retrospective cohort study identified frail AF patients using the same Johns Hopkins Claims-based Frailty Indicator (Segal et al., 2017), and observed similar stroke/SE risk for NOACs as compared to warfarin (Martinez et al., 2018). Apixaban was associated with a significantly lower major bleeding but similar intracranial bleeding risk (though the number of events was very low), whereas dabigatran and rivaroxaban with a similar major bleeding but significantly lower intracranial bleeding risk. Additionally, apixaban and dabigatran were associated with a similar gastrointestinal bleeding risk, but rivaroxaban with a higher risk.

In conclusion, although evidence is limited, these studies illustrate that the effectiveness and safety of NOACs appear to be consistent in frail patients, as observed in older AF patients, with apixaban having the most favourable benefit-risk profile. Nonetheless, more studies are needed on the role of individual NOACs in frail AF patients, especially of edoxaban.

Dementia

Data on the effectiveness and safety of OACs, especially NOACs, in AF patients with dementia are limited. Unfortunately, phase III RCTs did not include AF patients with dementia due to inability to comply with study-related procedures or to give an informed consent, so no randomized data in this population is available (Connolly et al., 2009; Lopes et al., 2010; Ruff et al., 2010; Granger et al., 2011; Patel et al., 2011; Giugliano et al., 2013; Fanning et al., 2020). However, some observational studies have provided exploratory data on this topic, illustrating the benefit of OAC continuation over discontinuation, as seen in the oldest AF patients ≥90 years old (**eTable 7**). Indeed, warfarin-treated AF patients with dementia in the Swedish Dementia Registry and Veterans Affairs database had significantly lower thromboembolic and mortality risks as compared to non-anticoagulated AF patients with dementia, without significantly increasing major bleeding or non-traumatic intracranial bleeding risks (Orkaby et al., 2017; Subic et al., 2018).

Regarding the comparative effectiveness and safety of NOACs versus VKAs, only one retrospective cohort study provided some preliminary data, illustrating similar stroke/SE and other major bleeding risks, a significantly lower intracranial bleeding risk, and significantly higher gastrointestinal bleeding and mortality risks for NOACs versus warfarin in AF patients with dementia (Fanning et al., 2020). However, analyses were not time-dependent, and results may have been influenced by selective prescribing and pooling of NOAC data, necessitating cautious interpretation of these results.

In conclusion, these limited results are comparable to those observed in AF patients ≥90 years old, namely a potential beneficial role for OAC continuation in AF patients with dementia instead of stopping the OAC (Orkaby et al., 2017; Subic et al., 2018). In other words, dementia in itself should not be viewed as a general contraindication for OACs. However, the severity of dementia should also be assessed when evaluating the necessity for OAC continuation. Moreover, it is still unclear what type of OAC should be preferred in these patients as strong evidence is lacking. This highlights the urgent need for more studies investigating the benefit-risk profile of NOACs in AF patients with cognitive impairment and dementia.

DISCUSSION

General Trends

The use of OACs in vulnerable geriatric AF patients is a matter of concern for physicians, faced with the challenge of outweighing the benefits of stroke reduction against the risk of bleeding. Vulnerable older AF patients are frequently characterized by multimorbidity, polypharmacy, increased falling risk, frailty and dementia (Jaspers Focks et al., 2016; Piccini et al., 2016; Steffel et al., 2016; Martinez et al., 2018; Rao et al., 2018; Alexander et al., 2019). Consequently, OACs tend to be inappropriately underdosed or discontinued in these patients subgroups (Viscogliosi et al., 2017; Oqab et al., 2018; Madhavan et al., 2019; Proietti et al., 2019; Besford et al., 2020; Kapoor et al., 2020; Sanghai et al., 2020). However, even in AF patients ≥90 years old (Raposeiras-Roubín et al., 2020), at high risk of falling (Man-Son-Hing et al., 1999) or with dementia (Orkaby et al., 2017; Subic et al., 2018), OAC continuation was still beneficial compared to omitting the OAC. Therefore, very high age, recent fall or cognitive impairment should not be considered as strict contraindications for OAC use, provided that an individual benefit-risk assessment is performed.

Even though the pivotal phase III RCTs were not designed and powered to investigate OAC use in geriatric patients, the available randomized evidence and also post-surveillance observational studies suggest that the effectiveness and safety of NOAC as compared to warfarin remain consistent, with apixaban exhibiting the most favourable benefit-risk profile of all OACs

across patient subgroups (see **Table 1** for general overview of results). Our meta-analysis including results of 6 *post hoc* analyses of RCTs and 6 observational studies, highlighted superior results on stroke/SE, mortality and intracranial bleeding risks, whereas non-inferior results on major bleeding and gastrointestinal bleeding risks for NOACs as compared to VKAs in AF patients ≥75 years old. Even after additionally including seven observational studies investigating patients ≥80, ≥85, or ≥90 years old, consistent results were demonstrated, though the major bleeding risk was significantly lower for NOACs as compared to VKAs. However, safety differences between individual NOACs were identified, as increasing age above 75 years significantly interacted with the safety of dabigatran and rivaroxaban, illustrating non-inferior to inferior safety results in older AF patients, especially due to a higher gastrointestinal bleeding risk of both NOACs and a similar intracranial bleeding risk of rivaroxaban as compared to warfarin (Eikelboom et al., 2011; Halperin et al., 2014; Lin et al., 2015; Avgil-Tsadok et al., 2016; Lai et al., 2018; Deitelzweig et al., 2019; Hohmann et al., 2019; Wong et al., 2020). On the contrary, the superior safety profile of apixaban was preserved in older AF patients, with a significantly lower major, intracranial and gastrointestinal bleeding risk as compared to warfarin (Halvorsen et al., 2014; Lin et al., 2015; Deitelzweig et al., 2019; Hohmann et al., 2019; Alcusky et al., 2020; Wong et al., 2020). Likewise, edoxaban was associated with a similar (standard dose) to significantly lower (reduced dose) major bleeding risk and a lower intracranial bleeding risk as compared to warfarin, although higher gastrointestinal bleedings risks were also noted (Kato et al., 2016).

Similarly, in AF patients with multimorbidity or polypharmacy, apixaban (Granger et al., 2011; Jaspers Focks et al., 2016; Alexander et al., 2019; Harskamp et al., 2019; Hohmann et al., 2019) was associated with the most favourable effectiveness and safety profile of all NOACs, followed by edoxaban (Giugliano et al., 2013), dabigatran (Connolly et al., 2009; Oldgren et al., 2011; Hernandez et al., 2018; Mentias et al., 2018; Hohmann et al., 2019; Wong et al., 2020), and rivaroxaban (Piccini et al., 2016; Hernandez et al., 2018; Mentias et al., 2018; Harskamp et al., 2019; Hohmann et al., 2019; Martinez et al., 2019; Wong et al., 2020).

In AF patients at high risk of falling, with frailty or dementia, considerably less evidence was available, mostly due to exclusion of these subjects in RCTs, which complicates recommendations for clinical practice. Therefore, more studies are necessary in these patient subgroups. Notwithstanding, apixaban's preferential benefit-risk profile was maintained in patients prone to fall and with frailty, illustrating a similar effectiveness and non-inferior to superior safety as compared to warfarin (Rao et al., 2018; Hohmann et al., 2019). The preserved significantly lower intracranial bleeding risk is of particular importance in high-risk fallers (Rao et al., 2018). Furthermore, dabigatran in frail patients (Hohmann et al., 2019) and edoxaban in patients prone to fall (Steffel et al., 2016) illustrated similar benefit-risk profiles as compared to warfarin, whereas rivaroxaban showed a non-inferior to inferior safety profile in frail patients (Martinez et al., 2018; Hohmann et al., 2019). As only one study examined the effectiveness and safety of NOACs as compared to warfarin in AF patients with dementia, illustrating a similar stroke/SE and major bleeding risk, as opposed to a higher gastrointestinal bleeding and mortality risk, there is an urgent need for more research on the effectiveness and safety of individual NOACs in dement AF patients (Fanning et al., 2020).

Pathophysiological Mechanisms

Several mechanisms for differential safety results of individual NOACs in older AF patients have been proposed. As the decline in renal function gradually progresses with age and the metabolism of dabigatran is the most dependent on renal clearance of all NOACs (80% renal clearance as opposed to only 27% for apixaban) (Steffel et al., 2018), the subsequent higher plasma concentrations of fixed-dose dabigatran may partially explain the increased bleeding risk in older patients (Eikelboom et al., 2011; Lauw et al., 2017). Moreover, as the bioavailability of dabigatran after oral ingestion is the lowest of all NOACs (only 3–7%) (Steffel et al., 2018), intra-intestinal metabolism of the prodrug dabigatran etexilate to the active drug during transit could lead to gradually higher concentrations and local bleeding of the gastrointestinal tract by direct drug exposure at bleeding sensitive foci such as diverticulosis, angiodysplasia and colorectal polyposis (Eikelboom et al., 2011). Since warfarin has a high bioavailability and its anticoagulant mechanism of action depends on hepatic enzymes (vitamin K-dependent γ-carboxylation of coagulation factors II, VII, IX, and X) resulting in less direct drug exposure at intra-intestinal bleeding sensitive foci, this could explain the higher gastrointestinal bleeding risk of dabigatran at higher age as compared to warfarin (Eikelboom et al., 2011). Although rivaroxaban has a very high bioavailability (80%–100% if taken together with food), intestinal clearance through P-glycoprotein (P-gp)-dependent biliary and intestinal excretion is substantial, as rivaroxaban's clearance is 65% non-renal, 47% of which through intestinal excretion (Steffel et al., 2018). This may lead to high intra-intestinal concentrations of rivaroxaban, locally affecting diseased mucosa and resulting in higher gastrointestinal bleeding risks in older patients as compared to warfarin (Eikelboom et al., 2011). Similarly, the higher gastrointestinal bleeding risk of edoxaban in older patients (Kato et al., 2016) may be due to its 62% bioavailability and 46% intestinal clearance (Steffel et al., 2018). However, as the bioavailability of apixaban is also 50% and the intestinal clearance is similar (48%) (Steffel et al., 2018), this pathophysiological mechanism cannot explain why the gastrointestinal bleeding risk is less pronounced in apixaban. Other age-related pharmacokinetic and -dynamic changes may also play a role, such as the decreased hepatic function with reduced drug clearance (relevant for apixaban and rivaroxaban, being +/- 18% and 25% respectively hepatically metabolized (Steffel et al., 2018)), changes in plasma protein binding due to decreasing albumin levels (most important for rivaroxaban and apixaban, being 95% and 87% plasma protein bound respectively (Steffel et al., 2018)) and the prolonged elimination half-life in older patients (11–13 h for rivaroxaban versus 5–9 h in younger patients) (Grandison and Boudinot, 2000; McLean and Le Couteur, 2004; Mueck et al., 2011; Steffel et al., 2018).

Potential mechanisms on the reduced risk for intracranial haemorrhage in NOACs as compared to VKAs have also been

TABLE 1 | The effectiveness and safety of each NOAC as compared to vitamin K antagonists in atrial fibrillation patients at increased age (≥75 years old), multimorbidity, polypharmacy, high falling risk, frailty, and baseline dementia.

		DABIGATRAN		RIVAROXABAN		APIXABAN		EDOXABAN
≥75 YEARS OLD		**150 mg**	**110 mg**					
Stroke/systemic embolism (SE)	*RCT*	↘	=	=		↘		=
	Obs.	= to ↘		= to ↘		= to ↘		NR
Major bleeding	*RCT*	=	=	=		↘		↘
	Obs.	= to ↘		= to ↗		↘		NR
Intracranial hemorrhage (ICH)	*RCT*	↘	↘	=		↘		↘
	Obs.	↘		= to ↘		↘		NR
Gastrointestinal bleeding (GIB)	*RCT*	↗	↗	↗		NR		↗
	Obs.	= to ↗		= to ↗		= to ↘		NR
Mortality	*RCT*	=	=	NR		NR		NR
	Obs.	↘		= to ↘		↘		NR
MULTIMORBIDITY‡		**150 mg**	**110 mg**			**3-5†**	**≥6†**	
Stroke/SE	*RCT*	↘	=	=		↘ ↘‡	=	=
	Obs.	= to ↘		= to ↘		= to ↘		NR
Major bleeding	*RCT*	=	=	=		↘ ↘‡	=	=
	Obs.	=		= to ↗		=		NR
ICH	*RCT*	↘	↘	NR		NR		NR
	Obs.	= to ↘		= to ↘		= to ↘		NR
GIB	*RCT*	NR	NR	NR		NR		NR
	Obs.	= to ↘		↗		= to ↘		NR
Mortality	*RCT*	=	=	NR		=	=	NR
	Obs.	↘		= to ↘		↘		NR
POLYPHARMACY				**≥5 drugs**	**≥10 drugs**	**>5 drugs**	**≥9 drugs**	
Stroke/SE	*RCT*	NR		=		=	=	NR
	Obs.	NR		↘	=	NR		NR
Major bleeding	*RCT*	NR		↗	=	↘	=	NR
	Obs.	NR		=	=	NR		NR
ICH	*RCT*	NR		=		↘	↘	NR
	Obs.	NR		NR		NR		NR
GIB	*RCT*	NR		NR	NR	=	=	NR
	Obs.	=		↗		↘		NR
Mortality	*RCT*	NR		=		=	=	NR
	Obs.	NR		NR		NR		NR
HIGH FALLING RISK								
Stroke/SE	*RCT*	NR		NR		=		=
Major bleeding	*RCT*	NR		NR		=		=
ICH	*RCT*	NR		NR		↘		↘
GIB	*RCT*	NR		NR		NR		=
Mortality	*RCT*	NR		NR		=		=
FRAILTY								
Stroke/SE	*Obs.*	=		=		=		NR
Major bleeding	*Obs.*	=		=		↘		NR
ICH	*Obs.*	↘		↘		= to ↘		NR
GIB	*Obs.*	=		↗		= to ↘		NR
Mortality	*Obs.*	NR		NR		NR		NR
DEMENTIA[i]						**NOACs[i]**		
Stroke/SE	*Obs.*	=						
Major bleeding	*Obs.*	=						
ICH	*Obs.*	↘						
GIB	*Obs.*	↗						
Mortality	*Obs.*	↗						

*= (yellow): non-inferior results (similar risk) when comparing NOAC to VKAs; ↘ (green): superior results (significantly lower risk) when comparing NOAC to VKAs; ↗ (red): inferior results (significantly higher risk) when comparing NOAC to VKAs; = **to** ↘ (yellow-green): non-inferior to superior results, varying across studies; = **to** ↗ (yellow-red): non-inferior to inferior results, varying across studies. †number of baseline comorbidities; ‡high clinical risk score (e.g. CHA_2DS_2-VASc score ≥3); [i]careful interpretation of results necessary, as only one observational study provided preliminary (pooled) data. GIB, gastrointestinal bleeding; ICH, intracranial bleeding; NR, not reported; Obs., longitudinal observational cohort study; RCT, (post hoc analysis of) randomized clinical trial; Stroke/SE, stroke/systemic embolism.*

suggested in previous literature. As the elimination half-life of NOACs is approximately 12 h, which is significantly shorter than that of VKAs, early discontinuation in case of head trauma or spontaneous bleeding might limit development and progression of intracranial bleeding (Rao et al., 2018; Steffel et al., 2018). Moreover, as NOACs only target factor IIa (dabigatran) or Xa (rivaroxaban, apixaban and edoxaban), whereas VKAs target factor II, VII, IX, and X, it has been proposed that the lack of impact on factor VII by NOACs may help to decrease trauma-related bleeding, especially intracranial haemorrhage (Eikelboom et al., 2011; Rao et al., 2018). Factor VII is an important coagulation factor of the extracellular pathway, initiating clot formulation together with tissue factor (Eikelboom et al., 2011; Rao et al., 2018). Tissue factor is found in high concentrations in the brain, where it may provide supplemental haemostatic protection together with factor VII in case of trauma (Mackman, 2009; Eikelboom et al., 2011). Indeed, in an exploratory case series analysis in factor VII deficient AF patients, severe bleeding risk was increased in warfarin-treated patients, whereas no haemorrhagic events occurred in dabigatran-treated patients, providing preliminary data on the importance of factor VII in major bleeding events (Arletti et al., 2019). However, larger studies are needed to confirm these findings.

The risk of stroke in older AF patients varies across studies, documenting similar to significantly lower stroke/SE risks for NOACs as compared to warfarin. This may be due to the VKA-associated increase in vascular calcification (Weijs et al., 2011; Deng et al., 2020; Millenaar et al., 2020). However, it should be mentioned that not all stroke events in AF patients are necessarily cardio-embolic in origin, which may affect stroke incidence rates of individual OACs in different studies by chance (Paciaroni et al., 2019). For example, in the RENo study examining NOAC-treated AF patients with an acute ischemic stroke, about 30% of patients had a stroke due to causes other than cardio-embolism (e.g. small vessel disease) (Paciaroni et al., 2019).

Another frequently proposed mechanism, increasing the risk for adverse outcomes in older AF patients, are DDIs. The risk of DDIs increases with the number of comorbidities and comedication use (Jaspers Focks et al., 2016; Piccini et al., 2016; Alexander et al., 2019; Harskamp et al., 2019). VKAs have multiple common drug-drug and drug-food interactions, requiring frequent dose adjustments due to the narrow therapeutic window (Kirchhof et al., 2016; Piccini et al., 2016; Steffel et al., 2018). NOACs have less DDIs, but these should not be neglected (Steffel et al., 2018). Two types can be identified: pharmacokinetic and pharmacodynamic DDIs. For NOACs, two major pharmacokinetic interaction mechanisms are present. First, all NOACs are a substrate of the P-gp efflux transporter, which is mostly present in the gastrointestinal lumen, resulting in gastrointestinal excretion of NOACs after absorption in the gut (Leslie et al., 2005; Steffel et al., 2018; Kim et al., 2019; Washam et al., 2019). Its presence in the liver contributes to hepatobiliary drug excretion, while P-gp transporters located in proximal tubules play a role in the active renal clearance of NOACs (Leslie et al., 2005; Gnoth et al., 2011; Steffel et al., 2018; Kim et al., 2019). Moreover, as P-gp is also expressed in capillary endothelial cells making up the blood-brain barrier to prevent passage of drugs into the brain, P-gp inhibition might slightly increase NOAC concentrations in the brain and potentially decrease the beneficial safety of NOACs on intracranial bleeding risks (Leslie et al., 2005; Gnoth et al., 2011; Kim et al., 2019). Second, apixaban and rivaroxaban are partially dependent on hepatic clearance, mostly mediated through the cytochrome P450 3A4 isoenzyme (CYP3A4) (Steffel et al., 2018; Washam et al., 2019). On the contrary, CYP3A4-mediated hepatic metabolism is not involved in the clearance of dabigatran and only minimally (<4%) in edoxaban (Steffel et al., 2018). Therefore, CYP3A4-mediated DDIs do not significantly affect dabigatran and edoxaban plasma concentrations. P-gp and/or CYP3A4 inhibitors (e.g. amiodarone, dronedarone, verapamil…) can increase NOAC plasma concentration due to a decreased gastrointestinal excretion and/or hepatic metabolism respectively, resulting in an increased bleeding risk (Piccini et al., 2016; Steffel et al., 2018; Kim et al., 2019; Washam et al., 2019). Similarly, P-gp and/or CYP3A4 inducers may decrease plasma concentrations, subsequently increasing thromboembolic risks (Steffel et al., 2018; Washam et al., 2019). It should be noted that in all phase III RCTs, the use of strong CYP3A4 and/or P-gp inhibitors and inducers was prohibited, limiting the generalizability of the results to real-life clinical practice (Connolly et al., 2009; Lopes et al., 2010; Ruff et al., 2010; Granger et al., 2011; Patel et al., 2011; Giugliano et al., 2013; Jaspers Focks et al., 2016). Common pharmacodynamically interacting drugs are antiplatelets, NSAIDs, selective serotonin reuptake inhibitors and corticosteroids, which may increase the risk of bleeding (Steffel et al., 2018). Several studies have been published on the impact of (strong) individual DDIs on NOAC effectiveness and safety. However, the potential synergistic impact of multiple weak-moderate DDIs in one patient may also influence outcomes and should not be neglected, especially not in patients with polypharmacy.

Nevertheless, the differential safety profiles of NOACs in older AF patients cannot be fully explained by these mechanisms, so other unidentified age-dependent pathophysiological mechanisms may contribute as well.

Strengths and Limitations of Available Literature

The included RCTs have many strengths, such as the use of rigorous methodologies, detailed protocols, pre-specified statistical analyses and well-defined patient cohorts (Beyer-Westendorf et al., 2016). However, RCTs are usually underpowered for subgroups analyses and run too short for (long-term) safety outcomes, do not take into account the complexity of real-world clinical decision-making, and difficult-to-reach populations tend to be underrepresented due to ethical and practical considerations (Beyer-Westendorf et al., 2016; Maetens et al., 2016; Camm et al., 2018). The included observational studies tackle these shortcoming in part, including large vulnerable patient subgroups with long follow-up in a real-world setting. However, when comparing different studies in geriatric AF patients, several limitations were present influencing the interpretability of results.

First, lack of power due to small sample sizes was present in most studies, which frequently resulted in pooling data of all NOACs despite differential safety results. Some studies also included OAC-experienced patients, which may lead to healthy user bias (Giustozzi et al., 2019). Second, NOACs dosages differed across studies. For example, rivaroxaban was used in lower dosages in Japan than approved in Europe (15 and 10 mg as standard and reduced dose respectively) (Hori et al., 2012; Group JCSJW, 2014). Likewise, 75 mg twice daily is the approved reduced dosage of dabigatran in the US (Pradaxa), whereas 110 mg twice daily in Europe (Steffel et al., 2018). Moreover, differences in off-label NOAC over- or underdosing in observational studies complicated the comparability of results (Alcusky et al., 2020; Raposeiras-Roubín et al., 2020). Third, most results were compared to warfarin, but also other VKAs such as phenprocoumon were sometimes used. Besides VKAs, other studies used aspirin, no OAC or non-AF patients as comparator arm, necessitating exclusion of these studies. Fourth, outcomes varied notably, with studies investigating ischemic stroke, overall stroke, stroke/TIA, stroke/SE, stroke/TIA/SE or stroke/SE/myocardial infarction as effectiveness outcome. Likewise, primary safety endpoints varied, from location-specific bleeding, major bleeding, major or clinically relevant non-major bleeding to any bleeding. These differential outcomes made comparisons between studies difficult. Fifth, many included observational studies were performed in an Asian setting. However, results from Asian studies cannot always be automatically generalized to other populations. For example, Asian AF patients seem to have higher stroke rates (especially haemorrhagic stroke) than Caucasian AF patients, and are also more prone to warfarin-related major bleeding events, especially intracranial bleeding (Hori et al., 2013; Chiang et al., 2014; Chao et al., 2019). Japanese guidelines therefore recommend a target INR of 1.6–2.6 in AF patients ≥70 years old [instead of 2.0–3.0 in Western countries] (Hori et al., 2012; Group JCSJW, 2014; Steffel et al., 2018). Moreover, the mean TTR in warfarin-treated Asian patients tends to be lower than in Caucasian patients (Chiang et al., 2014; Piccini et al., 2014; Chao et al., 2019). Due to these underlying ethnic differences, NOACs tend to have a better effectiveness and safety than VKAs in Asian patients. Sixth, the classification of the geriatric patient subgroups varied across studies. For example, the assessment methods of frailty varied across studies, identifying frailty based on a questionnaire (Gullón et al., 2019), clinical frailty score (Shinohara et al., 2019) or a healthcare claims-based scoring algorithm (Segal et al., 2017). Likewise, different definitions for polypharmacy and multimorbidity were used, limiting the comparability of results (Jaspers Focks et al., 2016; Piccini et al., 2016). Lastly, differences in design and selection bias may have also influenced results. For example, in the RE-LY trial, no pre-specified dose reduction criteria for dabigatran were defined, resulting in approximately similar numbers of dabigatran 110 and 150 mg users in older AF patients, due to randomization (Connolly et al., 2009; Eikelboom et al., 2011). This potential inappropriate use of standard dose dabigatran may have resulted in worse adverse outcomes in older AF patients. Moreover, selection bias due to differences in baseline characteristics of the included trial population may have affected safety results. Exemplary, the median CHADS2 score ranged from 2.1 in the ARISTOTLE trial (Granger et al., 2011) to 3.5 in the ROCKET AF trial (Patel et al., 2011), which may suggest inclusion of healthier AF patients in the ARISTOTLE trial. Similarly, only 13.9% of older subjects required a reduced dose of apixaban in the ARISTOTLE trial (Halvorsen et al., 2014). Importantly, when assessing the quality of studies using the quality assessment tool 'QUALSYST' (Kmet et al., 2004), *post hoc* analyses of the RE-LY (Eikelboom et al., 2011; Lauw et al., 2017) and ARISTOTLE (Halvorsen et al., 2014) trial lacked the comparison between the baseline characteristics of NOAC versus VKA users in the subgroup of patients ≥75 years old, since only overall characteristics of this subgroup were reported. Included observational studies (Avgil-Tsadok et al., 2016; Hohmann et al., 2019; Alcusky et al., 2020; Chao et al., 2020; Wong et al., 2020) frequently lacked well defined outcomes which are robust to measurement bias or were limited in their controlling for important confounders.

Recommendation for Clinical Practice

Overall, across characteristics typical for vulnerable geriatric AF patients, apixaban was consistently associated with the best efficacy and safety profile and appears to be therefore preferred in geriatric patients. Although edoxaban ranked second on safety endpoints and third on efficacy outcomes in AF patients ≥75 years old (Deng et al., 2020), data are lacking on the impact of other geriatric patient characteristics, limiting the generalizability of the reassuring edoxaban results in older patients to all multimorbid, frail AF patients with polypharmacy. Dabigatran appears to have a more intermediate place in geriatric AF patients, especially due to the frequently noted higher gastrointestinal bleeding risks. Despite solid effectiveness results, rivaroxaban was mostly associated with worse safety outcomes across geriatric patient subgroups, due to similar intracranial and higher gastrointestinal bleeding risks.

Besides continuing and appropriately dosing NOACs, meticulous attention has to be addressed to recognizing and tackling modifiable bleeding risk factors such as hypertension, non-indicated NSAID or antiplatelet use, and excessive alcohol consumption (Kirchhof et al., 2016; Steffel et al., 2018). Moreover, prevention and management of falls using strength, balance and gait training; walking aids; correction of environmental hazards (e.g. loose carpets); and correction of footwear or structural impairments of the feet, are essential in the general approach of these geriatric patients, especially at high risk of falling (Avin et al., 2015). Furthermore, therapy adherence in community-dwelling AF patients, especially with cognitive impairment, should be optimized, for example by using weekly tablet boxes, electronically monitored medication dispensing systems or administration by a home health nurse or family member (Steffel et al., 2018). In addition, a thorough medication review and switching or discontinuing unnecessary, interacting or contraindicated comedication should be the cornerstone of management of older AF patients, especially with polypharmacy,

in order to increase therapy adherence and avoid potential clinically relevant drug-drug interactions (DDIs). To identify and address the presence of (multiple) DDIs, the 2018 European Heart Rhythm Association (EHRA) guidelines have made a practical guide on NOAC dosing in patients using interacting drugs (Steffel et al., 2018). Lastly, an individual benefit-risk assessment and shared decision making must always be the cornerstone of clinical practice when deciding on whether a vulnerable geriatric patient with AF should be anticoagulated or not. Severe cases, such as patients suffering major non-traumatic intracranial haemorrhage, highly repetitive falling due to generalized epilepsy or severe multisystem atrophy, or severely frail patients with limited life expectancy, should warrant OAC discontinuation (Kirchhof et al., 2016). Performing a comprehensive geriatric assessment (CGA) in hospitalized older patients with AF may help guide clinicians in this individual benefit-risk assessment (Ellis et al., 2011).

Research Gaps

Although a vast amount of evidence on the impact of increased age on the efficacy and safety of OACs was present, data are substantially lacking on the impact of most other geriatric patient subgroup characteristics. This systematic review has identified considerable research gaps on the impact of high falling risk, frailty and especially baseline dementia on NOAC effectiveness and safety. Moreover, more research on the impact of the number of baseline comorbidities to identify multimorbidity, as well as post-surveillance data on edoxaban in other than high age geriatric subgroups are needed.

CONCLUSION

Increased age, multimorbidity, polypharmacy, high falling risk, frailty and dementia are no formal contraindications for anticoagulation in geriatric AF patients, since the benefit-risk profile of NOAC as compared to VKAs remained consistently favourable in these patient subgroups. Indeed, our meta-analysis highlighted a superior effectiveness and non-inferior safety profile of NOACs in AF patients ≥75 years old as compared to VKAs. Instead of off-label underdosing or discontinuing OACs, physicians should tackle modifiable bleeding risk factors, optimize therapy adherence, initialize fall prevention, execute a thorough medication review and perform an individualized benefit-risk assessment with shared decision making in each geriatric AF patient. Importantly, apixaban was consistently associated with the most favourable benefit-risk profile across subgroups and should therefore be preferred in geriatric AF patients. However, regarding the impact of high falling risk, frailty and baseline dementia, important research gaps were identified, necessitating more research on these topics.

AUTHOR CONTRIBUTIONS

MG and LL contributed to the concept and design of the systematic review. MG performed the literature search, statistical analysis, interpretation and writing. SS, TB, MP, and LL revised the systematic review critically. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Mediating Effect of Self-Efficacy on the Relationship Between Medication Literacy and Medication Adherence Among Patients With Hypertension

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Background: Studies have reported that medication literacy had a positive effect on medication adherence in patients with hypertension. However, little is known about the mechanism underlying this relationship in patients with hypertension.

Objective: The purpose of this study was to investigate the mediating effect of self-efficacy between medication literacy and medication adherence.

Methods: A total of 790 patients with hypertension were investigated using the Chinese Medication Literacy Scale for Hypertensive Patients (C-MLSHP), the Morisky Medication Adherence Scale-8 (MMAS-8) and the Medication Adherence Self-efficacy Scale-Revision (MASES-R). Hierarchical regression and the bootstrap approach were used to analyze the mediating effect of self-efficacy on the relationship between medication literacy and medication adherence.

Results: A total of 60.9% of hypertensive patients were low adherent to their antihypertensive drug regimens. Self-efficacy had a significant positive correlation with medication literacy ($r = 0.408$, $p < 0.001$) and medication adherence ($r = 0.591$, $p < 0.001$). Self-efficacy accounts for 28.7% of the total mediating effect on the relationship between medication literacy and adherence to antihypertensive regimens for hypertensive patients.

Conclusion: More than half of the hypertensive patients in the study were low adherent to antihypertensive regimens. Self-efficacy had a partial significant mediating effect on the relationship between medication literacy and medication adherence. Therefore, it was suggested that hypertensive patients' medication adherence might be improved and driven by increasing self-efficacy. Targeted interventions to improve patients' self-efficacy should be developed and implemented. In addition, health care providers should also be aware of the importance of medication literacy assessment and promotion in patients with hypertension.

Keywords: self-efficacy, medication literacy, medication adherence, hypertension, mediating effect

INTRODUCTION

Hypertension has caused great damage to human health and consumed a large amount of medical resources worldwide, it is a leading problem in global public health management and promotion (Irazola et al., 2016). Poor blood pressure control can eventually lead to various complications and comorbidities, such as heart diseases, stroke and kidney failure, as well as increasing premature mortality and disability, which has contributed to high costs in dealing with these medical outcomes (World Health Organization, 2013). Strict early control of blood pressure has been shown to be beneficial in extending life expectancy in hypertensive patients (Vaduganathan et al., 2020). According to the latest data released by the "Report on Disease of Cardiovascular in China 2019", 330 million people in China have been suffering from cardiovascular diseases, among which 245 million patients have been diagnosed with hypertension (Hu et al., 2020).

Lifestyle change and antihypertensive medication are considered the most prevalent and agreed-upon guidelines for the effective management of hypertension (Weber et al., 2014). Adherence is recognized as a key factor in the effectiveness of antihypertensive medication treatment. However, patients' poor adherence to antihypertensive regimens is a prevalent problem that has limited the efficacy of antihypertensive drugs and leads to suboptimal blood pressure control (Abegaz et al., 2017; Hamdidouche et al., 2017). A review analyzed 24 studies and found that approximately 31% of cases of resistant hypertension may be attributed to poor adherence to the medication regimens (Hamdidouche et al., 2017). Another meta-analysis of 28 studies showed that among 12,603 hypertensive patients, 45.2% were nonadherent to antihypertensive medication, and 83.7% of patients with nonadherence were found to have uncontrolled blood pressure (Abegaz et al., 2017). In addition, nonadherence to antihypertensive drugs in patients with hypertension was significantly associated with a higher risk of stroke, coronary heart disease, and chronic heart failure (Shin et al., 2013; Lee et al., 2017; Jinkwon et al., 2018). Therefore, nonadherence to medication regimens continues to be a prevalent barrier to achieving optimal blood pressure and health outcomes in patients with hypertension.

For hypertensive patients in low- and middle- income countries, the rates of non-adherence to hypertensives regimen were up to from 45.2 to 66.7% (Abegaz et al., 2017; Nielsen et al., 2017; Rampamba et al., 2018). Only 6.2% of hypertensive patients had high adherence to their medication regimens in Saudi Arabia (Fatani et al., 2019). High rates of poor adherence to medication regimens for Chinese hypertensive patients were also found in several studies (63.6–78.7%) (Hou et al., 2016; Pan et al., 2017; Shi et al., 2019). In addition, different kinds of associated factors of poor or non-adherence have also been confirmed in lots of recent studies. For example, socio-demographic factors including gender, age, education level, occupational status, or even race; (Abegaz et al., 2017; Lee et al., 2017; Fatani et al., 2019) socio-economic status including annual income and medical insurance; (Boima et al., 2015; Nielsen et al., 2017) clinical characteristics for patients including family disease history, number of prescribed drugs, comorbidity, and duration of hypertension (Choi et al., 2018; Uchmanowicz et al., 2019). Most importantly, psychosocial factors also exert significant influence on medication adherence, including depressed emotion, perceived severity of disease, self-rated health, perceived symptoms, and self-efficacy (Al-Noumani et al., 2018; Asgari et al., 2019).

Previous studies have shown that hypertension patients with higher health literacy also have higher adherence to medication(Mcnaughton et al., 2014; Lor et al., 2019) People with low levels of health literacy were more likely to misinterpret information on drug labels and less likely to participate in drug decision-making and actively communicate drug information with doctors (Aboumatar et al., 2013; AbuAlreesh and Alburikan, 2019). In addition, medication literacy is health literacy in the context of medication use (Ngoh, 2009; Peiravian et al., 2014). The definition of medication literacy is the degree to which individuals can obtain, comprehend, communicate, calculate, and process patient-specific information about their medication to make informed medication and health decisions in order to safely and effectively use their medications regardless of the mode by which the content is delivered (e.g., written, oral, and visual) (Pouliot et al., 2018). Four core elements of medication literacy include knowledge, attitude, skill and behavior. Each domain is essential and critical for processing medication information and correct medication use (Zheng et al., 2017; Shi et al., 2019) In the process of disease self-management, medication literacy, to a certain extent, determines how well patients can manage their medication regimens correctly and tailor their medication behaviors. Medication literacy can be used as a significant predictor of correct medication use (Zheng et al., 2015). In the study of Shi et al. (Shi et al., 2019) medication literacy was found to be a positive independent predictor of medication adherence for hypertensive patients. However, the specific mechanism mediating the relationship between hypertensive patients' medication literacy and their adherence to medication regimens remains unclear and needs to be further studied.

Self-efficacy refers to the individual's confidence to make use of his or her own ability to achieve a certain goal, which can determine the individual's choices, persistence and effort toward the task. It also affects the individual's way of thinking and feeling in the process of executing the task (Bandura et al., 1999). Previous studies have shown that self-efficacy was one of the determinants of medication adherence in patients with chronic diseases (Daniali et al., 2017; Huang et al., 2018). Patients with high levels of self-efficacy had greater confidence that they would be willing to take antihypertensive drugs as prescribed on different occasions (Schoenthaler et al., 2016; Yang et al., 2016). In other words, individuals with higher self-efficacy level have significantly increased chances of adhering to medication regimens (Elder et al., 2012; Warren-Findlow et al., 2012; Alhalaiqa et al., 2013). Moreover, self-efficacy can not only directly affect patients' adherence to medication but also mediates the relationship between medication adherence and a variety of psychosocial factors, such as health literacy, depression, and weight discrimination (Richardson et al., 2014; Son and Won, 2017; Huang et al., 2018; Huang et al., 2018). Considering that

medication literacy is health literacy in the context of medication use, we can reasonably assume that self-efficacy may be an important mediating factor between medication literacy and medication adherence.

To our knowledge, there have been few studies exploring the role of self-efficacy in mediating medication literacy and medication adherence in patients with hypertension. Knowledge about the specific role of self-efficacy in the relationship between medication literacy and medication adherence may help to develop effective interventions to promote hypertensive patients' adherence to their medication regimens and improve health outcomes. Thus, the purpose of this study was to investigate the mediating effect of self-efficacy on the relationship between medication literacy and medication adherence.

METHODS

Study Design

This was a cross-sectional study and was conducted at five general hospitals and three community healthcare services in a southern province of China from March 2018 to August 2018. Purposive sampling method was used in this study. One questionnaire with three scales were administered to hypertensive patients in the outpatient department face to face. For completing three different evaluating scales along with the characteristic information questionnaires, it took about 20 min for each patient. All the patients who participated in the study signed the informed consent in person.

Participants and Procedures

Patients were included if they 1) were aged 18 years or older; 2) had been diagnosed with hypertension by a cardiologist; 3) had been on antihypertensive treatment for at least 2 weeks; 4) speak Chinese and communicated well with others; and 5) understood the purpose and process of the study and agreed to participate. Patients were excluded if they 1) had other serious diseases, such as cancer, acute myocardial infarction, cerebral hemorrhage or chronic renal failure; 2) had secondary hypertension, such as elevated blood pressure caused by chronic renal dysfunction diseases; or 3) were diagnosed as psychological or mental impairment according to International Classification of Diseases (ICD) guideline, or were on the psychotherapy treatment. Eligible hypertensive patients were invited to participate in the study. They were provided with information on the purpose and content of the study, the investigation procedures, and the principle of anonymity of this study. The questionnaires were completed after the patient signed the informed consent form. For illiterate patients, we communicated with both them and their family members, if they agree to participate in the study, then they were instructed by one of their family members to sign the informed consent forms. In the present study, 5 master's degree students were trained to distribute and collect the questionnaires. For the illiterate participants, the researchers read the questions verbatim and recorded their answers. All questionnaires were immediately collected onsite upon completion, and collected questionnaires were checked for any missing information to ensure data integrity.

Data Collection Tools

Sociodemographic and Clinical Characteristics

The following information about patients' sociodemographic and clinical characteristics was collected using a self-made questionnaire: age, gender, education level, annual income, duration of hypertension, number of antihypertensive drugs prescribed, and number of times antihypertensive drugs taken daily.

Chinese Medication Literacy Scale for Hypertensive Patients

C-MLSHP is a self-administered medication literacy measure for hypertensive patients, and it was developed by our research team (Zhong et al., 2020). This scale included 37 items on four domains of knowledge, attitude, skill, and behavior. The knowledge domain has 9 items, the attitude domain includes 8 items, the skill domain has 7 items, and the behavior domain involves 13 items. The total score for this scale ranges from 0 to 37, and higher scores indicate higher medication literacy levels. Specifically, in the knowledge and skill domains, answering right for each item scores 1, and a wrong answer for each item scores 0. Each item in the attitude and behavior domains has a 5-point Likert response, and scores of 1.0, 0.75, 0.5, 0.25, and 0 are assigned to the respective answers. In addition, 5 items in the attitude domain and 1 item in the behavior domain are scored in a reverse way.

For the C-MLSHP, 637 Chinese hypertensive patients were included for reliability and validity test. The calculated Cronbach's α coefficient for the overall scale was 0.849, and for each domain, the Cronbach's α coefficients ranged from 0.744 to 0.783. For the whole scale, the calculated split-half reliability was 0.893, and for each domain, it ranged from 0.793 to 0.872. The calculated test-retest reliability of the whole scale was 0.968. For each domain, the test-retest reliability coefficients ranged from 0.880 to 0.959. Therefore, good reliability of C-MLSHP was confirmed. Good content validity and acceptable construct validity of the whole scale was also confirmed. It showed a good content validity index above 0.8 for each item of this scale and for the overall scale (0.968).

Morisky Medication Adherence Scale-8

The MMAS-8 was originally developed by Morisky and his research team (Morisky et al., 2008). It is a concise, pragmatic and cost-effective self-administered measure, mainly used to evaluate medication adherence level. The scale includes 8 items and is confirmed to have good reliability and validity in patients with hypertension. The Cronbach's alpha coefficient of this scale was 0.83. In this scale, yes and no are the answer options for seven items, and the last question is answered on a 5-point Likert scale. The total score on this scale ranges from 0~8. Higher scores represent better adherence to hypertensive drugs. Morisky's suggested cut-off point of 6 was applied: MMAS score <6 (low adherence), score =8 (high adherence), and

score ≥ 6 and <8 (medium adherence). The Chinese version of the MMAS-8 (C-MMAS-8) was translated by Yan, and it was first applied in Chinese myocardial infarction patients (Yan et al., 2014). Good reliability and validity (Cronbach's α = 0.77, pretest–posttest correlation coefficient 0.88) were identified in Chinese myocardial infarction patients (Yan et al., 2014). Every item of the Chinese version of MMAS-8 that was used in the present study has nothing different from the original English version except from the language difference.

Medication Adherence Self-Efficacy Scale-Revision

MASES-R is a self-administered scale with a single domain including 13 items. It was originally adapted for hypertensive African Americans by Professor Ogedegbe and his group at New York University School of Medicine (Fernandez et al., 2008). It aims to measure medication adherence self-efficacy for hypertensive patients. All the items in this scale cover a variety of circumstances hypertensive patients may encounter during the process of their everyday medication administration. Each item has a 4-point Likert response scale (0 = not sure at all, 1 = a little sure, 3 = pretty sure, 4 = fully sure). The total score for this scale is calculated as the average score of all the items, ranging from 1 to 4. A higher score indicates higher medication adherence self-efficacy. We were authorized by Professor Ogedegbe to translate the MASES-R into Chinese version and test its reliability and validity in 445 Chinese hypertensive patients. Acceptable reliability and validity were identified. Specifically, the correlation coefficients between each item and the total scale ranged from 0.660 to 0.919, and the correlations for each item ranged from 0.514–0.872. As for the validity of this scale, the I-CVI for each item was 0.83–1.00, and the S-CVI for the whole scale was 0.961. For exploratory factor analysis, the KMO value was 0.920, and Bartlett's spherical test chi-square value was 6405.74 ($p < 0.001$). The factor loading coefficient ranged from 0.640 to 0.916, and the cumulative variance contribution rate of the overall scale was 68.72%. The Cronbach's α coefficient of the scale was 0.960, and the Spearman-Brown split-half reliability was 0.927.

Data Analysis

All data were analyzed using SPSS 24.0 (IBM Corp., Armonk, NY, USA). All continuous variables with normal distribution were described in means and standard deviation (mean ± SD), and the categorical variables were summarized by numbers or percentages. The scores of medication literacy, self-efficacy, and medication adherence among hypertensive patients with different sociodemographic and clinical characteristics were compared using the independent-sample *t* test or analysis of variance. Pearson correlation analysis was used to determine the correlation among medication literacy, self-efficacy, and medication adherence. The mediating analytic framework described by Baron and Kenny (Baron and Kenny, 1986) guided the analysis plan. The capital letters X, M, and Y were used to represent medication literacy, self-efficacy, and medication adherence, respectively. Variable M was considered a mediator if 1) X significantly predicted Y directly (Path c in **Figures 1, 2**) X significantly predicted M (Path a in **Figure 1**), or 3) M significantly predicted Y after controlling for X (Path b **Figure 1**) (Huang et al., 2018). Path c' meant the direct effect of X on Y after controlling for M (Path c' in **Figure 1**). If the regression correlation coefficient of path c' was not significant, then this mediating effect of M was complete mediation. If the regression correlation coefficient of path c' was significant, then this mediating effect of M was partial mediation. The mediation effect value was calculated as a*b, and the ratio of the mediating effect with the total effect was a*b/c. The mediation effect value was tested by a bootstrap approach to verify the existence of a mediation effect (a is the regression correlation coefficient of path a; b is the regression correlation coefficient of path b; c or c' is the regression correlation coefficient of path c or path c') (Preacher and Hayes, 2004). A two-sided test was performed at a 0.05 significance level.

RESULTS

Scores of Medication Literacy, Self-Efficacy, and Medication Adherence in Hypertensive Patients

In total, 850 hypertensive patients were surveyed in this study, and 790 surveys were completed, yielding a response rate of 92.94%. Demographic and clinical characteristics, medication literacy, self-efficacy, and medication adherence scores of the studied participants are presented in **Table 1**. Participants with different education levels, annual income and different number of antihypertensive drugs prescribed had significantly different scores of medication literacy, adherence to medication and self-efficacy. Age difference in patients could lead to varying medication adherence level in a significant level. Different duration of hypertension for participants had significantly different medication literacy level. In addition, seventy-two (9.1%) of the hypertensive patients had high medication adherence, 237 (30.0%) had moderate medication adherence, and 481 (60.9%) had low medication adherence. The average scores for medication literacy, self-efficacy, and medication adherence were 23.83 ± 4.99, 3.04 ± 0.54, and 4.95 ± 2.16, respectively.

Correlations Between Medication Literacy, self-efficacy, and Medication Adherence

The scores for the total medication literacy scale and for each dimension were positively correlated with the score for the self-efficacy scale at a significant level ($r = 0.408$, $p < 0.001$). The scores for the total medication literacy scale and for each dimension were also positively correlated with the score for the scale of medication adherence ($r = 0.585$, $p < 0.001$). In addition, the score for the self-efficacy scale was significantly positively correlated with the score for medication adherence ($r = 0.591$, $p < 0.001$) (**Table 2**).

Analysis of the Mediating Role of Self-Efficacy Between Medication Literacy and Medication Adherence

Figure 2 indicates the mediating role of self-efficacy in the relationship between medication literacy and medication adherence. The results showed that after controlling for

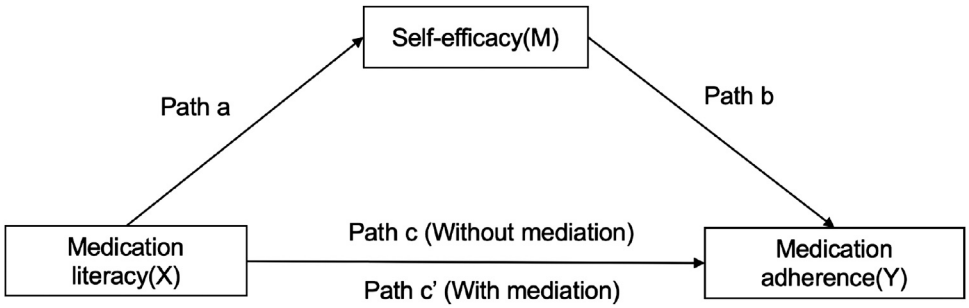

FIGURE 1 | Theoretical framework of this study.

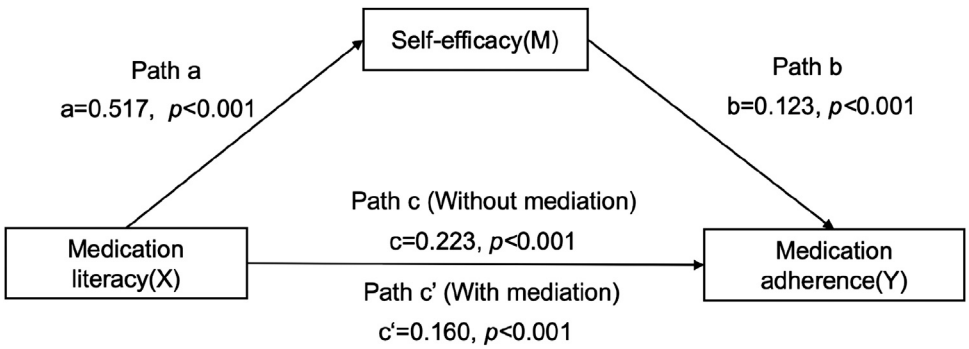

FIGURE 2 | Mediating role of self-efficacy on the relationships between. medication literacy and medication adherence.

sociodemographic and clinical variables, a significant total effect of medication literacy on medication adherence was identified (Path c: c = 0.223, t = 17.396, $p < 0.001$). In path a, medication literacy had a positive impact on self-efficacy (Path a:a = 0.517, t = 10.753, $p < 0.001$). In addition, both medication literacy and self-efficacy had a positive impact on medication adherence (Path c': c' = 0.160, t = 13.073, $p < 0.001$; b = 0.123, t = 14.514, $p < 0.001$). The mediation effect value was calculated as 0.517*0.123, that is, 0.064, and the ratio of the mediating effect over the total effect was 28.7% (0.064/0.223 = 0.287). A summary of the mediating effects of self-efficacy between medication literacy and medication adherence is shown in **Table 3**.

In addition, the mediating effect test was conducted by the bootstrap method with 1000 samples. The results showed that the 95% confidence interval of the mediating effect value of self-efficacy did not include zero (95% CI: 0.051~0.079, Z = 8.678, $p <$ 0.001), indicating that self-efficacy had a significant mediating effect on the relationship between medication literacy and medication adherence.

The regression correlation coefficients of Path a, Path b, Path c and Path c' were all significant. Therefore, self-efficacy had a partial mediating effect on the relationship between medication literacy and medication adherence. Medication literacy predicted hypertensive patients' adherence to medication partially through self-efficacy.

DISCUSSION

In this study, 60.9% of participating hypertensive patients were low adherent to their medication regimens. This result was consistent with findings in other studies worldwide (Warren-Findlow et al., 2012; Son and Won, 2017). Therefore, the majority of hypertensive patients in China and other countries have poor adherence to their medication regimens. That could be a major problem for hypertensive patients to reach an optimal blood pressure control. In addition, nonadherence to antihypertensive drugs could eventually accelerate the development of hypertension-related complications, increasing the hospital readmission rate and increasing the consumption of medical resources (Dragomir et al., 2010). Besides, education level, annual income, number of antihypertensive drugs prescribed and number of times antihypertensive drugs taken daily were identified as influencing factors of medication adherence in this study. Similar influencing factors of medication adherence for hypertensive patients have also been identified in previous studies (Al-Ruthia et al., 2017; Rampamba et al., 2018). The total score for the medication literacy scale was 23.83 ± 4.99 in our study. Several studies have also identified an insufficient medication literacy level using the same research tools as we did (Ma et al., 2019; Shi et al., 2019). Obviously, compared with the full score of 37, the medication literacy level for Chinese hypertensive patients need to be further improved. Inappropriate medication use was

TABLE 1 | Scores on medication literacy, self-efficacy and medication adherence of hypertensive patients of different characteristics (N = 790).

Factors	Items	N	Medication literacy	Self-efficacy	Medication adherence
Age	18–44	40	22.90 ± 5.84	2.92 ± 0.59	4.82 ± 2.43
—	45–59	329	23.56 ± 4.74	3.00 ± 0.52	4.65 ± 2.17
—	≥60	421	24.13 ± 5.09	3.08 ± 0.55	5.19 ± 2.09
F value	—	—	1.916	2.890	5.094
p value	—	—	0.148	0.056	0.003
Gender	Male	427	0.64 ± 0.14	3.03 ± 0.53	4.85 ± 2.25
—	Female	363	0.64 ± 0.13	3.05 ± 0.56	5.06 ± 2.04
F value	—	—	0.037	0.186	1.885
p value	—	—	0.847	0.666	0.170
Education level	Primary or below	233	0.59 ± 0.12	2.91 ± 0.52	4.13 ± 2.07
—	Junior middle school	213	0.65 ± 0.14	3.01 ± 0.58	4.85 ± 2.31
—	Senior high school or secondaryspecialized school	208	0.66 ± 0.12	3.11 ± 0.48	5.40 ± 1.98
—	Junior college	93	0.69 ± 0.13	3.17 ± 0.54	5.69 ± 1.79
—	Bachelor degree or above	43	0.74 ± 0.14	3.19 ± 0.62	6.13 ± 1.77
F value	—	—	18.301	6.938	18.296
p value	—	—	0.000***	0.000***	0.000***
Annual income	<10,000/year	94	0.61 ± 0.13	2.88 ± 0.60	4.06 ± 2.62
—	10,000–29,999/year	163	0.63 ± 0.15	2.94 ± 0.55	4.33 ± 2.09
—	30,000–49,999/year	241	0.62 ± 0.12	3.06 ± 0.54	5.09 ± 1.91
—	50,000–99,999/year	198	0.66 ± 0.12	3.10 ± 0.45	5.32 ± 2.00
—	≥100,000/year	94	0.72 ± 0.14	3.18 ± 0.57	5.79 ± 2.16
F value	—	—	11.370	5.563	13.416
p value	—	—	0.000***	0.000***	0.000***
Duration of hypertension	<3 years	105	0.62 ± 0.15	2.98 ± 0.54	4.79 ± 2.54
—	3–4.9 years	118	0.61 ± 0.14	3.02 ± 0.53	4.64 ± 2.10
—	5–9.9 years	288	0.65 ± 0.13	3.06 ± 0.48	4.99 ± 2.01
—	≥10 years	279	0.66 ± 0.14	3.04 ± 0.60	5.09 ± 2.17
F value	—	—	5.001	0.544	1.419
p value	—	—	0.002**	0.652	0.236
Number of antihypertensive drugs prescribed	One	629	0.65 ± 0.13	3.06 ± 0.52	5.01 ± 2.06
—	2–3 kinds	134	0.65 ± 0.14	2.95 ± 0.63	4.83 ± 2.45
—	4 or more	27	0.58 ± 0.13	2.82 ± 0.37	4.01 ± 2.74
F value	—	—	3.440	4.586	3.068
p value	—	—	0.033*	0.010*	0.047*
Number of times antihypertensive drugs taken daily	Once	632	0.64 ± 0.13	3.07 ± 0.52	4.92 ± 2.11
—	2–3 times	138	0.65 ± 0.15	2.91 ± 0.62	5.28 ± 2.39
—	4 or more	20	0.60 ± 0.12	2.87 ± 0.31	3.70 ± 1.44
F value	—	—	1.432	5.967	5.143
p value	—	—	0.240	0.003**	0.006**

*Note: *p < 0.05; **p < 0.01; ***p < 0.001. The level of adherence was measured through the eight-item Morisky Medication Adherence Scale (MMAS-8). Use of the MMAS is protected by US copyright laws. Permission for use is required. A licensing agreement is available from: Donald E. Morisky, ScD, ScM, MSPH. Use of the ©MMAS is protected by US copyright and registered trademark laws. Permission for use is required. A licensing agreement is available from: Donald E. Morisky, 294 Lindura Court, Las Vegas, NV 89138-4632; dmorisky@gmail.com. The scale's questions are available in the originally published article.*

TABLE 2 | Correlation between hypertensive patients' medication literacy,self-efficacy and medication adherence.

Variables	Knowledge literacy	Attitude literacy	Skill literacy	Behavior literacy	Medication literacy	Self-efficacy	Medication adherence
Knowledge literacy	1	—	—	—	—	—	—
Attitude literacy	0.377**	1	—	—	—	—	—
Skill literacy	0.412**	0.316**	1	—	—	—	—
Behavior literacy	0.325**	0.349**	0.235**	1	—	—	—
Medication literacy	0.768**	0.643**	0.705**	0.701**	1	—	—
Self-efficacy	0.294**	0.334**	0.264**	0.285**	0.408**	1	—
Medication adherence	0.422**	0.493**	0.295**	0.478**	0.585**	0.591**	1

*Note: **p < 0.01.*

TABLE 3 | Summary of the mediating effects of self-efficacy between medication literacy and medication adherence.

Effect	Independent variables	Dependent variables	B	SE	*t*	*p* value	95%CI
Total effect(c)	X	Y	0.223	0.013	17.396	0.000***	0.198–0.248
Indirect effect(a)	X	M	0.517	0.048	10.753	0.000***	0.422–0.611
Indirect effect(b)	M	Y	0.123	0.008	14.514	0.000***	0.107–0.140
Direct effect (c')	X	Y	0.16	0.012	13.073	0.000***	0.136–0.184

*Note: ***p < 0.001; B, unstandardized coefficient; SE, standard error; X, medication literacy; M, self-efficacy; Y, medication adherence.*

identified to be significantly associated with low medication literacy level (Chun-Hsien et al., 2017).

In addition, the results in the present study showed that education level, annual income, duration of hypertension, and number of antihypertensive drugs prescribed for hypertensive patients could also affect their medication literacy level. These findings were consistent with those in prior study (Ma et al., 2019). In previous study, occupational status and the type of medical insurance for hypertensive patients could also affect their medication literacy level (Ma et al., 2019). In the present study, patients with higher education level and annual income tended to have higher medication literacy and medication adherence levels. we speculate that patients with higher education and income might have more access to medication knowledge and have better understanding of antihypertensive drugs, which will be important basic abilities for patients to form positive attitudes and adherent behaviors to taking medication. Therefore, patients who are less educated and earned less should be targeted for medication literacy and medication adherence improvement. We also found that those who had longer duration of hypertension or had a smaller number of antihypertensive drugs prescribed were more likely to have higher medication literacy level. It indicated that health counsellors should focus on hypertensive patients who are with shorter duration since they were diagnosed and those who are prescribed with a more complexed medication regimen.

Furthermore, medication literacy was found to be positively correlated with medication adherence for hypertensive patients in the present study. The results of hierarchical regression analysis also showed that medication literacy was an independent predictor of medication adherence after controlling for sociodemographic and clinical information. This was consistent with the study of Shi et al. (Shi et al., 2019). The reason might be that patients with higher medication literacy are more likely to make medication decisions correctly according to acquired information. In contrast, inadequate medication literacy could result in misunderstanding of medication-related information or negative attitudes to taking antihypertensive drugs, leading to poor adherence to taking antihypertensive drugs.

Self-efficacy was found to be positively correlated with medication adherence for hypertensive patients. In addition, self-efficacy was also confirmed an independent predictor of medication adherence in the present study. This result was consistent with several previous studies (Bane and Mcelnay, 2010; Breaux-Shropshire et al., 2012; Francois, 2015) Individuals with a higher level of self-efficacy are more likely to be adherent to antihypertensive regimens. Possible reason might be that hypertensive patients who have insufficient self-efficacy negatively reckon they have no ability to persistent in lifetime medication taking.

After controlling for patient demographic and clinical characteristics, self-efficacy was found to be a partial mediator on the relationship between medication literacy and medication adherence in the present study. Medication literacy includes knowledge, attitude, behavior and skills to use specific medication for patients (Zhong et al., 2020). In the study of Shi et al. (Shi et al., 2019), knowledge, attitude, behavior and skills as well as the overall score of medication literacy were found to be significantly correlated with medication adherence, though, only attitude and behavior were confirmed as significant predictors of medication adherence. Moreover, identified significant predictors of attitude, behavior and annual income can only explain 15.8% of the variation in patients' adherence level. However, in the present study, we found that medication literacy had a significant total effect on medication adherence after other variables including demographic and clinical characteristics were controlled. Therefore, medication literacy was verified as an independent predicator for medication adherence in hypertensive patients. Consequently, self-efficacy exerted a significant effect on partially mediating the association between medication literacy and medication adherence, and the mediating effect value was 28.7%. This result was consistent with a previous study, in which the mediating effect of self-efficacy on the association between health literacy and medication adherence among patients with diabetes was tested and confirmed (Huang et al., 2018). Despite optimal medication literacy including knowledge, attitude, behavior and skills in the process of antihypertensives administration was extremely important for patients to have a better adherence in taking antihypertensive drugs, self-efficacy also played a critical mediating role in promoting patients' medication adherence. Possible explanation for this interaction is that optimal medication literacy could be basic essentials for hypertensive patients to process and administer antihypertensives in a correct and effective way, but higher self-efficacy even convinces themselves to believe that they have abilities to persist in taking antihypertensives in their lifetime. Basic essentials of optimal medication literacy level involve adequate hypertension related knowledge, positive attitudes to hypertension and treatment strategies, skills like numeracy and calculating, and correct behaviors in processing medication (Shi et al., 2019). In

previous studies, self-efficacy has also been identified as an important mediating factor on the relationship among weight discrimination and depression with medication adherence (Richardson et al., 2014; Son and Won, 2017). Therefore, self-efficacy is a vital mediating predictor of medication adherence. It is imperative that self-efficacy should be targeted to address the medication adherence gap worldwide.

According to the results of this study, we can put forward some suggestions from two aspects to improve hypertensive patients' adherence to their medication regimens. First, effective interventions to improve patients' medication literacy should be designed and implemented. In addition, hypertensive patients with suboptimal medication literacy should be tested using evaluation tools in the beginning. Besides, health education materials should be designed as simple and easy to understand as possible. Second, for hypertensive patients with low medication literacy, self-efficacy should also be focused on in order to promote their medication adherence. Some social cognitive and behavioral therapies in psychological treatment can be incorporated to improve self-efficacy for hypertension patients. For example, Sukwatjanee (Arissara, 2014) has effectively improved the perceived self-efficacy level of hypertension patients on a healthy diet by implementing a motivational project including health education, focus group discussion, diet supervision, mailed reminders and telephone consultation. Specifically, the knowledge gained through experience sharing, the understanding and self-confidence enhanced by group discussion, and the social support and authorization obtained by participating in incentive plans all played a significant role in the improvement of patients' self-efficacy.

STUDY LIMITATIONS

There are some limitations to this study. First, self-reported tools were used to measure medication adherence in the present study. Adherence results obtained from objective measures such as automated pill counters or biochemical indicators might be more convincing. Second, although the *C-MLSHP* and *MASES-R* are validated and reliable scales to measure medication literacy and self-efficacy, they both lack cut-off points to classify specific levels. Finally, all variables in this cross-sectional study were collected in a questionnaire survey, so we were unable to determine the continuous changes in medication literacy, self-efficacy and medication adherence. Continuous-follow-up investigations should be carried out on patients with hypertension.

CONCLUSION

Our study demonstrates that self-efficacy has a partial significant mediating effect on the relationship between medication literacy and medication adherence. Considering the prevalence of poor adherence to antihypertensive regimens among patients with hypertension, targeted interventions to improve patients' self-efficacy could increase the confidence of hypertensive patients to adhere to their medication regimens. In addition, health care providers should be aware of the importance of medication literacy assessment and promotion in patients with hypertension.

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 the Third Xiangya Hospital of Central South University (No. 2016-S050). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZZ was in charge of this whole project and designed and instructed the research; ZS made contributions to data analysis and drafted the manuscript; SS contributed to collecting data; SD instructed the data collection and data analysis.

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Use of Cardiovascular Drugs for Primary and Secondary Prevention of Cardiovascular Disease Among Rural-Dwelling Older Chinese Adults

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Cardiovascular risk factors and related disorders are common among older adults, and use of various classes of cardiovascular (CV) drugs could reduce the risk of cardiovascular disease (CVD). However, data are sparse with regard to the use of CV drugs among rural-dwelling older adults in China. Therefore, this population-based study aimed to describe use of CV drugs among older adults living in the rural communities in China, while taking into account the use of CV drugs for primary and secondary prevention of CVDs. This study included 5,246 participants (age ≥65 years; 57.17% women; 40.68% illiteracy) in the baseline examination of the MIND-China study. In March-September 2018, data on health-related factors, CVDs (ischemic heart disease, atrial fibrillation, heart failure, and stroke), and CV drug use were collected via face-to-face survey, clinical examination, and laboratory tests. We classified CV drugs according to the Anatomical Therapeutic Chemical classification system for western medications and specific cardiovascular effects for the products of traditional Chinese medicine (TCM). We conducted descriptive analysis. The overall prevalence of major cardiovascular risk factors ranged from 14.30% in diabetes and 23.81% in dyslipidemia to 66.70% in hypertension, and CVDs affected 35.07% of all participants (36.28% in women vs. 33.47% in men, p = 0.035). In the total sample, calcium channel blockers (C08) were most commonly used (10.39%), followed by TCM products (7.64%), hypoglycemic agents (A10, 4.73%), renin-angiotensin system (RAS)-acting agents (C09, 4.61%), and lipid-lowering agents (C10, 4.17%). The proportions of CV drugs for primary prevention (i.e., use of CV drugs among people without CVD) were 3.14% for antithrombotic agents (mainly aspirin), 1.38% for lipid-lowering agents, and 3.11% for RAS-acting agents; the corresponding figures for secondary prevention (i.e., use of CV drugs among people with CVD) were 13.97%, 9.35%, and 7.39%. In conclusion, despite highly prevalent cardiovascular risk factors and CVDs, a fairly low proportion of the rural-dwelling older adults take CV medications for primary and secondary prevention. Notably, TCM products are among the most commonly used CV drugs. These results call for additional efforts to promote

implementation of the evidence-based recommendations for prevention of CVDs in the primary care settings.

Keywords: cardiovascular drugs, cardiovascular disease, prevalence, prevention, rural

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of premature death in China, contributing to ~40% of all deaths (Zhou et al., 2016). Since the 1990s, the age-standardized mortality of CVD has steadily declined among urban residents in China, but the declining trend was not evident among people living in the rural areas (Sun et al., 2017).

Cardiovascular (CV) drugs are the most commonly used therapeutic classes of drugs in older adults (Schwartz et al., 2019). It has been well established that various CV drug therapies among people at risk could reduce the risk of developing CVD and death from CVD (Khatib et al., 2016). CV drugs, such as renin-angiotensin system (RAS)-acting agents, beta-blockers, antithrombotic agents, and lipid-lowering drugs, have been widely recommended by the international guidelines for the primary or secondary prevention of CVD (Smith et al., 2011; Arnett et al., 2019).

Despite the strong scientific evidence, a substantial gap between the guidelines of CV drug therapies and the implementation in primary health care remained in China (Du et al., 2019). The main risk factors for CVD, such as hypertension, dyslipidemia, and diabetes mellitus, remained highly prevalent and poorly managed in China, especially among elderly residents living in the rural areas (Song et al., 2014). Data from both the Prospective Urban Rural Epidemiological (PURE)-China study (Yusuf et al., 2011) and the China Kadoorie Biobank (CKB) study (Chen et al., 2014) showed that less than one-third of people with CVDs received the proven CV drugs for secondary prevention.

The majority of cardiovascular epidemiological studies in China have focused on urban populations, and relatively few studies on the management of CVDs in rural settings are available. Studying preventive and therapeutic CV drug use in the rural areas in China is important because over 50% of people live outside cities, and optimal use of scarce healthcare resources is vital (Liu et al., 2008). Therefore, the objective of this population-based study was to determine the prevalence of CV drug use among rural-dwelling older Chinese adults (age ≥65 years) and to identify CV drugs commonly used for primary and secondary prevention of CVDs.

METHODS

Study Design and Participants

This population-based study is planned within the Multimodal Interventions to Delay Dementia and Disability in Rural China (MIND-China) study (Kivipelto et al., 2020). In brief, the MIND-China study targeted residents from 52 villages in the rural areas of Western Shandong Province (Yanlou Town of Yanggu county). In March-September 2018, baseline assessments and screenings for participants were completed, during which 5,765 subjects who were 60 years of age or older were examined. After exclusion of subjects aged 60–64 years (n = 519) due to relatively low participating rate, a total number of 5,246 (91.0%) people were included in this analysis.

The MIND-China protocol has been approved by the Ethics Committee at Shandong Provincial Hospital, Jinan, Shandong, China. Written informed consent was obtained from all participants, or in the case of cognitively impaired persons, from a proxy (usually a guardian or a family member).

Data Collection and Definitions

The baseline examination included a face-to-face interview carried out by trained research staff with a structured questionnaire (e.g., lifestyle and medical history), physical and neurological examination (e.g., height, weight, blood pressure, pulse rate, and neurological disorders), electrocardiogram (ECG) examination, and laboratory test (e.g., fasting blood glucose and lipids). During the interview, a detailed medical history was sought from participants with the questions: "Has a doctor EVER told you that you had the following disease?", followed by a list of major health conditions, such as hypertension, dyslipidemia, diabetes mellitus, ischemic heart disease (IHD), heart failure (HF), atrial fibrillation (AF), and stroke. Then participants were asked: "Are you currently (in the past two weeks) taking any medicines, tablets or injections of any kind drugs, either you buy yourself or are prescribed by your doctor?". If the answer was 'Yes', details of medicines were recorded, including name, dosage, and frequency. All western medications were classified and coded according to the Anatomical Therapeutic Chemical (ATC) classification system. The classes of CV drugs included antithrombotic agents (ATC code B01), diuretics (C03), beta-blockers (C07), calcium channel blockers (C08), renin-angiotensin system (RAS)-acting agents (C09), lipid-lowering drugs (C10), and cardiac drugs (C01). Because products of traditional Chinese medicine (TCM) were widely provided to the local residents by the primary healthcare institutions, we also recorded TCM products that were used for the treatment and control of CVDs and risk factors, and classified the TCM products according to their specific cardiovascular effects (e.g., TCM products for CVDs, hypertension, lipids lowering, and diabetes). Numbers of concurrent use of CV drugs included both western medications and TCM products.

Hypertension was defined as systolic blood pressure of at least 140 mmHg or diastolic blood pressure of at least 90 mmHg, or use of any antihypertensive drugs (ATC codes C02, C03, C07-C09, and TCM products for lowering blood pressure) in the past two weeks (James et al., 2014; Joint Committee for Guideline Revision, 2019). Dyslipidemia was defined as total cholesterol (TC) ≥240 mg/dl, low-density lipoprotein cholesterol (LDL-C)

TABLE 1 | Characteristics of study participants in the total sample and by gender and cardiovascular disease.

Characteristics	Total Sample (n = 5,246)	Gender			Cardiovascular disease		
		Men (n = 2,247)	Women (n = 2,999)	*p*-value[a]	No (n = 3,406)	Yes (n = 1840)	*p*-value[a]
Age (years), mean (SD)	71.74 (5.52)	71.58 (5.36)	71.86 (5.63)	0.071	71.51 (5.49)	72.16 (5.54)	<0.0001
Age group (years)				0.001			<0.0001
65–69	2,209 (42.11)	969 (43.12)	1,240 (41.35)		1,535 (45.07)	674 (36.63)	
70–74	1,688 (32.18)	703 (31.29)	985 (32.84)		1,040 (30.53)	648 (35.22)	
75–79	792 (15.10)	371 (16.51)	421 (14.04)		485 (14.24)	307 (16.68)	
≥80	557 (10.62)	204 (9.08)	353 (11.77)		346 (10.16)	211 (11.47)	
Education level				<0.0001			0.741
Illiteracy	2,134 (40.68)	325 (14.46)	1809 (60.32)		1,388 (40.75)	746 (40.54)	
Primary school	2,270 (43.27)	1,210 (53.85)	1,060 (35.35)		1,481 (43.48)	789 (42.88)	
Middle school and above	842 (16.05)	712 (31.69)	130 (4.33)		537 (15.77)	305 (16.58)	
Obesity	1,201 (22.89)	427 (19.00)	774 (25.81)	<0.0001	682 (20.02)	519 (28.21)	<0.0001
Current smoking	1,064 (20.28)	1,025 (45.62)	39 (1.30)	<0.0001	762 (22.37)	302 (16.41)	<0.0001
Current drinking	1931 (36.81)	1713 (76.23)	218 (7.27)	<0.0001	1,301 (38.20)	630 (34.24)	0.005
Hypertension	3,499 (66.70)	1,444 (64.26)	2055 (68.52)	0.001	2,162 (63.48)	1,337 (72.66)	<0.0001
Diabetes	750 (14.30)	255 (11.35)	495 (16.51)	<0.0001	393 (11.54)	357 (19.40)	<0.0001
Dyslipidemia	1,249 (23.81)	352 (15.67)	897 (29.91)	<0.0001	693 (20.35)	556 (30.22)	<0.0001
Cardiovascular disease	1840 (35.07)	752 (33.47)	1,088 (36.28)	0.035	—	—	—
Ischemic heart disease	1,152 (21.96)	409 (18.20)	743 (24.77)	<0.0001	—	—	—
Stroke	840 (16.03)	391 (17.40)	449 (14.99)	0.018	—	—	—
Heart failure	153 (2.92)	60 (2.67)	93 (3.10)	0.359	—	—	—
Atrial fibrillation	84 (1.60)	39 (1.74)	45 (1.50)	0.502	—	—	—

Note: Data are n (%), unless otherwise specified.

[a]*p-value is for the test of differences between women and men or between participants without and with cardiovascular disease.*

≥160 mg/dl, high-density lipoprotein cholesterol (HDL-C) <40 mg/dl, triglycerides (TG) ≥200 mg/dl, or use of lipid-lowering medications (ATC code C10 and TCM products for lowering lipids) (Wang et al., 2020). Diabetes mellitus was defined as having a fasting blood glucose ≥126 mg/dl or self-reported physician diagnosis of diabetes or use of diabetes medications (ATC code A10 and TCM products for lowering blood glucose) (American Diabetes Association, 2019). Obesity for Chinese adults was defined as body mass index (BMI) ≥28 kg/m^2 (Wan et al., 2017). IHD was identified according to self-report history of myocardial infarction (MI), angina, coronary intervention, or pathological Q waves on ECG; clinical stroke as a combination of self-reporting history of stroke or the judgment of clinical stroke by a neurologist or physician via neurological examination; and HF as self-reported physician diagnosis of HF. The diagnosis of AF was made based on ECG examination. CVDs included IHD, HF, AF, and stroke (Du et al., 2019; Liu et al., 2019).

Drug use for primary prevention of CVD was defined as use of CV drugs among persons who were free from CVDs, and drug use for secondary prevention as use of CV drugs among people who had CVDs.

Statistical Analysis

We performed descriptive analysis on the use of CV drugs. We reported frequency (%) for categorical variables (e.g., disease and medication intakes), and mean (SD) for continuous variables. We compared the medication use between genders and different CVDs by using chi-square tests. All statistical analyses were performed by using SAS 9.4 software (SAS Institute Inc., 2013; Cary, NC, United States).

RESULTS

Characteristics of the Study Population

Table 1 details the demographic features of the study population. The average age of all participants was 71.74 years (SD 5.52), 57.17% were women, and 40.68% were illiterate. Out of the 5,246 participants, hypertension was diagnosed in 3,499 (66.70%) persons, diabetes in 750 (14.30%), and dyslipidemia in 1,249 (23.81%). Overall, 1840 (35.07%) participants were ascertained to have CVD, including 1,152 (21.96%) with IHD, 153 (2.92%) with HF, 84 (1.60%) with AF, and 840 (16.03%) with clinical stroke. The crude prevalence of hypertension, diabetes, dyslipidemia, and IHD was higher in women than in men ($p < 0.05$), whereas the prevalence of stroke was higher in men than in women (17.40% vs. 14.97%, $p = 0.018$). As expected, compared with participants who were free from CVD, people with CVD had a higher prevalence of hypertension (63.48% vs. 72.66%, $p < 0.05$), diabetes (11.54% vs. 19.40%, $p < 0.05$), and dyslipidemia (20.35% vs. 30.22%, $p < 0.05$).

Cardiovascular Drug Use in the Total Sample

Overall, calcium channel blockers (C08) were most commonly used (10.39%), followed by TCM products (7.64%) and antithrombotic agents (B01, 6.94%). The overall prevalence of using other CV drugs was less than 5%, ranging from around 1.5% for diuretics (C03), beta-blockers (C07), and cardiac therapy (C01) to around 4.5% for lipid-lowering agents (C10), hypoglycemic agents (A10), and RAS-acting agents (C09). The prevalence of CV drug use was higher in women than in men for

TABLE 2 | Use of cardiovascular drugs in the total sample and by gender.

Cardiovascular drugs (ATC code)	Total sample (n = 5,246)	Men (n = 2,247)	Women (n = 2,999)	*p*-value[a]
Antithrombotic agents (B01)	364 (6.94)	161 (7.17)	203 (6.77)	0.576
Aspirin (B01AC06)	354 (6.75)	157 (6.99)	197 (6.57)	0.550
Clopidogrel (B01AC04)	10 (0.19)	4 (0.18)	6 (0.20)	0.856
Warfarin (B01AA03)	5 (0.10)	1 (0.04)	4 (0.13)	0.302
Diuretics (C03)	73 (1.39)	31 (1.38)	42 (1.40)	0.949
Beta-blockers (C07)	77 (1.47)	27 (1.20)	50 (1.67)	0.165
Calcium channel blockers (C08)	545 (10.39)	230 (10.24)	315 (10.50)	0.753
RAS-acting agents (C09)	242 (4.61)	99 (4.41)	143 (4.77)	0.536
Lipid-lowering agents (C10)	219 (4.17)	102 (4.54)	117 (3.90)	0.253
Hypoglycemic agents (A10)	248 (4.73)	80 (3.56)	168 (5.60)	0.001
Cardiac drugs (C01)	87 (1.66)	37 (1.65)	50 (1.67)	0.954
TCM products	401 (7.64)	129 (5.74)	272 (9.07)	<0.001
TCM for CVDs	323 (6.16)	112 (4.98)	211 (7.04)	0.002
TCM for hypertension	16 (0.30)	1 (0.04)	15 (0.50)	0.003
TCM for dyslipidemia	57 (1.09)	19 (0.85)	38 (1.27)	0.145
TCM for diabetes	31 (0.59)	3 (0.13)	28 (0.93)	<0.001
Numbers of cardiovascular drugs				<0.001
0	3,556 (67.78)	1,593 (70.89)	1963 (65.46)	
1	717 (13.67)	265 (11.79)	452 (15.07)	
2	446 (8.50)	190 (8.46)	256 (8.54)	
3	287 (5.47)	111 (4.94)	176 (5.87)	
4	151 (2.88)	57 (2.54)	94 (3.13)	
≥5	88 (1.68)	31 (1.38)	57 (1.90)	

Note: Data are n (%).

Abbreviations: ATC, Anatomical Therapeutic Chemical; CVD, cardiovascular disease; RAS, renin-angiotensin system; TCM, traditional Chinese medicine.

[a]*p-value is for the test of differences between women and men.*

TABLE 3 | Use of cardiovascular drugs for primary prevention among participants free of cardiovascular disease.

Cardiovascular drugs (ATC code)	Total sample (n = 3,406)	Men (n = 1,495)	Women (n = 1911)	*p*-value[a]
Antithrombotic agents (B01)	107 (3.14)	49 (3.28)	58 (3.04)	0.687
Aspirin (B01AC06)	105 (3.08)	47 (3.14)	58 (3.04)	0.855
Clopidogrel (B01AC04)	2 (0.06)	2 (0.13)	0	0.110
Warfarin (B01AA03)	1 (0.03)	0	1 (0.05)	0.376
Diuretics (C03)	28 (0.82)	12 (0.80)	16 (0.84)	0.912
Beta-blockers (C07)	13 (0.38)	7 (0.47)	6 (0.31)	0.469
Calcium channel blockers (C08)	220 (6.46)	89 (5.95)	131 (6.86)	0.288
RAS-acting agents (C09)	106 (3.11)	42 (2.81)	64 (3.35)	0.368
Lipid-lowering agents (C10)	47 (1.38)	22 (1.47)	25 (1.31)	0.685
Hypoglycemic agents (A10)	126 (3.70)	42 (2.81)	84 (4.40)	0.015
Cardiac drugs (C01)	8 (0.23)	4 (0.27)	4 (0.21)	0.728
TCM products	93 (2.73)	27 (1.81)	66 (3.45)	0.003
TCM for CVDs	56 (1.64)	19 (1.27)	37 (1.94)	0.130
TCM for hypertension	5 (0.15)	0	5 (0.26)	0.048
TCM for dyslipidemia	23 (0.68)	6 (0.40)	17 (0.89)	0.084
TCM for diabetes	20 (0.59)	2 (0.13)	18 (0.94)	0.002
Numbers of cardiovascular drugs				0.121
0	2,600 (76.34)	1,171 (78.33)	1,429 (74.78)	
1	437 (12.83)	177 (11.84)	260 (13.61)	
2	233 (6.84)	98 (6.56)	135 (7.06)	
3	92 (2.70)	33 (2.21)	59 (3.09)	
4	30 (0.88)	9 (0.60)	21 (1.10)	
≥5	14 (0.41)	7 (0.47)	7 (0.37)	

Note: Data are n (%).

Abbreviations: ATC, Anatomical Therapeutic Chemical; CVD, cardiovascular disease; RAS, renin-angiotensin system; TCM, traditional Chinese medicine.

[a]*p-value is for the test of differences between women and men.*

TABLE 4 | Use of cardiovascular drugs for secondary prevention among participants with cardiovascular disease.

Cardiovascular drugs (ATC code)	Total sample (n = 1840)	Men (n = 752)	Women (n = 1,088)	*p*-value[a]
Antithrombotic agents (B01)	257 (13.97)	112 (14.89)	145 (13.33)	0.341
Aspirin (B01AC06)	249 (13.53)	110 (14.63)	139 (12.78)	0.254
Clopidogrel (B01AC04)	8 (0.43)	2 (0.27)	6 (0.55)	0.360
Warfarin (B01AA03)	4 (0.22)	1 (0.13)	3 (0.28)	0.518
Diuretics (C03)	45 (2.45)	19 (2.53)	26 (2.39)	0.852
Beta-blockers (C07)	64 (3.48)	20 (2.66)	44 (4.04)	0.111
Calcium channel blockers (C08)	325 (17.66)	141 (18.75)	184 (16.91)	0.309
RAS-acting agents (C09)	136 (7.39)	57 (7.58)	79 (7.26)	0.797
Lipid-lowering agents (C10)	172 (9.35)	80 (10.64)	92 (8.46)	0.114
Hypoglycemic agents (A10)	122 (6.63)	38 (5.05)	84 (7.72)	0.024
Cardiac drugs (C01)	79 (4.29)	33 (4.39)	46 (4.23)	0.868
TCM products	308 (16.74)	102 (13.56)	206 (18.93)	0.002
TCM for CVDs	267 (14.51)	93 (12.37)	174 (15.99)	0.030
TCM for hypertension	11 (0.60)	1 (0.13)	10 (0.92)	0.032
TCM for dyslipidemia	34 (1.85)	13 (1.73)	21 (1.93)	0.753
TCM for diabetes	11 (0.60)	1 (0.13)	10 (0.92)	0.032
Numbers of cardiovascular drugs				0.004
0	956 (51.96)	422 (56.12)	534 (49.08)	
1	280 (15.22)	88 (11.70)	192 (17.65)	
2	213 (11.58)	92 (12.23)	121 (11.12)	
3	195 (10.60)	78 (10.37)	117 (10.75)	
4	122 (2.63)	48 (6.38)	74 (6.80)	
≥5	74 (4.02)	24 (3.19)	50 (4.60)	

Note: Data are n (%).

Abbreviations: ATC, Anatomical Therapeutic Chemical; CVD, cardiovascular disease; RAS, renin-angiotensin system; TCM, traditional Chinese medicine.

[a]*p-value is for the test of differences between women and men.*

TCM products (9.07% vs. 5.74%, $p < 0.05$) and hypoglycemic agents (5.60% vs. 3.56%, $p < 0.05$). Of note, 67.78% participants did not receive any CV drugs, 13.67% took one type of CV drug, and 8.50% took at least two CV drugs (**Table 2**).

Cardiovascular Drug Use for Primary Prevention

Table 3 shows prevalence of CV drug use for primary prevention among participants who were free from CVD. The proportion of current use of CV drugs was 3.14% for antithrombotic agents (B01, mainly aspirin), 0.82% for diuretics (C03), 0.38% for beta-blockers (C07), 6.46% for calcium channel blockers (C08), 3.11% for RAS-acting agents (C09), 1.38% for lipid-lowering agents (C10), 3.70% for hypoglycemic agents (A10), 0.23% for cardiac drugs (C01), and 2.73% for TCM products (mostly for CVDs). The prevalence for use of CV drugs was higher in women than in men for TCM products (3.45% vs. 1.81%, $p < 0.05$) and hypoglycemic agents (4.40% vs. 2.81%, $p < 0.05$). There were no significant gender differences in use of any other CV drugs. Nearly 80% of the participants reported not taking any CV drug treatment.

Cardiovascular Drug Use for Secondary Prevention

Table 4 shows rates of CV drug use in participants with CVD for the secondary prevention. Among all CV drugs, the proportion of current use of CV drugs was 13.97% for antithrombotic agents (B01, mainly aspirin), 2.45% for diuretics (C03), 3.48% for beta-blockers (C07), 17.66% for calcium channel blockers (C08), 7.39% for RAS-acting agents (C09), 9.35% for lipid-lowering agents (C10), 6.63% for hypoglycemic agents (A10), 4.29% for cardiac drugs (C01), and 16.74% for TCM products. Over 50% of participants with CVDs reported not taking any CV drug treatment, whereas nearly 17% of them concurrently used three or more of the CV drugs.

Table 5 shows the use of various classes of CV drugs in patients with IHD, HF, AF, or stroke. Patients with stroke were more likely to use antithrombotic agents (B01, 17.62%), calcium channel blockers (C08, 22.26%), and lipid-lowering agents (C10, 12.02%), compared with patients with IHD (13.72%, 16.58%, and 9.46%, respectively). The use of beta-blockers (C07), RAS-acting agents (C09), diuretics (C03), and cardiac drugs (C01) in patients with HF was 3.92%, 7.84%, 3.92%, and 8.50%, respectively. The overall utilization of antithrombotic agents (B01) in patients with AF was 14.29%, and the use of warfarin (B01AA03) was only 2.38%. Moreover, ~50% of people with IHD, AF, or stroke, and ~45% of people with HF did not take any CV drugs.

DISCUSSION

Major findings from this large-scale community-based study of rural-dwelling older adults can be summarized into two points. First, overall, a very low proportion of older adults in the rural settings in China reported taking CV medications for primary and secondary prevention of CVDs, despite highly prevalent

TABLE 5 | Use of cardiovascular drugs by cardiovascular disease.

Cardiovascular drugs (ATC code)	Ischemic heart disease (n = 1,152)	Heart failure (n = 153)	Atrial fibrillation (n = 84)	Stroke (n = 840)
Antithrombotic agents (B01)	158 (13.72)	24 (15.69)	12 (14.29)	148 (17.62)
Aspirin (B01AC06)	154 (13.37)	24 (15.69)	10 (11.90)	143 (17.02)
Clopidogrel (B01AC04)	6 (0.52)	1 (0.65)	1 (1.19)	5 (0.60)
Warfarin (B01AA03)	2 (0.17)	0	2 (2.38)	2 (0.24)
Diuretics (C03)	32 (2.78)	6 (3.92)	4 (4.76)	19 (2.26)
Beta-blockers (C07)	54 (4.69)	6 (3.92)	6 (7.14)	24 (2.86)
Calcium channel blockers (C08)	191 (16.58)	25 (16.34)	11 (13.10)	187 (22.26)
RAS-acting agents (C09)	91 (7.90)	12 (7.84)	7 (8.33)	67 (7.98)
Lipid-lowering agents (C10)	109 (9.46)	15 (9.80)	7 (8.33)	101 (12.02)
Hypoglycemic agents (A10)	80 (6.94)	13 (8.50)	4 (4.76)	58 (6.90)
Cardiac drugs (C01)	70 (6.08)	13 (8.50)	14 (16.67)	25 (2.98)
TCM products	202 (17.53)	44 (28.76)	12 (14.29)	147 (17.50)
TCM for CVDs	179 (15.54)	38 (24.84)	10 (11.90)	125 (14.88)
TCM for hypertension	6 (0.52)	2 (1.31)	0	3 (0.36)
TCM for dyslipidemia	19 (1.65)	4 (2.61)	2 (2.38)	22 (2.62)
TCM for diabetes	8 (0.69)	2 (1.31)	0	4 (0.48)
Number of cardiovascular drugs				
0	578 (50.17)	69 (45.10)	43 (51.19)	425 (50.60)
1	198 (17.19)	20 (13.07)	14 (16.67)	107 (12.74)
2	121 (10.50)	26 (16.99)	9 (10.71)	95 (11.31)
3	121 (10.50)	20 (13.07)	4 (4.76)	101 (12.02)
4	79 (6.86)	7 (4.58)	11 (13.10)	73 (8.69)
≥5	55 (4.77)	11 (7.19)	3 (3.57)	39 (4.64)

Note: Data are n (%).

Abbreviations: ATC, Anatomical Therapeutic Chemical; CVD, cardiovascular disease; RAS, renin-angiotensin system; TCM, traditional Chinese medicine.

cardiovascular risk factors and CVDs; Second, this study investigated the use of TCM products for primary and secondary CVD prevention. TCM products were the second most commonly used drugs in the total sample, and the prevalence for use of TCMs was higher in women than in men. These findings have relevant policy implications for improving preventive and therapeutic management of CVDs among older adults living in the rural communities in China.

The management of long-term chronic health conditions (e.g., CVDs) is increasingly shifting from secondary care to general practitioners. The decreasing trends in CVD mortality since the 1980s in the United Kingdom are thought partly to be due to better early treatment (Townsend et al., 2015; Bhatnagar et al., 2016). Data on medicine use from two comparable population-based studies of older people (age 65 + years) in England showed that the proportion of people who did not take any medication had decreased from around one-fifth to one-thirteenth during the past 2 decades (Gao et al., 2018). Data from the Swedish National study on Aging and Care in Kungsholmen (SNAC-K) showed that antithrombotic agents and diuretics were the most commonly prescribed medications among elderly people aged ≥60 years, with over 20% of older adults using these drugs (Ding et al., 2014). However, underuse of CV medications and poor control of risk factors are still very serious in the rural settings and low- and middle-income countries (Yusuf et al., 2011). In our study, two-thirds of the participants did not receive any CV drugs. The two most commonly used CV drugs, calcium channel blockers and TCM products, were reported to be used in less than 10% of older adults. The suboptimal use of simple, inexpensive preventive CV drug therapies suggests that implementation of the proven strategies to reduce the risk and the burden of CVDs remains to be strengthened in the rural areas in China.

The prevalence of cardiovascular risk factors and CVDs increases as people age and pharmacological therapies are crucial to reduce risk of cardiovascular events and mortality (Karmali et al., 2016). Statin therapy for people with dyslipidemia is recommended as the first-line treatment for primary prevention of CVDs (Arnett et al., 2019), which could reduce the risk of major cardiovascular events by 21% (Baigent et al., 2005). The total prevalence of dyslipidemia in our study population was above 20%. However, only 4.17% of the participants received lipid-lowering drug treatment. Hypertension is common among older adults, yet it remains inadequately controlled (Lewington et al., 2016). Our results are consistent with a previous study (Lu et al., 2017) that hypertension affected two-thirds of the study participants, but fewer than a third were being treated with antihypertensive drugs, and calcium channel blockers was the most commonly used class of antihypertensive medications. This suggests that pharmacological management of certain cardiovascular risk factors among the community-dwelling older adults needs to be improved.

It has been well established that antithrombotic treatment has beneficial effects for secondary prevention of coronary heart disease, stroke, and AF (January et al., 2019). In our study, antithrombotic agents were used by only 14.29% of people with AF, which appears to be inadequate compared to the reports from a previous hospital-based study of patients with AF (Yu et al., 2012). Furthermore, despite the preventive effect of warfarin against stroke is superior to antiplatelet agents among patients with AF, the underuse of warfarin in clinical practice has been reported in several studies (Garcia and Hylek, 2006;

Stramba-Badiale, 2008). Use of RAS-acting agents, such as ACE inhibitors, has been considered to be cost-effective with regard to reduction of mortality and hospitalization in older patients with HF (Weintraub et al., 2002). However, in our study only 7.84% of patients with HF used RAS-acting agents, which is substantial below the optimal level (Klarin et al., 2003; Rushton et al., 2014). Moreover, evidence has shown that combination pharmacotherapy for secondary prevention of CVDs could reduce the overall risk of all-cause mortality by approximately 40% and cardiovascular events by 25%–30% compared to either monotherapy or no therapy (Aalto-Setala et al., 2019). Nevertheless, less than 30% of the participants in our study used two or more CV drugs together (including TCM products). This suggests that additional efforts are imperative to promote implementation of the evidence-based recommendations for secondary prevention of CVDs in the primary care settings in the rural regions.

Current evidence indicates that some TCM medications might be effective in control of cardiovascular risk factors and might be used as a complementary and alternative approach to the primary and secondary prevention of CVDs such as IHD and HF (Hao et al., 2017). The primary healthcare system in China includes a routine TCM health check and education for residents aged 65 years or older (Li et al., 2017). Our data showed that 7.64% of all participants took TCM products, and 16.74% of participants with CVD took TCM products. The most commonly used TCM product was Salvia miltiorrhiza Bunge (34.91%), which is a kind of herbs in formulations frequently prescribed for the clinical treatment of CVD in China (Wang et al., 2017). The active compounds of Salvia miltiorrhiza Bunge are considered to have cardioprotective effects through different cell signaling pathways (Ho and Hong, 2011). Thus, these TCM products might play a role in primary and secondary prevention of CVDs. However, TCM products have not been recommended in the current national guidelines of CVD management. Additional evidence from high-quality research (e.g., randomized controlled trials) is needed to support the effectiveness of TCM products in the prevention and treatment of CVDs (Gang et al., 2017).

Our findings corroborate and extend previous reports by showing that residents in the rural settings of China are less likely to receive CV drugs. Several factors could affect the use of CV drug therapy for primary and secondary prevention of CVDs, such as low awareness of cardiovascular risks and self-perceived health consequences, the failure of timely detection and diagnosis of risk factors and CVDs, concerns about adverse effects of CV drugs, and affordability (Haynes et al., 2008; Niens et al., 2010). Indeed, health insurance coverage could partly explain some of the disparities in CVD prevention. Although the majority of the rural population (~95%) have joined the New Rural Cooperative Medical Scheme, it only covers costs for in-hospital care and treatment, whereas long-term therapies with antihypertensive medications, statins, and antiplatelet agents still require out-of-pocket payment (Gu et al., 2015). Additionally, the prevalence of current harmful alcohol drinking and smoking in our rural population was above one-third and one-fifth, respectively. This might influence CV drug treatment for CVD prevention because regular smokers or alcohol drinkers may reflect the so-called "crowding out effect" where the costs of smoking and alcohol drinking compromise the allocation of expenditure for essential health care and treatment (Zhang et al., 2018).

The major strength of our study refers to the large sample of the general elderly population from the rural settings in China. In addition, our assessments with regard to risk factors and medical history were performed by trained staff following the standardized procedures. Of note, our study also covered the use of TCM products for control of cardiovascular risk factors and CVDs, which is unique and has been rarely reported in previous studies. However, our study also has limitations. First, despite our efforts to diagnose various CVDs through face-to-face survey on medical history, clinical and neurological examinations, and ECG examination, some CVDs might still be missed. Second, we did not take into account adherence to the reported treatments and outcome measures. Third, the study participants were derived exclusively from the rural areas with limited education and low-to-medium socioeconomic status, so cautiousness is needed when generalizing our research findings to other populations, even other rural populations.

In conclusion, health care reform in rural China since 2009 has significantly improved the rural public healthcare system by meeting the need of health care of rural residents (Baradaran et al., 2013). However, there is still a gap in the preventive and therapeutic management of CVDs with regard to the evidence-based recommendations for primary and secondary prevention in primary care. Furthermore, despite the fact that some TCM products might have potential preventive and therapeutic effects on cardiovascular risk factors and related CVDs, rigorously designed randomized controlled trials are warranted to evaluate the cardiovascular benefits of TCM products for the primary and secondary prevention of CVDs.

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 MIND-China protocol has been approved by the Ethics Committee at Shandong Provincial Hospital, Jinan, Shandong, China. Written informed consent was obtained from all participants, or in the case of cognitively impaired persons, from a proxy (usually a guardian or a family member).

AUTHOR CONTRIBUTIONS

The study concept and design: LC, YW, YD, and CQ. Writing of the manuscript: LC. Data analysis: YR and LC. Obtaining data: LC, YW, YR, TH, XH, YD, QZ, RL, LW, and SX. Interpretation of results, critical revisions of the manuscript, and approval of the version for submission: All authors.

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Pros and Cons of Aspirin for the Primary Prevention of Cardiovascular Events: A Secondary Study of Trial Sequential Analysis

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Background and Aims: Aspirin leads to substantial benefits for the secondary prevention of cardiovascular disease (CVD). We aimed to cast more light on aspirin's role for the primary prevention of CVD.

Methods: Databases were searched for clinical trials comparing aspirin vs. no aspirin use in this meta-analysis. Efficacy and safety profiles were rigorously investigated. Trial sequential analysis (TSA) was used to determine the robustness of the results.

Results: Fourteen studies with 163,840 participants were eligible (mean follow-up 6.2 y). Aspirin intake was found to be associated with 9, 13, and 12% reductions in the risk of cardiovascular events (CV events) (relative risk [RR]: 0.91, 95% confidence intervals [CI]: 0.87–0.96; risk difference (RD): 0.29%; absolute risk percentage (AR%): 7.61%; number needed to treat (NNT): 345), myocardial infarction (RR: 0.87, 95% CI: 0.77–0.97; RD: 0.21%; AR%: 11.11%; NNT: 488) and ischemic stroke (RR: 0.88, 95% CI: 0.80–0.96; RD: 0.21%; AR%: 16.14%; NNT: 476), respectively; aspirin intake was also associated with 40%, 30%, and 57% increases in the risk of major bleeding (RR: 1.40, 95% CI: 1.29–1.53; RD: 0.47%; AR%: 27.85; NNT: 214), intracranial bleeding (RR: 1.30, 95% CI: 1.11–1.52; RD: 0.10%; AR%: 22.99%; NNT: 1,000) and major gastrointestinal bleeding (RR: 1.57, 95% CI: 1.38–1.78; RD: 0.32%; AR%: 36.70%; NNT: 315), respectively. Further, populations with low doses of aspirin intake (≤100 mg), populations <65 y old or populations with body mass index (BMI) ≧ 25 experienced more advantages; high-risk (10-y cardiovascular risk ≧10%) and full diabetic individuals reported hardly clinical benefits.

Conclusion: Aspirin intake was associated with a reduced risk of CV events and an increased incidence of bleeding profiles in primary prevention. It is necessary to identify individual's CVD risk using clear examinations or assessments before aspirin intake, and truly realize individualized prescription.

Keywords: aspirin, primary prevention, cardiovascular disease, secondary study, trial sequential analysis

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INTRODUCTION

Currently, many patients are at high risk because their health is influenced by occlusive vascular disease; indeed, a long-term antiplatelet regimen (e.g., aspirin therapy) reduces the yearly risk of worse vascular events (such as nonfatal myocardial infarction, nonfatal stroke and vessel-related death) by almost one-quarter (Antiplatelet Trialists' Collaboration, 1994). Distinct benefits are observed with respect to the incidence of non-fatal cardiovascular events (CV events), with a small but definitive absolute risk reduction of approximately 10–20 CV events per 1,000 per year. Despite the benefits of aspirin, the absolute risk of major gastrointestinal or other major extracranial bleeding is also increased by an order of magnitude, so in secondary prevention, the benefits exceed the risks (Antithrombotic Trialists' Collaboration, 2002).

For primary prevention in patients without prior cardiovascular disease (CVD), both the risk without aspirin and absolute benefits of aspirin are smaller than those in secondary prevention. Although rates of death from coronary heart disease (CHD) and stroke in America have significantly decreased, CVD and cerebrovascular disease remain a large health and economic burden (Bibbins-Domingo, 2016). New guidelines suggest that regardless of bleeding risk, the wide use of aspirin is recommended for patients with a moderate risk of CHD, and a low dosage of aspirin (75–100 mg daily) may be reasonably recommended to 40- to 70-year-old adults at high risk of CVD without increasing major bleeding (IIb grade). New guidelines also recommended that age should be considered as a key determinant of the CVD risk, as a daily dose aspirin (alone or in combination with other drugs) has been recommended for all people above a specific age. Low doses of aspirin should not be recommended as primary prevention for 70-year-olds or for individuals with a high risk of bleeding (Pearson et al., 2002; Wald and Law, 2003; Elwood et al., 2005; Bulugahapitiya et al., 2008; Fox et al., 2015a; Bibbins-Domingo, 2016; Piepoli et al., 2016; Grundy et al., 2019; Mortensen and Nordestgaard, 2020). However, a moderate risk of CVD is hard to define, and whether the high CVD risk populations as well as the diabetic populations can get real benefits from aspirin or not.

Deferring the start of long-term aspirin use for primary prevention is a noted alternative that has the main advantage of avoiding an increased risk of slight or major bleeding events but has the disadvantage that the initial manifestation may be a disabling or fatal event. In previous primary prevention trials (Peto et al., 1988; Steering Committee of the Physicians' Health Study Research Group, 1989; The Medical Research Council's General Practice Research Framework, 1998; Hansson et al., 1998; de Gaetano, 2001; Ridker et al., 2005; Belch et al., 2008; Ogawa et al., 2008; Fowkes et al., 2010; Ikeda et al., 2014; Saito et al., 2017; Bowman et al., 2018; Gaziano et al., 2018; McNeil et al., 2018), control populations with non-fatal CVD (non-fatal CHD or non-fatal occlusive stroke) would probably be prescribed long-term aspirin use to avoid recurrence, hence helping to compare the efficacy of immediate vs. deferred aspirin use.

A previous meta-analysis (Whitlock et al., 2016) noted that aspirin reduced all-cause mortality, myocardial infarction (MI), and ischemic stroke while increasing the risk of major bleeding; another pooled study (Zheng and Roddick, 2019) showed that aspirin reduced nonfatal MI but did not significantly influence all-cause mortality. Above mentioned studies had heterogeneous results on all-cause mortality because they had involved different number of trials conducted in different time. Another key controversial point was on individuals' CVD risk classification that whether the higher risk individuals or the lower risk individuals could derive real prevention benefits from aspirin discussed by various guidelines or researchers. Actually, there are a lot of meta-analysis discussing this topic emerging yearly, not so many addressed their "cost-effectiveness", which is to say if the conclusions are statistically sufficient and robust, no repetitive meta-analyses or further evidence are needed to some extent so that saving the cost on public health.

Given the large number of individuals affected by current studies and guidelines, and less helpful of the impact from no-innovative work on global health policy making, we conducted a comprehensive meta-analysis with the aim to resolve clinical controversial points under intention-to-treat principles and to evaluate the sufficiency of current synthesized evidence using trial sequential method.

METHODS

The current study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, the PRISMA Checklist was shown in **Supplementary Table S1**. The protocol is available in PROSPERO (CRD42019127570).

Data Source and Study Selection

A rigorous search was performed in the PubMed, EMBASE, Cochrane Library, Web of Science and ClinicalTrials.gov databases from inception to February 1, 2020, to retrieve randomized controlled trials (RCTs) relating to aspirin use in patients without prior CVD. The search had no language restrictions. The main key words used were "aspirin", "cardiovascular disease", "cardiovascular events", "coronary heart disease", and "randomized controlled trials". Reference lists of the eligible studies and identified meta-analyses were also reviewed (**Supplementary Material S1**).

The inclusion criteria were as follows: 1) enrolled adult participants (≥18 y) without preexisting CV events [CV events here include peripheral arterial disease, CHD, prior myocardial infarction (MI), ischemic stroke, prior percutaneous coronary intervention, prior coronary artery bypass grafting]; 2) compared aspirin use to no aspirin use (placebo included); 3) had a follow-up no less than 1 year to confirm the high quality of primary studies; 4) provided reliable and available outcome data (at least one primary efficacy outcome of interest was reported); and 5) was an RCT.

Studies with the most comprehensive outcomes were included to avoid duplications; studies that assessed patients with diabetes but without atherosclerosis were also considered. JPAD (Ogawa et al., 2008) and JPAD2 (Saito et al., 2017) trials were both

included for they had different characteristics and proportion of the incorporated individuals as well as the differed follow-up. We excluded pure basic studies, reviews, and animal experiments.

Data Extraction and Outcome Definition

Two authors (Binghao Zhao, Yiping Wei) independently performed the study screening and extracted the baseline characteristics of each eligible trial. The baseline characteristics included demographic characteristics of included populations, clinical information about the intervention/control arms, and essential outcome data as well as the study design. Fully adjusted models for adjusted hazard ratio (HR), odd ratio (OR) and relative risk (RR) of analyzed outcomes were used if the models were available in included studies. Fully adjusted variables were varied, however, mostly included sex, age, country, hypertension, diabetes and smoking status. If some studies used intention-to-treat principles, we extracted the intention-to-treat data. Any discrepancies between the reviewers were resolved by a third author. If there were any missing data, the original authors were contacted.

The primary efficacy outcomes were CV events, all-cause mortality and cardiovascular mortality due to their universal definitions and balance of efficacy and safety, which reduce heterogeneity among eligible studies. The secondary efficacy outcomes were all MI, total stroke, ischemic stroke, cancer incidence and cancer mortality. The safety profile outcomes were major bleeding, intracranial bleeding and major gastrointestinal bleeding, as defined by each eligible trial. Intracranial bleeding was treated as a potential outcome of aspirin use in addition to CV events. All these definitions follow per included study's definition (Grundy et al., 2019).

Some studies even noted that aspirin increased the probability of cancer mortality, therefore, cancer outcomes were also appointed as exploratory outcome for robust evidence. The 10-y major adverse cardiovascular event rate (10-y MACE%) was extracted and calculated by multiplying the annualized event rate for cardiovascular mortality, nonfatal MI, and nonfatal stroke. A 10-y MACE% ≥ 10% was regarded as high risk; the others were regarded as low risk (**Supplementary Material S1**).

Study Quality Assessment

Methodological quality assessment was performed by three co-authors (Binghao Zhao, Li Wang, Wenxiong Zhang). We used the Cochrane Risk and Bias Tool (Higgins et al., 2011) recommended by the Cochrane handbook to evaluate the quality of each eligible study. There were several terms regarding the methodological quality of RCTs, and each study could be categorized as low, high or unclear quality; low-quality studies and those with unclear quality had a high risk of bias. Details are provided in the **Supplementary Material S1**.

Statistical Analysis

For descriptive purposes and statistical convenience, weighted frequencies were calculated for categorical variables using the provided sample size of each trial. Multivariable RRs and 95% confidence intervals (95% CIs) (De Lima Taga and Singer, 2018) for primary/secondary efficacy outcomes of interest and primary safety outcomes were estimated using the DerSimonian-Laird (D-L) random effects model considering the existence of within- and between-study variability. To further illustrate these outcome estimations, risk difference (RD), absolute risk percentage (AR%) and number needed to treat (NNT) were also analyzed. For further statistical purposes, HRs and ORs were considered RRs in this study. Fully adjusted effect sizes (ESs) were logarithmically transformed to stabilize the variance; hence, the data distribution could be normalized.

Between-study heterogeneity and variability were quantified by Cochran's Q test and I^2, whereby an $I^2 > 50\%$ or a p-value for the Q test <0.10 was considered to represent significant heterogeneity (Higgins et al., 2003). To provide more clinical implications, we conducted comprehensive subgroup analyses mainly focusing on several significant variables, including region (North America vs. Europe vs. Asia vs. multiple nations), individuals' main age (<65 vs. ≧ 65 y), mean body mass index (BMI) (<25 vs. ≧ 25), aspirin dose taken (≤100 vs. > 100 mg) and 10-y MACE% (low risk vs. high risk). For 10-y MACE%, the computed value of 10-y MACE% < 10% was defined as low risk, but the other populations were high risk. To provide more useful clinical data as well as to investigate the influence of individual studies on final results, we carried out sensitivity analyses by omitting one study each turn.

Publication bias was assessed by funnel plots and Egger's test (Egger et al., 1997), with $p < 0.05$ indicating significant bias. All analyses were performed using *R* project software (version 3.5.3, https://www.r-project.org/, United States) with forest, ggplot2, survminer etc. public packages; a two-sided $p < 0.05$ was considered statistically significant except where otherwise specified. More details are provided in the **Supplementary Material S1**.

Trial Sequential Analysis

Previous studies have confirmed that the risk of type 1 error from interim analyses can be reasonably reduced through monitoring boundaries and modifying the p-value. Similar in meta-analyses, random errors caused by sparse data and repetitive testing also enhance the risk of type 1 error. Such a method setting analogous trial sequential monitoring boundaries to meta-analyses is called trial sequential analysis (TSA), is used to determine whether evidence is reliable or conclusive (Wetterslev et al., 2008; Brok et al., 2009). Actually, random errors can be rectified and reduced using TSA software [version 0.9 beta (http://www.ctu.dk/tsa)] because it combines the estimation of the required information size (RIS) with an adjusted threshold for statistical significance. We assumed that if the Z-curve crossed the TSA boundary or entered the futility area, a sufficient effect was obtained, and further studies were not required; otherwise, the amount of evidence was considered insufficient. TSA was performed for a 10% relative risk reduction, conservatively, according to the TSA manual; there was also a 5% ($\alpha = 0.05$; two-sided) risk of a type 1 error and 80% statistical power. Other parameters were set empirically following default settings.

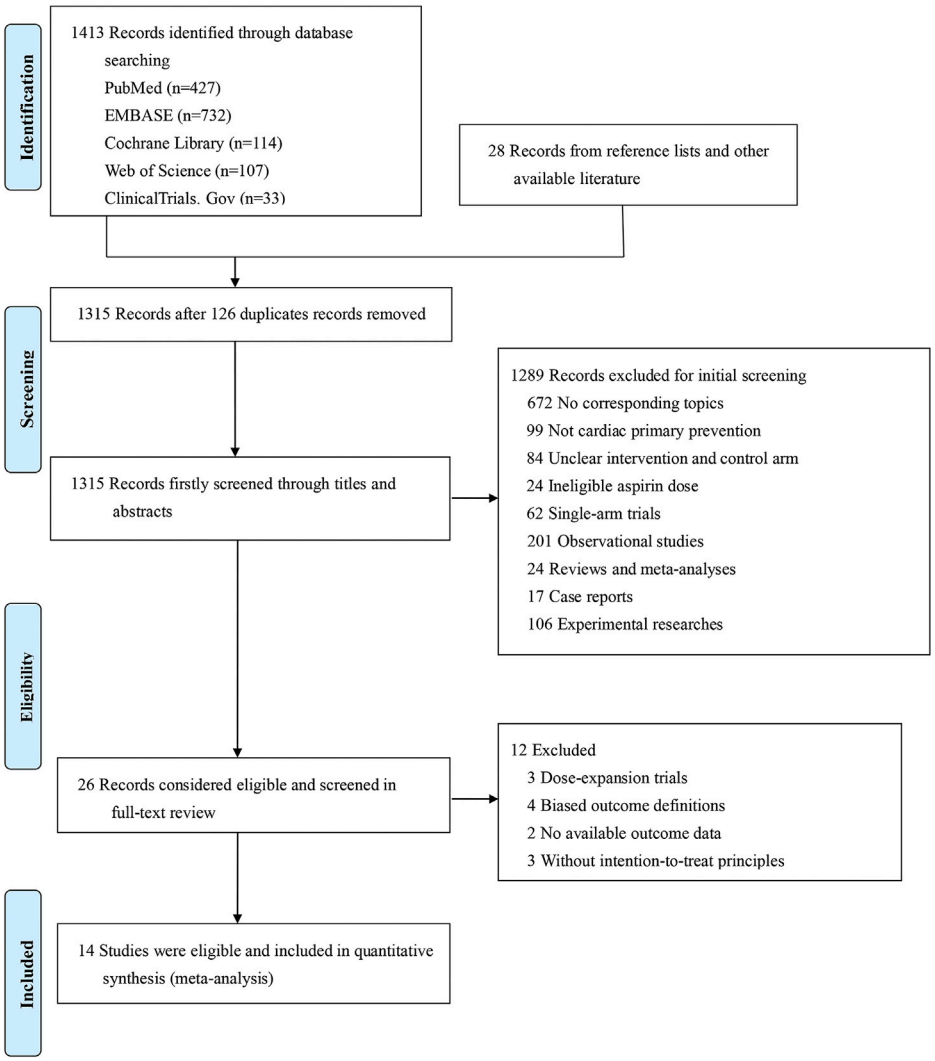

FIGURE 1 | Flow chart for literature search.

RESULTS

Study Selection and Characteristics

Among 1,441 searched articles (1,423 from database searching and 28 from other available source), we identified 26 studies for full-text review, of which 14 studies were eligible for qualitative and quantitative analyses (**Figure 1**). The 14 included studies (Peto et al., 1988; Steering Committee of the Physicians' Health Study Research Group, 1989; The Medical Research Council's General Practice Research Framework, 1998; Hansson et al., 1998; de Gaetano, 2001; Ridker et al., 2005; Belch et al., 2008; Ogawa et al., 2008; Fowkes et al., 2010; Ikeda et al., 2014; Saito et al., 2017; Bowman et al., 2018; Gaziano et al., 2018; McNeil et al., 2018) encompassed a total of 163,840 patients and used intention-to-treat principles. The detailed study characteristics are summarized in **Table 1**.

Two studies (Steering Committee of the Physicians' Health Study Research Group, 1989; Ridker et al., 2005) were conducted in America, six studies were conducted in Europe (5 (Peto et al., 1988; The Medical Research Council's General Practice Research Framework, 1998; Belch et al., 2008; Saito et al., 2017; Bowman et al., 2018) in the United Kingdom and 1 (de Gaetano, 2001) in Italy), three studies (Ogawa et al., 2008; Ikeda et al., 2014; Saito et al., 2017) were performed in Japan, and three studies (Hansson et al., 1998; Gaziano et al., 2018; McNeil et al., 2018) were performed in multiple nations. The comparator treatment was a placebo group in nine studies (Steering Committee of the Physicians' Health Study Research Group, 1989; The Medical Research Council's General Practice Research Framework, 1998; Hansson et al., 1998; Ridker et al., 2005; Belch et al., 2008; Fowkes et al., 2010; Bowman et al., 2018; Gaziano et al., 2018; McNeil et al., 2018) and was a no aspirin group in five studies. Of note, in addition to aspirin and placebo, six studies used a factorial design,

TABLE 1 | Characteristics of included studies and participants.

Publication	Study population	Number of population	Mean age y/ Male (%)	Aspirin use (mg/ day)	Control group	Diabetes No. (%)	Current smokers NO. (%)	Hypertension NO. (%)	Mean SBP (mean ± SD) mmHg	Total Cholesterol (mean ± SD) mmol/L	BMI	Outcomes	Study period (follow-up y)	Quality assessment[b]
Peto 1988; United Kingdom, (BDS) (Peto et al., 1988)	Male physicians	5,139 (3,429/ 1710)	61/ 5,139 (100)	300 or 500	No aspirin	101 (2)	661 (13)	508 (10)	136 ± 17	NA	24.4 ± 2.5	②③④⑤⑥⑦⑧⑨⑩	1978–1984 (NA)	High risk
Steering 1989; America, (PHS) (Steering Committee of the Physicians' Health Study Research Group, 1989)	Male physicians	22,071 (11,037/ 11,034)	53/ 22,071 (100)	325	Placebo	533 (2)	2,438 (11)	5,297 (24)	126 ± 12	5.5 ± 1.2	24.9 ± 3.0	②③④⑤⑥⑧⑨⑩⑪	1982–1988 (5)	High risk
Meade 1998; United Kingdom, (TPT) (The Medical Research Council's General Practice Research Framework, 1998)	Males in the top 20–25% risk of CV events	2,540 (1,268/ 1,272)[c]	57/ 2,540 (100)	75	Placebo	51 (2)	83 (3)	278 (11)	139 ± 18	6.4 ± 1.0	27.4 ± 3.6	②③④⑤⑥⑧⑨⑩⑪	1984–1997 (NA)	High risk
Hansson 1998; multi-nations, (HOT) (Hansson et al., 1998)	Hypertensive populations	18,790 (9,399/ 9,391)	61/ 9,959 (53)	75	Placebo	1,503 (8)	2,988 (16)	18,790 (100)	170 ± 14	6.0 ± 1.1	28.4 ± 4.7	①②③④⑤⑦⑧⑨⑩⑪	1992–1997 (3.8)	Low risk
De Gaetano 2001; Italy, (PPP) (de Gaetano, 2001)	Populations with ≥1 CV risk factor	4,495 (2,226/ 2,269)	64/ 1912 (42)	100	No aspirin	742 (17)	667 (15)	3,065 (68)	145 ± 16	6.1 ± 1.2	27.6 ± 4.7	①②③④⑤⑥⑦⑧⑨⑩⑪	1994–1998 (3.6)	High risk
Ridker 2005; America, (WHS) (Ridker et al., 2005)	Healthy females	39,876 (19,934/ 19,942)	54/0 (0)	100	Placebo	1,037 (3)	5,224 (13)	10,328 (26)	NA	5.2 ± 1.0	26.1 ± 5.2	①②③④⑤⑥⑦⑧⑨⑩⑪	1992–2004 (10.1)	Low risk
Belch 2008; United Kingdom, (POPADAD) (Belch et al., 2008)	Diabetic populations (ABPI ≤0.99)	1,276 (638/638)	60/ 563 (44)	100	Placebo	1,276 (100)	NA	NA	145 ± 21	5.5	29.2	②③④⑤⑦⑧	1997–2006 (6.7) (ISRCTN53295293)	Low risk
Ogawa et al, 2008; Japan, (JPAD) (Ogawa et al., 2008)	Diabetic populations	2,539 (1,262/ 1,277)	65/ 1,387 (55)	81 or 100	No aspirin	2,539 (100)	537 (21)	1,473 (58)	135 ± 15	5.2 ± 0.9	24.0 ± 4.0	①②③④⑤⑥⑦⑧⑨⑩⑪	2002–2008 (4.37) (NCT00110448)	High risk

(Continued on following page)

TABLE 1 | (*Continued*) Characteristics of included studies and participants.

Publication	Study population	Number of population	Mean age y/ Male (%)	Aspirin use (mg/ day)	Control group	Diabetes No. (%)	Current smokers NO. (%)	Hypertension NO. (%)	Mean SBP (mean ± SD) mmHg	Total Cholesterol (mean ± SD) mmol/L	BMI	Outcomes	Study period (follow-up y)	Quality assessment[b]
Fowkes 2010; United Kingdom, (AAA) (Fowkes et al., 2010)	Populations with ≤0.95 ABPI	3,350 (1,675/ 1,675)	62/ 954 (28)	100	Placebo	88 (3)	1,085 (32)	NA	148 ± 22	6.2 ± 1.1	NA	①②③④⑤⑥⑦⑧⑨⑩⑪	1998–2008 (8.2) (ISRCTN66587262)	Low risk
Ikeda 2014; Japan. (JPPP) (Ikeda et al., 2014)	Hypertensive, hyperlipidemic or diabetic populations	14,464 (7,220/ 7,244)	71/ 6,123 (42)	100	No aspirin	4,903 (34)	1893 (13)	12,278 (85)	137 ± 16	5.3 ± 0.8	24.2 ± 3.5	①②③④⑤⑥⑦⑧⑨⑩	2005–2012 (5.02) (NCT00225849)	High risk
Saito et al, 2017; Japan, (JPAD2) (Saito et al., 2017)	Diabetic populations	2,160 (992/ 1,168)	65/ 1,195 (55)	81 or 100	No aspirin	2,160 (100)	459 (21)	2,142 (58)	135 ± 15	5.2 ± 0.9	24.0 ± 4.0	①③④⑤⑥⑨⑩⑪	2002–2015 (10.3) (NCT00110448)	High risk
Bowman 2018; United Kingdom, (ASCEND) (Bowman et al., 2018)	Diabetic populations	15,480 (7,740/ 7,740)	63/ 9,684 (63)	100	Placebo	15,480 (100)	1,279 (8)	9,533 (62)	136 ± 15	4.2 ± 0.9	30.7 ± 6.3	①②③④⑤⑥⑦⑧⑨⑩⑪	2007–2016 (7.4) (NCT00135226)	Low risk
Gaziano 2018; multi-nations, (ARRIVE) (Gaziano et al., 2018)	Males with ≥2 and females with ≥3 CV risk factors, with 10–20% 10-y MACE risk	12,546 (6,270/ 6,276)	64/ 8,838 (70)	100	Placebo	0 (0)	3,594 (29)	7,866 (63)	144 (90–199)[a]	NA	28.4 ± 4.3	①②③④⑤⑩⑪	2007–2016 (5) (NCT00501059)	Low risk
McNeil 2018; multi-nations, (ASPREE) (McNeil et al., 2018)	≥65 y populations	19,114 (9,525/ 9,589)	74/ 8,331 (44)	100	Placebo	2057 (11)	735 (4)	14,283 (74)	140 ± 17	5.3 ± 1.0	28.1 ± 4.7	①②③④⑤⑥⑦⑧⑨⑩⑪	2010–2014 (4.7) (NCT01038583)	Low risk

Abbreviations: SBP, systolic blood pressure; BMI, body mass index; MACE, major adverse cardiovascular events; CV risk, cardiovascular risk; ABPI, ankle-brachial pressure index; SD, standard deviation; MI, myocardial infraction; NA, not available.

Outcome classification: ①, CV events; ②, All-cause mortality; ③, Cardiovascular mortality; ④, All MI; ⑤, Total stroke; ⑥, Ischemic stroke; ⑦, Cancer incidence; ⑧, Cancer mortality; ⑨, Major bleeding; ⑩, Intracranial bleeding; ⑪, Major gastrointestinal bleeding.

[a]*10-y MACE% was calculated by multiplying the annualized event rate for cardiovascular outcomes in the control group by 10 years. MACE was defined as composite of cardiovascular mortality, non-fatal myocardial infraction and non-fatal stroke etc.*

[b]*Methodology quality was assessed by Cochrane risk and Bias tool.*

[c]*There were 5,085 participants randomized in a 2*2 factorial design with warfarin, aspirin, warfarin and aspirin or placebo, we excluded 2,545 populations with warfarin or warfarin and aspirin. 2,540 were randomized to aspirin and placebo.*

in which 1 (The Medical Research Council's General Practice Research Framework, 1998) study used warfarin, 2 (de Gaetano, 2001); (Ridker et al., 2005) used vitamin E, 1 (Bowman et al., 2018) prescribed n-3 fatty acid, 1 (Belch et al., 2008) used antioxidants, and 1 (Peto et al., 1988) supplied anti-hypertension drugs. Three studies (Peto et al., 1988; Steering Committee of the Physicians' Health Study Research Group, 1989; The Medical Research Council's General Practice Research Framework, 1998) exclusively enrolled male individuals (29,750 males), and one study (Ridker et al., 2005) specially enrolled female individuals (39,876 females). Across the included studies, 78,696 (48%) patients were males. Four studies (Belch et al., 2008; Ogawa et al., 2008; Saito et al., 2017; Bowman et al., 2018) exclusively enrolled diabetic patients (including type I and type II diabetes). The mean BMI of eligible participants was 28.5, and the mean 10-y MACE% was 7.24. The median duration was 8.1 y (4 (de Gaetano, 2001) to 13 (The Medical Research Council's General Practice Research Framework, 1998; Saito et al., 2017)), and the mean follow-up was 6.2 y. The studies were published between 1988 (Peto et al., 1988) and 2018 (Bowman et al., 2018; Gaziano et al., 2018; McNeil et al., 2018). All studies were written in English, and there was no attempt to ask the primary authors for raw data.

METHODOLOGICAL QUALITY ASSESSMENT

Of the 14 included studies, nine studies used double-blind methods and five studies (Peto et al., 1988; de Gaetano, 2001; Ogawa et al., 2008; Ikeda et al., 2014; Saito et al., 2017) used open-label settings. Three studies (Steering Committee of the Physicians' Health Study Research Group, 1989; The Medical Research Council's General Practice Research Framework, 1998; de Gaetano, 2001) had selective reporting or other bias. Of the included studies, 7 (Hansson et al., 1998; Ridker et al., 2005; Belch et al., 2008; Fowkes et al., 2010; Bowman et al., 2018; Gaziano et al., 2018; McNeil et al., 2018) were of low risk and 7 (Peto et al., 1988; Steering Committee of the Physicians' Health Study Research Group, 1989; The Medical Research Council's General Practice Research Framework, 1998; de Gaetano, 2001; Ogawa et al., 2008; Ikeda et al., 2014; Saito et al., 2017) were of high risk (**Supplementary Figure S1**; **Supplementary Table S2**).

The Primary Efficacy Outcomes

For the primary efficacy outcomes, twelve studies (Peto et al., 1988; Steering Committee of the Physicians' Health Study Research Group, 1989; Hansson et al., 1998; de Gaetano, 2001; Ridker et al., 2005; Ogawa et al., 2008; Fowkes et al., 2010; Ikeda et al., 2014; Saito et al., 2017; Bowman et al., 2018; Gaziano et al., 2018; McNeil et al., 2018) involving 160,024 individuals reported CV event outcomes, and we found that the use of aspirin was associated with a 9% reduction in CV events (RR: 0.91, 95% CI: 0.87–0.96; $p < 0.001$; RD: 0.29%; AR%: 7.61%; NNT = 345) compared to no aspirin use, and there was no significant heterogeneity ($I^2 = 0$; $p = 0.64$). Thirteen studies (Peto et al., 1988; Steering Committee of the Physicians' Health Study Research Group, 1989; The Medical Research Council's General Practice Research Framework, 1998; Hansson et al., 1998; de Gaetano, 2001; Ridker et al., 2005; Belch et al., 2008; Ogawa et al., 2008; Fowkes et al., 2010; Ikeda et al., 2014; Bowman et al., 2018; Gaziano et al., 2018; McNeil et al., 2018) including 161,680 individuals examined all-cause mortality outcomes; aspirin use did not lead to a significant reduction in all-cause mortality (RR: 0.97, 95% CI: 0.93–1.02; $p = 0.22$; RD: 0.04%; AR%: 0.99%; NNT = 2,273), and there was no heterogeneity ($I^2 = 0$; $p = 0.60$). Fourteen studies (Peto et al., 1988; Steering Committee of the Physicians' Health Study Research Group, 1989; The Medical Research Council's General Practice Research Framework, 1998; Hansson et al., 1998; de Gaetano, 2001; Ridker et al., 2005; Belch et al., 2008; Ogawa et al., 2008; Fowkes et al., 2010; Ikeda et al., 2014; Saito et al., 2017; Bowman et al., 2018; Gaziano et al., 2018; McNeil et al., 2018) (163,840 participants) examined cardiovascular mortality; aspirin use was not significantly associated with cardiovascular mortality reduction (RR: 0.95, 95% CI: 0.87–1.03; $p = 0.23$; RD: 0.02%; AR%: 1.91%; NNT = 4,348), and there was no significant heterogeneity ($I^2 = 0$; $p = 0.57$) (**Figure 2**).

The Secondary Efficacy Outcomes

Regarding the secondary efficacy outcomes, fourteen studies (Peto et al., 1988; Steering Committee of the Physicians' Health Study Research Group, 1989; The Medical Research Council's General Practice Research Framework, 1998; Hansson et al., 1998; de Gaetano, 2001; Ridker et al., 2005; Belch et al., 2008; Ogawa et al., 2008; Fowkes et al., 2010; Ikeda et al., 2014; Saito et al., 2017; Bowman et al., 2018; Gaziano et al., 2018; McNeil et al., 2018) with 163,840 individuals revealed that aspirin intake was associated with a 13% reduction in all MIs (RR: 0.87, 95% CI: 0.77–0.97; $p = 0.02$; RD: 0.21%; AR%: 11.11%; NNT = 488), and there was significant heterogeneity ($I^2 = 58\%$; $p < 0.01$). Eleven studies (Peto et al., 1988; Steering Committee of the Physicians' Health Study Research Group, 1989; The Medical Research Council's General Practice Research Framework, 1998; de Gaetano, 2001; Ridker et al., 2005; Ogawa et al., 2008; Fowkes et al., 2010; Ikeda et al., 2014; Saito et al., 2017; Bowman et al., 2018; McNeil et al., 2018) (131,228 individuals) revealed that aspirin intake was associated with a 12% risk reduction in ischemic stroke (RR: 0.88, 95% CI: 0.80–0.96; $p < 0.01$; RD: 0.21%; AR%: 16.14%; NNT = 476), and there was no significant heterogeneity ($I^2 = 0$; $p = 0.62$). Fourteen studies (Peto et al., 1988; Steering Committee of the Physicians' Health Study Research Group, 1989; The Medical Research Council's General Practice Research Framework, 1998; Hansson et al., 1998; de Gaetano, 2001; Ridker et al., 2005; Belch et al., 2008; Ogawa et al., 2008; Fowkes et al., 2010; Ikeda et al., 2014; Saito et al., 2017; Bowman et al., 2018; Gaziano et al., 2018; McNeil et al., 2018) (163,840 individuals) revealed that aspirin use was not significantly associated with total stroke (RR: 0.94, 95% CI: 0.88–1.02; $p = 0.13$; RD: 0.09%; AR%: 5.30%; NNT = 1,111), and there was no significant heterogeneity ($I^2 = 0$; $p = 0.59$).

Furthermore, we explored the cancer outcomes. Ten studies (Peto et al., 1988; Hansson et al., 1998; de Gaetano, 2001; Ridker et al., 2005; Belch et al., 2008; Ogawa et al., 2008; Fowkes et al., 2010; Ikeda et al., 2014; Bowman et al., 2018; McNeil et al., 2018) including 124,523 participants and 12 studies (Peto et al., 1988; Steering Committee of the Physicians' Health Study Research Group, 1989; The Medical Research Council's General Practice Research Framework, 1998; Hansson et al., 1998; de Gaetano, 2001; Ridker et al., 2005; Belch et al., 2008; Ogawa et al., 2008; Fowkes et al., 2010; Ikeda et al., 2014; Bowman et al., 2018; McNeil et al., 2018) including 149,134 participants reported cancer incidence and cancer mortality, respectively. There was no significant difference in cancer incidence (RR: 1.00, 95% CI: 0.95–1.06; $p = 0.87$; RD: 0.02%; AR%: 0.28%; NNT = 5,000) or cancer mortality (RR: 1.03, 95% CI: 0.94–1.12; $p = 0.87$; RD: 0.07%; AR%: 3.41%; NNT = 1,449) between the aspirin use and no aspirin use groups, and there was no significant heterogeneity ($I^2 = 36\%$, $p = 0.12$; $I^2 = 21\%$, $p = 0.24$, respectively). Aspirin showed the potential to increase the risk of cancer mortality (**Supplementary Figure S2**).

The Safety Profile Outcomes

Safety profiles outcomes included major bleeding, intracranial bleeding and major gastrointestinal bleeding. Twelve studies (Peto et al., 1988; Steering Committee of the Physicians' Health Study Research Group, 1989; The Medical Research Council's General Practice Research Framework, 1998; Hansson et al., 1998; de Gaetano, 2001; Ridker et al., 2005; Ogawa et al., 2008; Fowkes et al., 2010; Ikeda et al., 2014; Saito et al., 2017; Bowman et al., 2018; McNeil et al., 2018) including 150,397 patients examined major bleeding events; aspirin use was found to significantly increase the risk of major bleeding by 40% (RR: 1.40, 95% CI: 1.29–1.53; $p < 0.01$; RD: 0.47%; AR%: 27.85%; NNT = 214), and there was no significant heterogeneity ($I^2 = 0\%$; $p = 0.54$). Thirteen studies (Peto et al., 1988; Steering Committee of the Physicians' Health Study Research Group, 1989; The Medical Research Council's General Practice Research Framework, 1998; Hansson et al., 1998; de Gaetano, 2001; Ridker et al., 2005; Ogawa et al., 2008; Fowkes et al., 2010; Ikeda et al., 2014; Saito et al., 2017; Bowman et al., 2018; Gaziano et al., 2018; McNeil et al., 2018) (162,934 participants) examined intracranial bleeding; aspirin use was associated with a 30% increase in intracranial bleeding (RR: 1.30, 95% CI: 1.11–1.52; $p < 0.01$; RD: 0.10%; AR %: 22.99%; NNT = 1,000), and there was no heterogeneity ($I^2 = 0\%$; $p = 0.84$). Eleven trials (Steering Committee of the Physicians' Health Study Research Group, 1989; The Medical Research Council's General Practice Research Framework, 1998; Hansson et al., 1998; de Gaetano, 2001; Ridker et al., 2005; Ogawa et al., 2008; Fowkes et al., 2010; Saito et al., 2017; Bowman et al., 2018; Gaziano et al., 2018; McNeil et al., 2018) (143,340 participants) examined major gastrointestinal bleeding; aspirin intake was associated with a 57% increase in major gastrointestinal bleeding (RR: 1.57, 95% CI: 1.38–1.78; $p < 0.01$; RD: 0.32%; AR%: 36.70%; NNT = 315), and there was no heterogeneity ($I^2 = 0\%$; $p = 0.57$). The finding that aspirin use significantly increased the risk of bleeding events led us to identify the proper indicators for balancing the benefits and harm of clinical routines (**Figure 3**).

Subgroup Analysis for Further Clinical Implications

Subgroups involving region, mean age, mean BMI, aspirin dosage in the intervention arm and 10-y MACE% were constructed, and subgroup analyses were performed (**Table 2**). We observed that populations with a dosage of ≤100 mg/day experienced more benefits with respect to CV events, MI, total stroke and ischemic stroke than those with a dosage >100 mg/day. Individuals with a BMI ≧ 25 seemed experience more aspirin-induced benefits with respect to cardiovascular and cerebrovascular outcomes (CV events, RR: 0.91, 95% CI: 0.86–0.98; total stroke, RR: 0.90, 95% CI: 0.82–0.99; ischemic stroke, RR: 0.85, 95% CI: 0.76–0.95) than individuals with a BMI < 25 with similar bleeding events. Aspirin-induced cardiovascular benefits were consistently found in participants with a mean age < 65 y; however, they were not as robust in the patients with a mean age ≥ 65 y, with only one statistically significant outcome for CV events (RR: 0.90, 95% CI: 0.81–1.00). Participants with a low 10-y MACE% risk had the potential to obtain more cardiovascular advantages from aspirin use than those with a high 10-y MACE% risk. There was no significant difference in cardiovascular outcomes and bleeding events between patients from different regions. Across the subgroup analyses, aspirin still had no statistically significant effects on cancer incidence or mortality. All of the above results are presented in **Table 2**.

Sensitivity Analysis

In sensitivity analyses, many variables were classified into different subgroups. To better eliminate bias and heterogeneous interactions (TPT (The Medical Research Council's General Practice Research Framework, 1998) trial was excluded for warfarin use), we used the inverse variance (IV) statistical method. Most of the results were consistent with the primary results and remained robust through sensitivity analyses. Interestingly, we observed increased aspirin-induced benefits for cardiac outcomes (CV events, RR: 0.90, 95% CI: 0.85–0.95; all MI, RR: 0.83, 95% CI: 0.72–0.96; ischemic stroke, RR: 0.86, 95% CI: 0.76–0.97) among trials with diabetic and nondiabetic patients compared to the trials involving only diabetic patients. We also observed aspirin-induced benefits when excluding patients with asymptomatic peripheral artery disease (PAD). Furthermore, after excluding trials published before 2000, the cardiovascular benefits were still obvious. No effects on cancer were found across sensitivity analyses (**Table 3**). The omission process as well as the results of the heterogeneity analyses can be found in **Table 3** and **Supplementary Material S2–S12**.

These findings implied that aspirin use among diabetic individuals may not lead to the primary prevention of CVD because diabetes, which is known as a risk factor for CVD, might indirectly enhance the CV risk estimated by the MACE; similarly, the efficacy of aspirin use in studies including both diabetic and nondiabetic patients was excellent. Second, diagnosis technology

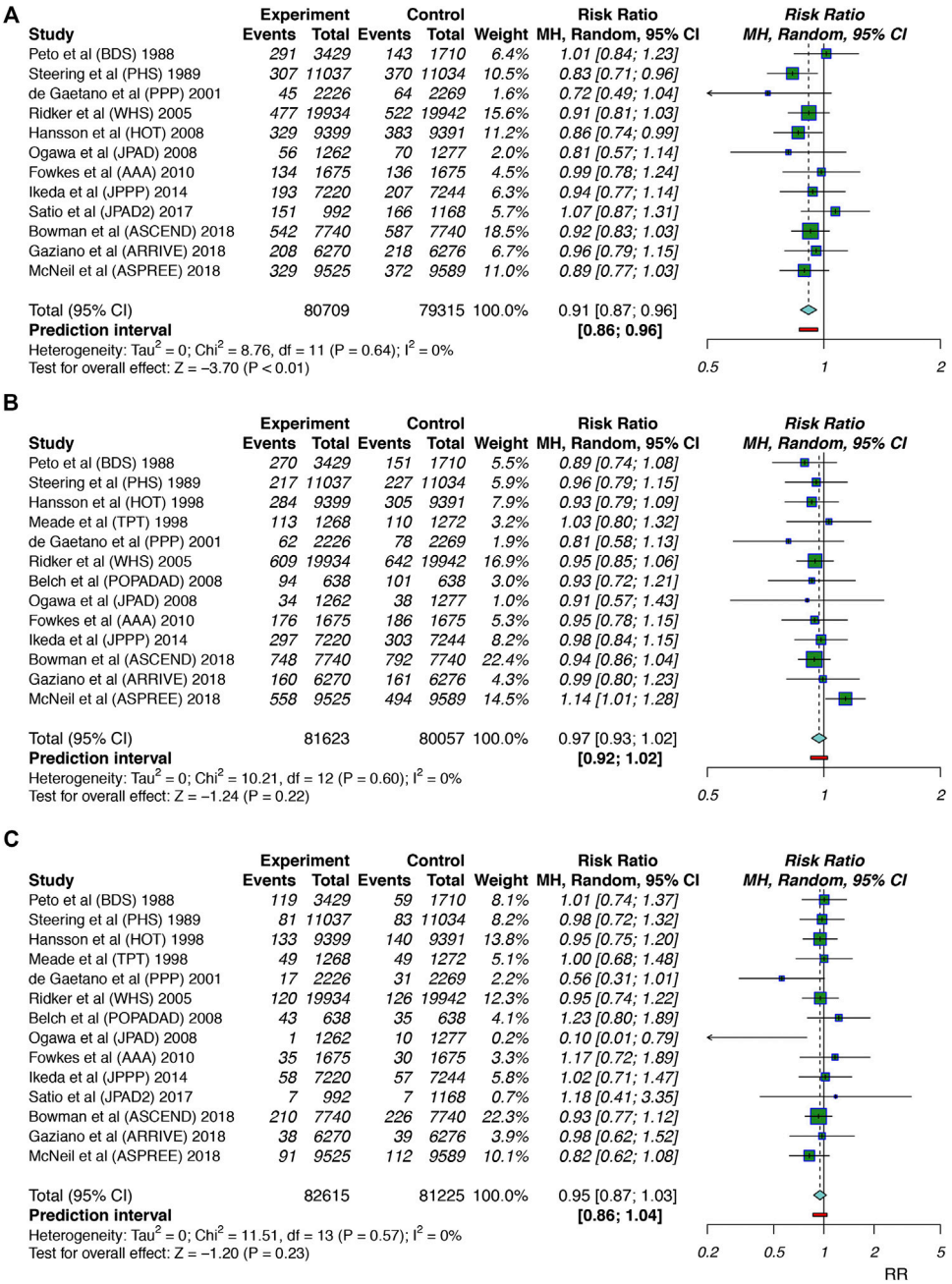

FIGURE 2 | Summary forest plots for the primary efficacy outcomes. **(A)** Forest plot for CV events. **(B)** Forest plot for all-cause mortality. **(C)** Forest plot for cardiovascular mortality.

is developing over time, which means that more patients with potential or asymptomatic CVD could be properly diagnosed and excluded before entering clinical trials or taking aspirin for "primary prevention". Therefore, the preferable role of aspirin in the primary prevention of CVD would be highlighted, especially in recently published studies (after 2000). Finally, early screening for PAD was equally important to help identify individuals who may not benefit from aspirin.

Trial Sequential Analysis

In TSA, we observed the Z-curve cross the trial sequential analysis boundary (TSA boundary) for CV events, all MI, ischemic stroke, major bleeding, intracranial bleeding and major gastrointestinal bleeding outcomes under conditions of 5% relative risk reduction, 5% for two-sided type 1 error risk, 80% statistical power and 5% control event incidence. The Z-curve did not cross the traditional boundary or the TSA boundary but crossed the futility boundary for cardiovascular mortality. The Z-curve crossed the traditional

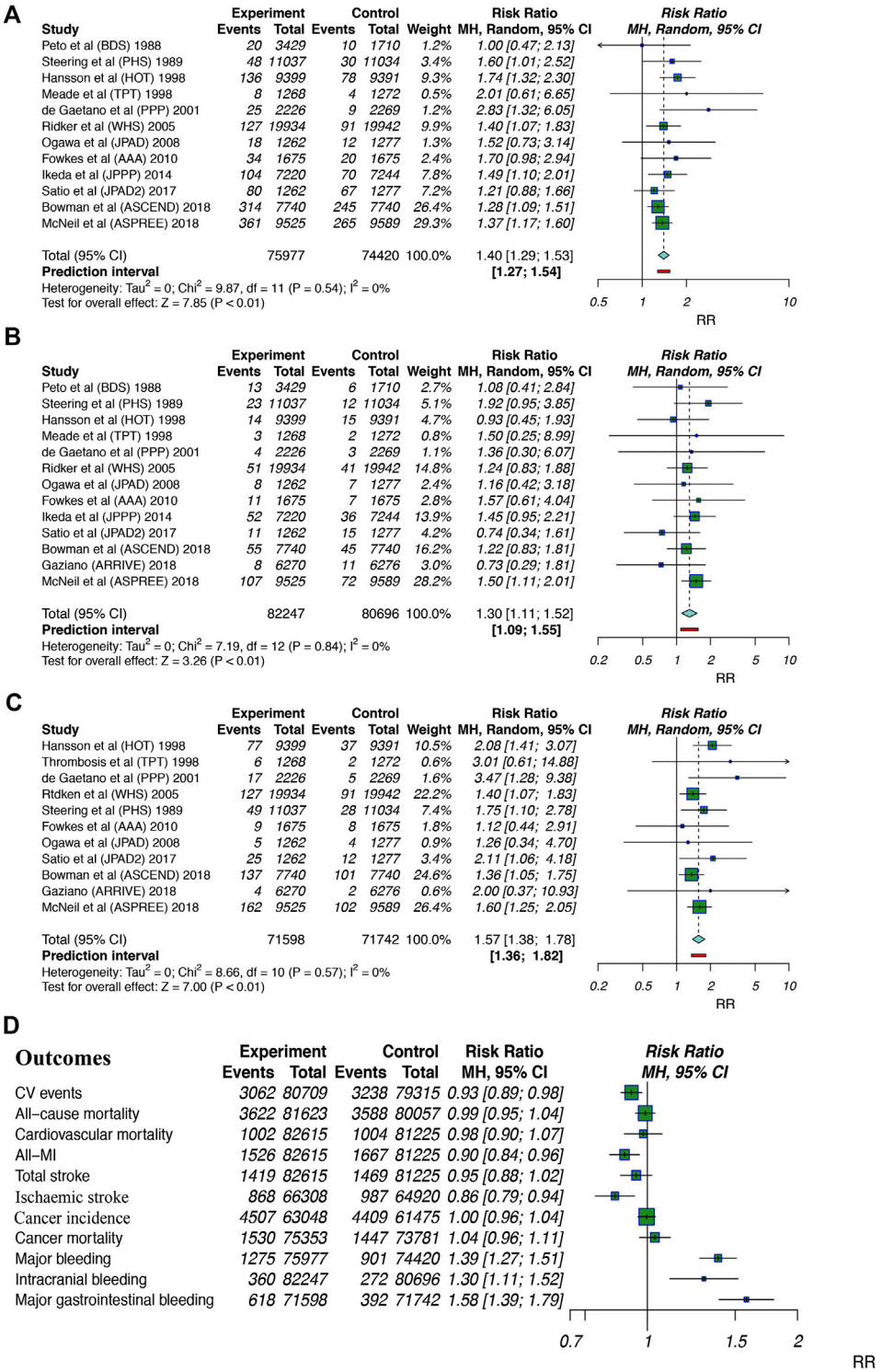

FIGURE 3 | Summary forest plots for the outcomes of bleeding. **(A)** Forest plot for major bleeding. **(B)** Forest plot for intracranial bleeding. **(C)** Forest plot for major gastrointestinal bleeding. **(D)** Forest plot for summarized outcomes analyzed in the current study. MI, myocardial infarction; 95% CI, 95% confidence interval.

and futility boundaries but did not cross the TSA boundary for all-cause mortality. These findings showed that conclusions on the abovementioned outcomes were robust and were hardly modified with additional related trials. However, the Z-curve did not cross the TSA boundary or the futility boundary for total stroke, cancer incidence and cancer mortality, which suggested

TABLE 2 | Summarized results of total and subgroup analyses.

Items/ Outcomes[b]	Total	By region				By mean age (y)		By mean BMI		By aspirin dose (mg)		By 10y-MACE%[a]	
		North America	Europe	Asia	Multiple nations	<65	≧65	<25	≧25	≤100	>100	Low risk	High risk
CV events	0.91 (0.87–0.96)	0.88 (0.80–0.97)	0.94 (0.86–1.03)	0.97 (0.85–1.10)	0.90 (0.82–0.98)	0.92 (0.87–0.97)	0.90 (0.81–1.00)	0.91 (0.84–0.99)	0.91 (0.86–0.98)	0.92 (0.87–0.97)	0.91 (0.75–1.10)	0.89 (0.84–0.96)	0.94 (0.87–1.01)
All-cause mortality	0.97 (0.93–1.02)	0.95 (0.87–1.05)	0.94 (0.88–1.01)	0.98 (0.84–1.13)	1.03 (0.91–1.17)	0.95 (0.90–1.00)	1.06 (0.95–1.18)	0.94 (0.87–1.03)	0.99 (0.92–1.06)	0.98 (0.93–1.03)	0.93 (0.81–1.06)	1.00 (0.92–1.08)	0.94 (0.88–1.01)
Cardiovascular mortality	0.95 (0.87–1.03)	0.96 (0.79–1.17)	0.97 (0.85–1.11)	0.76 (0.31–1.90)	0.90 (0.77–1.07)	0.96 (0.88–1.06)	0.82 (0.53–1.29)	0.97 (0.84–1.12)	0.92 (0.83–1.03)	0.94 (0.85–1.03)	0.99 (0.80–1.23)	0.91 (0.79–1.04)	0.96 (0.85–1.08)
All MI	0.87 (0.77–0.97)	0.78 (0.45–1.34)	0.95 (0.86–1.05)	0.89 (0.69–1.16)	0.81 (0.66–1.01)	0.87 (0.76–1.00)	0.90 (0.75–1.08)	0.78 (0.61–0.99)	0.93 (0.86–1.02)	0.91 (0.83–0.99)	0.78 (0.44–1.38)	0.81 (0.66–1.00)	0.90 (0.79–1.02)
Total stroke	0.94 (0.88–1.02)	0.99 (0.69–1.43)	0.89 (0.78–1.01)	0.99 (0.82–1.18)	1.00 (0.87–1.14)	0.94 (0.86–1.02)	0.97 (0.84–1.13)	1.04 (0.92–1.17)	0.90 (0.82–0.99)	0.92 (0.85–1.00)	1.16 (0.94–1.44)	0.97 (0.86–1.11)	0.94 (0.84–1.05)
Ischemic stroke	0.88 (0.80–0.96)	0.91 (0.64–1.29)	0.89 (0.76–1.03)	0.88 (0.71–1.10)	0.89 (0.72–1.11)	0.88 (0.78–1.00)	0.88 (0.74–1.04)	0.98 (0.82–1.16)	0.85 (0.76–0.95)	0.85 (0.78–0.94)	1.14 (0.86–1.52)	0.87 (0.76–0.98)	0.91 (0.79–1.05)
Cancer incidence	1.00 (0.95–1.06)	1.01 (0.94–1.08)	0.98 (0.91–1.06)	1.06 (0.79–1.42)	1.01 (0.94–1.09)	0.99 (0.94–1.04)	1.05 (0.92–1.21)	1.02 (0.88–1.19)	1.01 (0.97–1.06)	1.02 (0.96–1.07)	0.91 (0.77–1.08)	1.05 (0.98–1.13)	0.97 (0.91–1.04)
Cancer mortality	1.03 (0.94–1.12)	1.00 (0.84–1.18)	0.94 (0.84–1.05)	1.07 (0.88–1.30)	1.18 (0.94–1.48)	0.97 (0.89–1.05)	1.19 (1.04–1.36)	1.03 (0.90–1.18)	1.04 (0.91–1.19)	1.03 (0.95–1.12)	0.97 (0.68–1.40)	1.11 (0.96–1.27)	0.96 (0.87–1.07)
Major bleeding	1.40 (1.29–1.53)	1.44 (1.15–1.82)	1.46 (1.10–1.95	1.35 (1.10–1.67)	1.49 (1.18–1.88)	1.39 (1.21–1.59)	1.42 (1.25–1.62)	1.47 (1.26–1.71)	1.36 (1.21–1.53)	1.39 (1.28–1.52)	1.40 (0.92–2.12)	1.42 (1.27–1.60)	1.36 (1.20–1.54)
Intracranial bleeding	1.30 (1.11–1.52)	1.40 (0.96–2.05)	1.26 (0.91–1.74)	1.21 (0.82–1.77)	1.18 (0.77–1.80)	1.18 (0.96–1.47)	1.46 (1.15–1.84)	1.25 (0.95–1.65)	1.31 (1.08–1.60)	1.28 (1.08–1.51)	1.57 (0.89–2.77	1.40 (1.15–1.70)	1.12 (0.85–1.47)
Major gastrointestinal bleeding	1.57 (1.38–1.78)	1.47 (1.17–1.86)	1.61 (1.02–2.54)	1.87 (1.02–3.44)	1.72 (1.40–2.11)	1.58 (1.35–1.85)	1.58 (1.24–2.01)	1.92 (1.47–2.51)	1.49 (1.28–1.72)	1.55 (1.36–1.77)	1.75 (1.10–2.78)	1.57 (1.33–1.85)	1.57 (1.28–1.93)

Abbreviations: BMI, body mass index; MACE, major adverse cardiovascular event rate; CV event, cardiovascular event; MI, myocardial infraction.

[a]*A 10-y MACE% of at least 10% was regarded as high CV risk and less than 10% was low.*

[b]*All the outcomes were shown in RR and 95% CI form.*

that additional studies should be conducted to evaluate those effects (**Figure 4**; **Supplementary Figure S3**).

Egger's test revealed no significant publication bias for CV events ($p = 0.882$), all-cause mortality ($p = 0.362$), CV mortality ($p = 0.390$), major bleeding ($p = 0.126$), intracranial bleeding ($p = 0.236$), or major gastrointestinal bleeding ($p = 0.152$) (**Supplementary Figure S4**).

DISCUSSION

As one of the most widely used drugs worldwide, aspirin celebrated its 121st birthday in 2020 and the remarkable store is still going on (Vranckx et al., 2018). In this study, aspirin was observed to be significantly associated with a 9, 13, and 12% reduction in the risk of CV events, all-MI and ischemic stroke, respectively; however, aspirin was associated with a 40, 30, and 57% increase in the risk of bleeding profiles, including major bleeding, intracranial bleeding and major gastrointestinal bleeding, respectively. No causal outcomes were found in all-cause mortality, cardiovascular mortality, total stroke, cancer incidence or cancer mortality. Low doses of aspirin (≤100 mg) might offer more clinical benefits than high doses of aspirin; individuals who are <65 y old and have a BMI ≥ 25 demonstrated stronger effects of aspirin on the primary prevention of CVD; the data indicated that aspirin did not confer benefits in the high 10-y MACE% risk group. The results were not significantly modified after excluding asymptomatic PAD trials and trials with only diabetic individuals. Besides recommendations from contemporary guidelines, we hypothesized that aspirin might be prescribed depending on body size (BMI), that is, individuals with varied BMI should take different dose of aspirin, for we observing significant differences between <25 and ≧25 BMI, ≤100 and >100 aspirin intake groups on few intended CV outcomes (Rothwell et al., 2018). It is still crucial to perform complete screening and examinations on large populations to evaluate populations' CVD risk, hence quantifying their probability of obtaining real benefits from aspirin. This study provides further insights through updated data on comprehensive subgroup and sensitivity analyses to display potential utility on CVD primary prevention. Indeed, the one-dose-fits-all intake strategy is unlikely optimal, and a more tailored and wise dosing approach is called for to maximize substantial benefits and reduce potential risk.

The endorsed role of aspirin in the primary prevention of ischemic events (all-MI, ischemic stroke) has been supported by several studies (Fox et al., 2015b). The potential mechanism for preventing ischemic events is based on the inhibition of thrombus propagation and plaque rupture (Cleland, 2013). This study also suggested a beneficial role of aspirin in all-MI and ischemic stroke outcomes. Notably, only two eligible trials (HOT and PHS) (Steering Committee of the Physicians' Health Study Research Group, 1989; Hansson et al., 1998) exhibited significant risk reduction in all-MI; however, their conducting time was rather early, and no significant risk reduction was observed in cardiovascular mortality and all-cause mortality under the long follow-up period. Because the two trials were conducted early, researchers could not properly emphasize the biases from risk factors such as smoking status, blood glucose, blood cholesterol level or blood pressure. Another concern is that almost 50% of MIs are considered to be clinically silent; accordingly, it is not easy to ascertain the clinical benefit from long-term aspirin use through this endpoint (Zhang et al., 2016). It may be that all CV events are assessed to be proper endpoints to evaluate all these cases. Some studies have suggested that populations with substantially increased CVD risk may benefit from preventive aspirin use, and guidelines from the US Preventive Services Task Force also suggested prescribing low doses of aspirin in adults aged 50–59 years with a CVD risk of at least 10% (Guirguis-Blake et al., 2016), which was in contrast to our findings that low-risk individuals seemed to obtain more clinical benefits. We used the 10-y MACE% to reflect participants' CVD risk and hypothesized that the CVD risk of participants tended to be overestimated due to the lack of agreement on unified risk calculators in primary trials (Rana et al., 2016). For example, the ARRIVE trial (Gaziano et al., 2018) mixed predicted and observed CVD risk, such that the enrolled moderate risk populations had a standard risk of 17.3% as estimated by American Heart Association (AHA)/American College of Cardiology (ACC) 10-y CV risk estimated criteria (Allan et al., 2013; Rana et al., 2016) but had an observed CVD risk rate of 6.9%. Similarly, the ASPREE trial (McNeil et al., 2018) enrolled patients who were older than 65 or 70 y old; the CVD risk of these older patients was hard to evaluate, and the reported 10-y MACE% of 7.8% differed from the 8.3% figure found herein, although both 10-y MACE% were less than 10%. The reason for this discrepancy was that MACE in the ASPREE trial was defined as a composite of fatal coronary heart disease, nonfatal MI and fatal or nonfatal ischemic stroke, which differed from the unified definition. In this study, CV event risk was reduced by 11% in the low 10-y MACE% risk group.

Guidelines driven by the AHA/American Diabetes Association (ADA) recommend aspirin use in diabetic populations with intermediate risk (5–10% 10-y MACE%) for primary prevention (Fox et al., 2015b). JPAD (Ogawa et al., 2008) and ASCEND (Bowman et al., 2018) trials specifically incorporated diabetic populations, but the cardiovascular benefits seemed to be higher in the ASCEND trial. The total proportion of statin use was 75% in the ASCEND trial vs. 25% in the JPAD trial, which might have resulted in higher benefits seen in the ASCEND trial. Additionally, this study indicated fewer CVD benefits among populations with diabetes, which was supported by recent European Society of Cardiology guidelines recommending against aspirin use in diabetic populations who have no history of CVD (Piepoli et al., 2016). Routine aspirin use was not enough for primary prevention among individuals with a high risk of CVD; at that time, blood pressure and blood glucose were controlled, cholesterol levels were reduced with statins, and physical activity and healthy eating were reduced are also necessary. Aspirin use increased the risk of bleeding profiles but was not associated with cardiovascular mortality considering that deaths caused by bleeding were rare. Since the strategy to reduce harm of long-term aspirin use is not understood from current evidence, prescribing proton pump inhibitors (PPIs) might limit the risk of major gastrointestinal bleeding and enhance the benefit-risk ratio toward intended populations (Fowkes et al., 2010). Aspirin appears to be not

TABLE 3 | Summarized results of the sensitivity analysis.

Outcomes (RR, 95% CI)	Excluding before 2000 trials[a]	Excluding open-label trials[b]	Excluding high risk trials[c]	Excluding asymptomatic PAD trials[d]	Excluding 100% male individual trials[e]	Excluding 100% diabetic individuals trials[f]	Restricting on 100% diabetic individuals trials[g]	Excluding placebo use trials[h]	Excluding TPT study[i]
Primary efficacy outcomes									
CV Events	0.91 (0.87–0.96)	0.90 (0.85–0.95)	0.91 (0.86–0.97)	0.91 (0.87–0.96)	0.92 (0.87–0.97)	0.90 (0.85–0.95)	0.95 (0.84–1.06)	0.92 (0.84–1.02)	NA
All-cause mortality	0.98 (0.93–1.04)	0.98 (0.93–1.03)	0.98 (0.92–1.04)	0.97 (0.93–1.02)	0.98 (0.93–1.03)	0.98 (0.93–1.04)	0.94 (0.86–1.03)	0.93 (0.83–1.03)	0.97 (0.93–1.02)
Cardiovascular mortality	0.93 (0.82–1.07)	0.95 (0.87–1.05)	0.95 (0.85–1.05)	0.93 (0.85–1.02)	0.94 (0.84–1.04)	0.94 (0.85–1.05)	0.97 (0.65–1.45)	0.85 (0.59–1.22)	0.95 (0.86–1.03)
Secondary efficacy outcomes									
All MI	0.95 (0.88–1.03)	0.86 (0.74–0.99)	0.93 (0.83–1.04)	0.84 (0.74–0.95)	0.92 (0.84–1.00)	0.83 (0.72–0.96)	0.97 (0.85–1.10)	0.94 (0.79–1.12)	0.88 (0.78–0.99)
Total stroke	0.92 (0.84–1.00)	0.94 (0.86–1.03)	0.92 (0.84–1.00)	0.95 (0.89–1.03)	0.92 (0.85–1.00)	0.96 (0.88–1.05)	0.90 (0.88–1.02)	0.98 (0.84–1.15)	0.95 (0.88–1.02)
Ischemic stroke	0.86 (0.78–0.94)	0.88 (0.78–0.98)	0.85 (0.76–0.95)	0.88 (0.80–0.97)	0.86 (0.78–0.98)	0.86 (0.76–0.97)	0.92 (0.79–1.07)	0.89 (0.72–1.09)	0.88 (0.81–0.97)
Cancer incidence	1.01 (0.94–1.08)	0.99 (0.95–1.05)	0.99 (0.95–1.05)	1.02 (0.97–1.07)	1.00 (0.94–1.07)	1.02 (0.95–1.10)	0.94 (0.82–1.08)	1.06 (0.90–1.25)	NA
Cancer mortality	1.03 (0.93–1.15)	1.03 (0.92–1.15)	1.02 (0.89–1.16)	1.05 (0.96–1.14)	1.03 (0.94–1.12)	1.04 (0.93–1.16)	0.98 (0.86–1.12)	1,01 (0.86–1.19)	1.03 (0.94–1.12)
Safety outcomes									
Major bleeding	1.37 (1.12–1.50)	1.40 (1.28–1.54)	1.39 (1.26–1.53)	1.40 (1.28–1.52)	1.40 (1.28–1.54)	1.48 (1.33–1.64)	1.27 (1.11–1.47)	1.42 (1.11–1.80)	1.40 (1.29–1.52)
Intracranial bleeding	1.30 (1.10–1.54)	1.33 (1.11–1.59)	1.29 (1.07–1.56)	1.29 (1.10–1.52)	1.28 (1.08–1.51)	1.36 (1.14–1.63)	1.11 (0.80–1.54)	1.22 (0.89–1.68)	1.30 (1.11–1.52)
Gastrointestinal bleeding	1.49 (1.30–1.72)	1.52 (1.33–1.74)	1.51 (1.38–1.78)	1.58 (1.39–1.80)	1.55 (1.36–1.77)	1.63 (1.41–1.90)	1.43 (1.13–1.80)	2.23 (1.33–3.74)	1.56 (1.38–1.78)

Note: Sensitivity analysis was conducted by omitting one/several study/studies each turn to show more clinical useful data.

Abbreviations: MI, myocardial infraction; PAD, peripheral artery disease; NA, Not available; RR, Relative risk; CI, Confidence interval.

[a]*Total 10 trials (de Gaetano, 2001; Ridker et al., 2005; Belch et al., 2008; Ogawa et al., 2008; Fowkes et al., 2010; Ikeda et al., 2014; Saito et al., 2017; Bowman et al., 2018; Gaziano et al., 2018; McNeil et al., 2018), N = 115,300.*

[b]*Total nine trials (Steering Committee of the Physicians' Health Study Research Group, 1989; The Medical Research Council's General Practice Research Framework, 1998; Hansson et al., 1998, Ridker et al., 2005; Belch et al., 2008; Fowkes et al., 2010; Bowman et al., 2018; Gaziano et al., 2018; McNeil et al., 2018), N = 135,042.*

[c]*Total seven trials (Hansson et al., 1998; Ridker et al., 2005; Belch et al., 2008; Fowkes et al., 2010; Bowman et al., 2018; Gaziano et al., 2018; McNeil et al., 2018), N = 110,432.*

[d]*Total 12 trials (Peto et al., 1988; Steering Committee of the Physicians' Health Study Research Group, 1989; The Medical Research Council's General Practice Research Framework, 1998; Hansson et al., 1998; de Gaetano, 2001; Ridker et al., 2005; Ogawa et al., 2008; Ikeda et al., 2014; Saito et al., 2017; Bowman et al., 2018; Gaziano et al., 2018; McNeil et al., 2018); N = 159,214.*

[e]*Total 11 trials (Hansson et al., 1998; de Gaetano, 2001; Ridker et al., 2005; Belch et al., 2008; Ogawa et al., 2008; Fowkes et al., 2010; Ikeda et al., 2014; Saito et al., 2017; Bowman et al., 2018; Gaziano et al., 2018; McNeil et al., 2018), N = 134,090.*

[f]*Total 10 trials (Peto et al., 1988; Steering Committee of the Physicians' Health Study Research Group, 1989; The Medical Research Council's General Practice Research Framework, 1998; Hansson et al., 1998; de Gaetano, 2001; Ridker et al., 2005; Fowkes et al., 2010; Ikeda et al., 2014; Gaziano et al., 2018; McNeil et al., 2018), N = 142,385.*

[g]*Total four trials (Belch et al., 2008; Ogawa et al., 2008; Saito et al., 2017; Bowman et al., 2018), N = 21,455.*

[h]*Total five trials (Peto et al., 1988; de Gaetano, 2001; Ogawa et al., 2008; Ikeda et al., 2014; Saito et al., 2017), N = 28,797.*

[i]*Total 13 trials (Peto et al., 1988; Steering Committee of the Physicians' Health Study Research Group, 1989; Hansson et al., 1998; de Gaetano, 2001; Ridker et al., 2005; Belch et al., 2008; Ogawa et al., 2008; Fowkes et al., 2010; Ikeda et al., 2014; Saito et al., 2017; Bowman et al., 2018; Gaziano et al., 2018; McNeil et al., 2018), N = 161,300.*

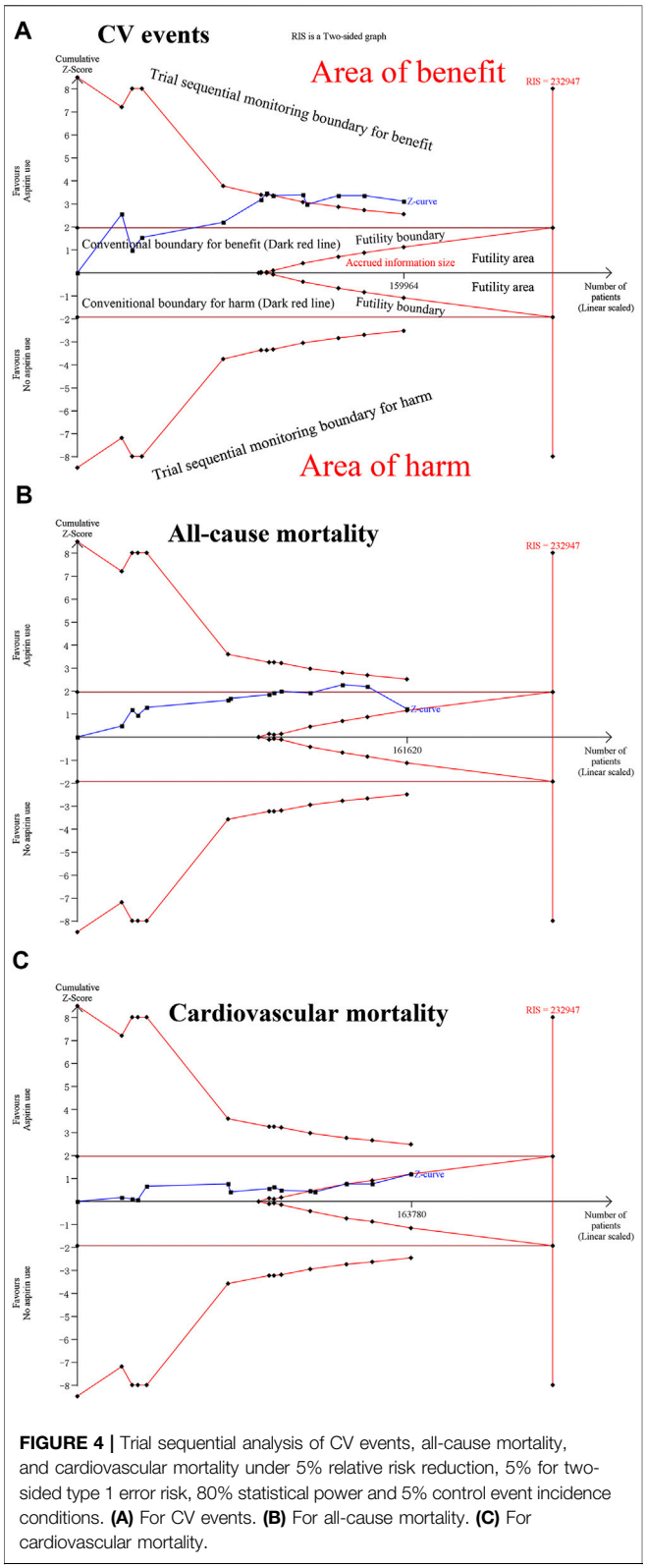

FIGURE 4 | Trial sequential analysis of CV events, all-cause mortality, and cardiovascular mortality under 5% relative risk reduction, 5% for two-sided type 1 error risk, 80% statistical power and 5% control event incidence conditions. **(A)** For CV events. **(B)** For all-cause mortality. **(C)** For cardiovascular mortality.

associated with all-cause mortality; however, several trials revealed that aspirin reduced the risk of colorectal cancer (RR: 0.73, 95% CI: 0.69–0.78), squamous-cell oesophageal cancer (RR: 0.67, 95% CI: 0.57–0.79), gastric cancer (RR: 0.64, 95% CI: 0.51–0.82) and pancreatic cancer (RR: 0.78, 95% CI: 0.68–0.89) (Bosetti et al., 2020). At this time, the reduction in cancer mortality appeared after 5 y of follow-up, and this result was not duplicated in the ASCEND trial (Bowman et al., 2018). Current findings suggest a neutral role of aspirin in cancer outcomes; therefore, no suggestions could be made regarding benefit-risk balance from current evidence.

Added Value and Limitations

Contrast to prior similar studies, current study has several innovations. Mahmoud et al. (Mahmoud et al., 2019) conducted a TSA meta-analysis, the authors mainly focused on CVD-related outcomes including all-cause mortality, all MI, bleeding events. Comparing to Mahmoud et al. (Mahmoud et al., 2019), current study is more comprehensive because we also investigated cancer outcomes. Study from Mahmoud et al. (Mahmoud et al., 2019) included 11 RCTs, in our prospective, it was not enough, trials like POPADAD (Belch et al., 2008), AAA (Fowkes et al., 2010) were not reasonably included. Also, several 10y-MACE% values presented in that study were not in consistent with current study, for example ASCEND (Bowman et al., 2018), ARRIVE (Gaziano et al., 2018) and ASPREE (McNeil et al., 2018). 10y-MACE% for BDS (Peto et al., 1988) and TPT (The Medical Research Council's General Practice Research Framework, 1998) was also absent in Mahmoud et al. (Mahmoud et al., 2019) study. Lin et al. (Lin et al., 2019) investigated the role of low-dose of aspirin on CVD primary prevention, they demonstrated low-dose aspirin had no role in all MI, but did reduce stroke incidence, which was in contrast to findings from current paper (that aspirin might significantly reduce all MI incidence instead of total stroke, ischemic stroke could be reasonably reduced). Current study had included more comprehensive RCTs than Lin et al. (Lin et al., 2019), subgroup analyses aiming to low-dose of aspirin (<100 mg/d) were also conducted. This study clearly pinpointed low CVD risk individuals might get more clinical benefits than the high risk from aspirin. Only one TSA for MACE outcome in Lin et al. (Lin et al., 2019) was far enough to draw robust conclusions. Major controversial issues from current study and Gelbenegger et al. (Gelbenegger et al., 2019) were the outcomes on diabetic populations, this study supported there were no substantial benefits of aspirin on diabetic populations primary prevention. POPADAD (Belch et al., 2008), JPAD (Ogawa et al., 2008), JPAD2 (Saito et al., 2017) and ASCEND (Bowman et al., 2018) were special trials conducted on full diabetic populations (100% diabetic individuals), to our great knowledge, it was more proper to investigate the intended results on the four trials, data stem from calculation on other small diabetic-proportion trials (Ridker et al., 2005; Ikeda et al., 2014) would add extra reporting bias. Zheng et al. (Zheng and Roddick, 2019) also performed a similar research, however, no TSA results were revealed and merits from network meta-analysis methods seemed not so obvious. Overall, current study with particular subgroup and sensitivity analyses clearly addressed the less priority of aspirin on high 10y-MACE% risk and diabetic populations, such populations may need more aggressive therapy or combined

pharmaceutical intervention. We believe these results add new evidence to the discussion on aspirin primary prevention in CVD and may arouse new disputes.

Limitations were also detected. First, definitions of reported outcomes were different, reflecting advances in CVD diagnosis and treatment. To best overcome this heterogeneity, we defined unified primary and secondary efficacy outcomes and safety profiles and then properly extracted the required data in eligible studies. Second, aspirin use in the included studies was not consistent with the major dose of 75–100 mg. Importantly, more clinical benefits with bleeding risk were found in trials restricted to ≤100 mg/d intake. Third, several trials (BDS (1998), PHS (1989), TPT (1998), HOT (1998)) were published rather early, and thus, some examinations and screening methods may not have been as accurate as expected. This contributed to an overestimated 10-y MACE%. Long-term follow-up studies are welcomed to better characterize individuals who may benefit from aspirin for primary prevention outweighing the unexpected bleeding events. Objective influence on all-cause mortality and cancer incidence should be re-evaluated. Considering no individual-patients-data was involved, therefore, a more precise study based on individual data is quite encouraged.

CONCLUSION

Aspirin intake was associated with reduced risk of CV events, all MI, and ischemic stroke, and was associated with increased incidences of major bleeding, intracranial bleeding, and major gastrointestinal bleeding in the primary prevention of CVD. The use was not associated with an increased risk of all-cause mortality, cardiovascular mortality, total stroke, cancer incidence or cancer mortality. No substantial benefits with respect to CVD were observed in the diabetic and high 10-y MACE% risk group populations. A one-dose-fits-all strategy is not optimal, and BMI may be a potential indicator to guide aspirin prescription. It is also necessary to identify individuals who may benefit from aspirin by more accurate cardiovascular-relating examinations. Overall, the benefits and harm of aspirin for primary prevention should be re-evaluated. Based on these findings, we believe it is not yet the time to quit the aspirin era.

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 designed and conducted this review. BZ wrote the paper. QW, LW, CL, YD, JX, YW, and WZ helped the study design. BZ, YW, and WZ revised the statistical methodology. BZ and WZ had primary responsibility for the final content. All authors read and approved the final manuscript. Notably, BZ and WZ equally share the corresponding authorship.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2020.592116/full#supplementary-material

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Risk of Hospitalization Associated with Cardiovascular Medications in the Elderly Italian Population: A Nationwide Multicenter Study in Emergency Departments

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Background: There is a significant gap in knowledge addressing cardiovascular (CV) medications safety in elderly. In this context, our purposes were to define clinical and pharmacological characteristics of outpatients' adverse drug events (ADEs) related to CV medications leading to emergency department (ED) visits in the elderly Italian patients according to different age groups, and to evaluate the risk of hospitalization associated to ADEs in this population.

Methods: A multicentre, retrospective study was performed on reports of suspected ADEs collected between 2007–2018 in 94 EDs involved in the MEREAFaPS Study. Elderly patients who experienced one or more CV medications-related ADEs leading to ED visit were selected. Patients' characteristics, suspected (ATC classes B and C) and concomitant drugs, and ADE description were collected. Elderly patients were stratified into three age groups (65–74, 75–84, and ≥85 years) and compared to adults (18–64 years). Logistic regression analyses were used to estimate the reporting odds ratios (RORs) with 95% confidence intervals (CIs) of ADE-related hospitalization adjusting for sex, presence of two or more suspected drugs, concomitant drugs, and one or more comorbidities.

Results: Among elderly, 16,926 reports of suspected ADE related to CV medications were collected, and 6,694 (39.5%) resulted in hospitalization. Patients were mostly female, Caucasians, and middle-old (75–84). 78.9% of patients were treated with only one suspected drug, and 71.9% and 47.1% reported concomitant medications and

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comorbidities, respectively. Compared to adults, risk of hospitalization was significantly higher for middle-old and oldest-old patients exposed to vitamin K antagonists (1.29 [1.09–1.52] and 1.56 [1.30–187]), direct thrombin inhibitors (3.41 [1.44–8.08] and 4.12 [1.67–10.17]), antiplatelets (1.51 [1.26–1.81] and 2.09 [1.71–2.57]), and beta-blockers (1.89 [1.38–2.59 and 2.31 [1.60–3.35]). Overall, a higher risk of hospitalization was observed for renin-angiotensin system inhibitors (1.32 [1.04–1.68], 1.65 [1.32–2.06], and 2.20 [1.70–2.85]), presence of two or more concomitant drugs, and concomitant conditions.

Conclusion: Our real-world findings underline relevant safety aspects of CV medications in the elderly Italian population. ED clinicians must always consider the higher risk of hospitalization related to the use of CV drugs in elderly, particularly in oldest-old ones, for antiarrhythmics, beta-blocking agents, renin-angiotensin system inhibitors, antiplatelets, and anticoagulants.

Keywords: emergency department, hospitalization, adverse drug event, cardiovascular drug, elderly

INTRODUCTION

In the last century, the number of individuals aged 65 years and older increased significantly in high-income countries, as well as the number of patients affected by acute and chronic cardiovascular (CV) comorbidities (Christensen et al., 2009), many of which are characterized by a widespread use of CV medications for the prevention of morbidity and mortality (Fleg et al., 2011).

Elderly patients are known to be generally underrepresented in randomized clinical trials testing the efficacy and the safety of medications, including CV ones, and those who are usually included in the trials are often highly selected (Konrat et al., 2012), which limits generalization of the research findings to the general older populations.

Furthermore, as individuals age, elderly patients are at increased risk of developing adverse drug events (ADEs) (Perez et al., 2018) due to specific factors, including changes in drug metabolism as well as the presence of several concomitant medications, which can frequently lead to drug-drug and drug-disease interactions (Routledge et al., 2004; Davies and O'Mahony, 2015; Turgeon et al., 2017).

ADEs are an important cause of morbidity and emergency department (ED) visits and hospitalisations among the elderly (Budnitz et al., 2011). Although some studies have reported that the incidence of ADEs may be as high as 25% (Tecklenborg et al., 2020), a rate that is fourfold higher than in young adults (aged 18–64 years), the evidence that age is the sole predisposing factor for ADEs in the elderly is still debated (Davies and O'Mahony, 2015).

In evaluating real-world safety aspects of CV medications in the elderly, EDs can certainly represent a valuable observatory to perform pharmacovigilance active investigations about the clinical impact of ADEs in outpatients (Lombardi et al., 2018; Lombardi et al., 2020a; Lombardi et al., 2020b). Numerous investigations have been published on ED visits related to ADEs, but none of those found in the scientific literature have focused on CV medications in elderly.

Therefore, the purposes of the present study were to define the clinical and pharmacological characteristics of outpatients' ADEs related to CV medications as cause of ED visits in the elderly Italian population, and to calculate the risk of hospitalization associated to ADEs in different elderly age groups compared to young adults.

MATERIALS AND METHODS

This is an observational retrospective study performed on data retrieved by pharmacovigilance reports of suspected ADE collected between January 1, 2007 and December 31, 2018 in the 94 EDs participating to the MEREAFaPS Study, an on-going multicentre study of active pharmacovigilance whose features have already been extensively described (Lombardi et al., 2020b). The involved hospitals belong to the territories of five Italian Regions: Lombardy and Piedmont (north), Tuscany and Emilia-Romagna (center), and Campania (south).

Within the MEREAFaPS Study database, all elderly patients (individuals aged 65 years and older) who experienced one or more CV medications-related ADEs leading to ED visit and hospitalization were selected and analyzed. Hospitalization was defined as an admission to the hospital following the ED visit. Independently from the time duration of ED stay, hospitalization was not considered when the patient was discharged after the visits.

For each elderly patient the following demographic, clinical, and pharmacological characteristics were evaluated: 1) age, gender, ethnicity; 2) clinical status on ED admission; 3) suspected and concomitant drugs (for each one, administration route, therapy duration, dosages, and therapeutic indication were recorded); 4) presence of concomitant conditions; 5) use of complementary and alternative medicines (CAM); 5) ADEs description; 6) ADEs outcome (in particular the presence or absence of ADE-related hospitalisation).

Anatomical Therapeutic Chemical (ATC) classification system was used to classify both suspected and concomitant drugs. ADEs reported from elderly outpatients having at least one clinical manifestation related to one or more CV medications were included in the analysis, considering only medications belonging to the ATC classes B and C, in particular: B01* (antithrombotic agents); B02* (antihemorrhagics); B03* (antianemic preparations); B05* (blood substitutes and perfusion solutions); C01* (cardiac therapy); C02* (antihypertensives); C03* (diuretics); C04* (peripheral vasodilators); C05* (vasoprotectives); C07* (beta blocking agents); C08* (calcium channel blockers); C09* (agents acting on the renin-angiotensin system); and C10* (lipid modifying agents). Patients who developed an ADE while in the ED for any other reason rather than CV medications were excluded. The Medical Dictionary for Regulatory Activities (MedDRA, version 21.0) was used to describe ADEs and comorbidities, that were coded and organized by System Organ Class (SOC) and Preferred Term (PT).

All cases extracted from the MEREAFaPS Study database were evaluated in order to assess the causality relationship between the suspected CV drugs and their related ADEs. Probability was assigned via a score termed definite (≥9), probable (5–8), possible (1–4) or doubtful (0) (Naranjo et al., 1981). This evaluation was performed by two groups of authors. In particular, GC and NL discussed each case independently from the evaluation performed by SP and GS. Any discrepancies were resolved by a third group of authors (MT, MR, AC, and AV). The application of the Naranjo score found a "possible" or "probable" association in most of the cases included in the present analysis.

Data were summarized using descriptive statistics. Categorical data were reported as frequencies and percentages and compared using the Chi-square test, while continuous data were reported as median values with the related interquartile ranges (IQRs) and compared using the Mann-Whitney test. Elderly patients were stratified according to the following age groups (Lee et al., 2018): group 1 (youngest-old), ranging from 65 to 74 years; group 2 (middle-old), ranging from 75 to 84 years; and group 3 (oldest-old), aged more than 85 years. For each CV medication group, as compared to all others belonging to the ATC classes of interest, univariate logistic regression was used to calculate the reporting odds ratios (RORs) of hospitalization with 95% confidence intervals (CIs) among each elderly group and compared to young adults (18–64 years). Multivariate logistic regression was performed and adjusted for sex, presence of two or more suspected drugs, presence of concomitant drugs, and presence of one or more comorbidities.

Adjustment was performed for all the above mentioned covariates. All results were considered to be statistically significant at $p < 0.05$. Data management and statistical analysis were carried out using STATA 16.

The coordinating center of Tuscany Region (Italy) approved the MEREAFaPS Study (Notification number 1225—December 21, 2009), and the local institutional ethics committee approved MEREAFaPS Study (Study number 3055/2010, Protocol number 45288—August 6, 2014) according to the legal requirements concerning observational studies. Due to the retrospective nature of the present study and data anonymization, patient's consent to participate was not required.

RESULTS

Over the 12 years study period, a total of 61,855 ADE reports related to ED visits was assessed; of them, 16,926 (27.4%) were observed in elderly patients and related to CV medications (Youngest-Old n = 4,531; Middle-Old n = 8,006; Oldest-Old n = 4,389). Overall, 6,694 (39.5%) elderly patients were hospitalized due to the drug-related manifestation (Youngest-Old n = 1,463; Middle-Old n = 3,181; Oldest-Old n = 2050). Overall, we calculated that 40.1% (3,503/8,739) of female patients were hospitalized for ADEs related to CV medications vs 39.0% of male patients (3,191/8,187).

Table 1 reports demographic and clinical characteristics of elderly patients by age groups. Male patients were most represented in the youngest-old group (56.0%), while females were prevalent in middle-old (50.8%) and oldest-old (61.1%) groups. Overall, the majority of ADEs occurred in Caucasians and, at the time of adverse event, elderly patients were mostly treated with only one suspected drug. Among these, ATC class B was mostly reported in all elderly age groups (68.6, 73.1, and 73.1%), followed by medications belonging to the ATC class C (29.9, 25.3, and 25.0%). Concomitant drugs were reported in 67.7% of youngest-old, 72.4% middle-old, and 75.5% oldest-old. Most frequent concomitant drugs were those belonging to the cardiovascular system (ATC class C), followed by alimentary tract and metabolism (ATC class A), nervous system (ATC class N), blood and blood forming organs (ATC class B), and musculo-skeletal system (ATC class M). With increasing age, we observed an increase in the reported frequency for all ATC classes of concomitant drugs. The majority of patients among youngest-old (58.1%) and middle-old (52.6%) groups did not present concomitant conditions, while 52.5% of oldest patients reported to be affected by one or more comorbidities. Although with different percentages within the individual elderly age groups, the most frequently reported concomitant conditions were arterial hypertension, atrial fibrillation, ischaemic cardiomyopathy, dyslipidemia, and chronic renal failure. With increasing age, we observed an increase in the reported frequency for arterial hypertension, atrial fibrillation, and chronic renal failure. CAMs were reported in 1% of ADE reports. Moreover, with increasing age, we also observed an increase of the frequency of hospitalization among female patients. Among ED visits, a statistically significant difference was observed for all demographic and clinical characteristics analyzed, excluding the presence of CAMs. Demographic and clinical characteristics of young adults, who represent our comparison group, are described in **Supplementary Table S1**.

Table 2 reports the most frequently reported CV medication groups and risk of hospitalization for elderly patients by age groups. Out of the total of suspected drugs, 68.3% belonged to the ATC class B and 31.7% to the ATC class C. In particular,

TABLE 1 | Characteristics of elderly patients visiting the emergency department for an adverse drug event related to cardiovascular medications (ATC classes B and C).

Characteristics	Youngest-old 65–74 years N = 4,531 (%)	Middle-old 75–84 years N = 8,006 (%)	Oldest-old ≥85 years N = 4,389 (%)	*p*-value
Sex				
Female	1,993 (44.0)	4,065 (50.8)	2,681 (61.1)	<0.001
Male	2,538 (56.0)	3,941 (49.2)	1,708 (38.9)	
Patients' ethnicity				
Asian	16 (0.4)	9 (0.1)	2 (0.1)	<0.001
Black or African-American	6 (0.1)	5 (0.1)	0	
Caucasian	4,115 (90.8)	723 (90.4)	3,900 (88.9)	
Others	7 (0.2)	8 (0.1)	3 (0.1)	
Not available	387 (8.5)	750 (9.4)	484 (11.0)	
No. of suspected drugs involved in ADE				
1	3,494 (77.1)	6,388 (79.8)	3,488 (79.5)	0.006
2	782 (17.3)	1,230 (15.4)	669 (15.2)	
>3	255 (5.6)	388 (4.9)	232 (5.3)	
ATC class of suspected drugs				
ATC class B	3,107 (68.6)	5,855 (73.1)	3,208 (73.1)	<0.001
ATC class C	1,354 (29.9)	2,026 (25.3)	1,095 (25.0)	
Both classes	70 (1.5)	125 (1.6)	86 (2.0)	
Concomitant drugs				
No	1,464 (32.3)	2,207 (27.6)	1,074 (24.5)	<0.001
Yes	3,067 (67.7)	5,799 (72.4)	3,315 (75.5)	
No. of concomitant drugs				
0	1,464 (32.3)	2,207 (27.6)	1,074 (24.5)	<0.001
1	595 (13.1)	845 (10.6)	386 (8.8)	
2	503 (11.1)	818 (10.2)	445 (10.1)	
3–4	867 (19.1)	1,607 (20.1)	1,031 (23.5)	
>5	1,102 (24.3)	2,529 (31.6)	1,453 (33.1)	
ATC class of most frequently reported concomitant drugs				
ATC class C	2,407 (53.1)	4,785 (59.8)	2,808 (64.0)	
ATC class A	1,450 (32.0)	2,915 (36.4)	1,723 (39.3)	
ATC class N	743 (16.4)	1,817 (22.7)	1,183 (27.0)	
ATC class B	816 (18.0)	1,700 (21.2)	996 (22.7)	
ATC class M	386 (8.5)	936 (11.7)	592 (13.5)	
Concomitant conditions				
No	2,632 (58.1)	4,210 (52.6)	2,086 (47.5)	<0.001
Yes	1,899 (41.9)	3,796 (47.4)	2,303 (52.5)	
No. of concomitant conditions				
0	2,632 (58.1)	4,210 (52.6)	2,086 (47.5)	<0.001
1	756 (16.7)	1,306 (16.3)	783 (17.8)	
2	454 (10.0)	838 (10.5)	493 (11.2)	
>3	689 (15.2)	1,652 (20.6)	1,027 (23.4)	
Most frequently reported concomitant conditions[b]				
Arterial hypertension	850 (18.8)	1,698 (21.2)	969 (22.1)	
Atrial fibrillation	316 (7.0)	905 (11.3)	611 (13.9)	
Diabetes	296 (6.5)	617 (7.7)	280 (6.4)	
Ischaemic cardiomyopathy	255 (5.6)	470 (5.9)	238 (5.4)	
Dyslipidaemia	207 (4.6)	376 (4.7)	136 (3.1)	
Chronic renal failure	169 (3.7)	470 (5.9) ↑	370 (8.4) ↑	
COPD	87 (1.9)	252 (3.1)	135 (3.1)	
Presence of CAM				
No	4,483 (98.9)	7,940 (99.2)	4,343 (99.0)	0.305
Yes	48 (1.1)	66 (0.8)	46 (1.1)	
Hospitalization				
No	3,068 (67.7)	4,825 (60.3)	2,339 (53.3)	<0.001
Female	1,416 (46.1)	2,417 (50.1)	1,403 (60.0)	
Male	1,652 (53.9)	2,408 (49.9)	936 (40.0)	
Yes	1,463 (32.3)	3,181 (39.7)	2,050 (46.7)	<0.001
Female	577 (39.4)	1,648 (51.8)	1,278 (62.3)	
Male	886 (60.6)	1,533 (48.2)	772 (37.7)	

ADE, adverse drug event; ATC, anatomical therapeutic chemical; CAM, complementary and alternative medicine; COPD, chronic obstructive pulmonary disease.

[a]*Most frequently reported concomitant drugs (as ATC class, first level): A, alimentary tract and metabolism; B, blood and blood forming organs; C, cardiovascular system; M, musculo-skeletal system; N, nervous system.*

[b]*Most frequently reported concomitant conditions (as preferred terms) out of 20,824 reported low-level terms MedDRA.*

TABLE 2 | Suspected cardiovascular medication groups (ATC classes B and C) and risk of hospitalization for elderly patients.

Cardiovascular medication groups	Youngest-old	Middle-old	Oldest-old	Youngest-old	Middle-old	Oldest-old
	65–74 years	75–84 years	≥85 years	65–74 years	75–84 years	>85 years
	N = 4,531 (%)	N = 8,006 (%)	N = 4,389 (%)	ROR (95%CI)[a]	ROR (95%CI)[a]	ROR (95%CI)[a]
ATC class B, blood and blood forming organs						
Anticoagulants	2,024 (44.7)	4,119 (51.5)	2,210 (50.4)	1.02 (0.86–1.20)	1.35 (1.16–1.56)	1.61 (1.37–1.89)
Vitamin K antagonists (warfarin)	1,756 (38.8)	3,473 (43.4)	1,833 (41.8)	0.97 (0.81–1.17)	1.29 (1.09–1.52)	1.56 (1.30–1.87)
Factor Xa inhibitors	75 (17.7)	231 (2.9)	145 (3.3)	1.28 (0.46–3.54)	1.33 (0.52–3.42)	1.35 (0.51–3.58)
Unfractionated and low-molecular-weight heparins	143 (3.2)	251 (3.1)	142 (3.2)	1.15 (0.71–1.87)	1.49 (0.97–2.30)	1.63 (1.00–2.65)
Direct thrombin inhibitors	83 (1.8)	218 (2.7)	111 (2.5)	2.14 (0.83–5.49)	3.41 (1.44–8.08)	4.12 (1.67–10.17)
Antiplatelets	1,189 (26.2)	1,905 (23.8)	1,074 (24.5)	1.17 (0.95–1.42)	1.51 (1.26–1.81)	2.09 (1.71–2.57)
Acetylsalicylic acid	984 (21.7)	1,513 (18.9)	852 (19.4)	1.15 (0.92–1.43)	1.45 (1.19–1.77)	1.99 (1.59–2.48)
Platelet $P2Y_{12}$ receptor antagonists	375 (8.3)	560 (7.0)	273 (6.2)	1.00 (0.71–1.42)	1.57 (1.14–2.17)	2.37 (1.63–3.44)
Enzymes	3 (0.1)	4 (0.1)	—	—	—	—
Other blood agents[b]	22 (0.5)	41 (0.5)	27 (0.6)	0.43 (0.12–1.53)	1.16 (0.50–2.71)	1.74 (0.67–4.54)
ATC class C, cardiovascular system						
Renin-angiotensin system inhibitors	620 (13.7)	893 (11.2)	469 (10.7)	1.32 (1.04–1.68)	1.65 (1.32–2.06)	2.20 (1.70–2.85)
Diuretics	221 (4.9)	509 (6.4)	425 (9.7)	1.13 (0.76–1.70)	1.21 (0.85–1.72)	1.54 (1.07–2.22)
Beta blocking agents	327 (7.2)	467 (5.8)	227 (5.2)	1.16 (0.82–1.63)	1.89 (1.38–2.59)	2.31 (1.60–3.35)
Calcium channel blockers	190 (4.2)	262 (3.3)	99 (2.3)	1.15 (0.72–1.85)	1.42 (0.91–2.19)	1.09 (0.61–1.95)
Antiarrhythmics	118 (2.6)	190 (2.4)	73 (1.7)	1.46 (0.80–2.64)	1.63 (0.94–2.83)	2.80 (1.42–5.54)
Lipid modifying agents	84 (1.9)	73 (0.9)	19 (0.4)	1.32 (0.74–2.34)	1.44 (0.79–2.63)	2.02 (0.73–5.61)
Digitalis glycosides	28 (0.6)	124 (1.6)	154 (3.5)	0.66 (0.13–3.26)	1.62 (0.38–6.94)	1.03 (0.24–4.40)
Antiadrenergic agents	81 (1.8)	94 (1.2)	30 (0.7)	0.88 (0.43–1.82)	0.72 (0.35–1.49)	1.22 (0.48–3.15)
Other cardiovascular agents[c]	220 (4.9)	346 (4.3)	146 (3.3)	2.10 (1.42–3.09)	2.46 (1.73–3.52)	2.68 (1.72–4.17)

ATC, anatomical therapeutic chemical; ROR, reporting odds ratio.

[a]*As compared to adults (18–64 years); models are adjusted for sex, presence of 2+ suspected drugs, presence of concomitant drugs, and presence of 1+ comorbidities.*

[b]*Other blood agents: B02*; B03*; B05*.*

[c]*Other cardiovascular agents: C01* (excl. C01AA*); C04*; C05*.*

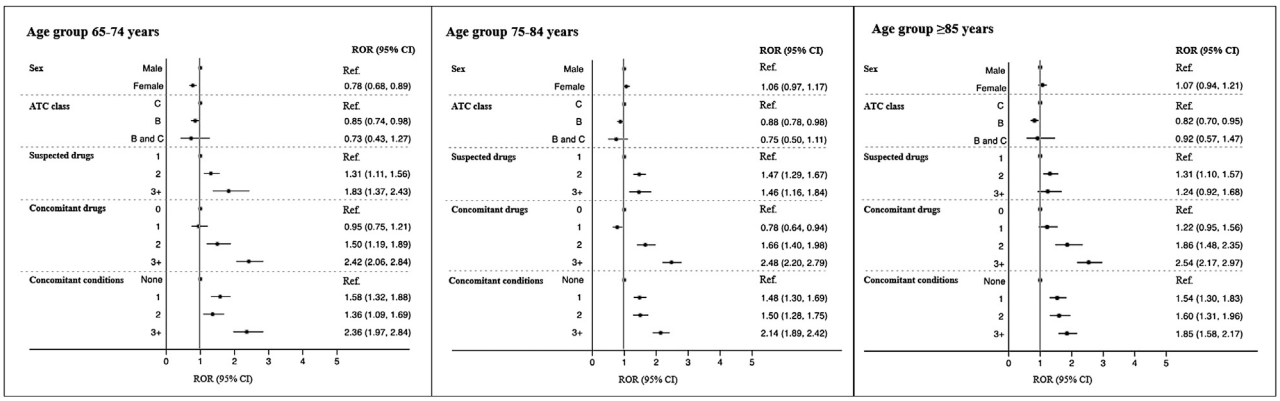

FIGURE 1 | Predictors of hospitalization among the elderly age groups expressed as reporting odds ratio (ROR). CAM, complementary and alternative medicine.

anticoagulants, antiplatelets, and renin-angiotensin system inhibitors were the pharmacological groups most represented among the three study cohorts. Among ATC class B, the risk of hospitalization was significantly higher for middle-old and oldest-old patients compared to young adults for vitamin K antagonists (ROR 1.29, 95% CI [1.09–1.52] and 1.56 [1.30–1.87]), direct thrombin inhibitors (3.41 [1.44–8.08] and 4.12 [1.67–10.17]), acetylsalicylic acid (1.45 [1.19–1.77] and 1.99 [1.59–2.48]), and platelet $P2Y_{12}$ receptor antagonists (1.57 [1.14–2.17] and 2.37 [1.63–3.44]). Considering ATC class B, the risk of hospitalization was significantly higher for all elderly age groups compared to young adults for renin-angiotensin system inhibitors (1.32 [1.04–1.68], 1.65 [1.32–2.06], and 2.20 [1.70–2.85]). Middle-old and oldest-old patients were at higher risk of hospitalization if exposed to beta blocking agents (1.89 [1.38–2.59] and 2.31 [1.60–3.35]), while only oldest-old patients were at higher risk if exposed to diuretics (1.54 [1.07–2.22]) and to antiarrhythmics (2.80 [1.42–5.54]).

TABLE 3 | Suspected drugs among cardiovascular medications (ATC classes B and C) leading to emergency department visit.

Suspected drugs	Elderly overall	Youngest-old	Middle-old	Oldest-old
		65–74 years	75–84 years	>85 years
ATC class B, blood and blood forming organs	N = 13,700 (%)	N = 3,586 (%)	N = 6,587 (%)	N = 3,527 (%)
Warfarin	5,445 (39.7)	1,614 (45.0)	2,178 (48.3)	1,653 (46.9)
Acetylsalicylic acid	3,349 (24.4)	984 (27.4)	1,513 (23.0)	852 (24.2)
Clopidogrel	737 (5.4)	242 (6.8)	333 (5.1)	162 (4.6)
Acenocoumarol	617 (4.5)	142 (4.0)	295 (4.5)	180 (5.1)
Dabigatran	412 (3.0)	83 (2.3)	218 (3.3)	111 (3.2)
Rivaroxaban	387 (2.8)	83 (2.3)	207 (3.1)	97 (2.8)
Enoxaparin	383 (2.8)	100 (2.8)	179 (2.7)	104 (3.0)
Ticlopidine	356 (2.6)	69 (1.9)	184 (2.8)	103 (2.9)
Apixaban	184 (1.3)	27 (0.8)	83 (1.3)	74 (2.1)
Edoxaban	91 (0.7)	—	53 (0.8)	38 (1.1)
Ticagrelor	50 (0.4)	50 (1.4)	—	—
ATC class C, cardiovascular system	N = 6,370 (%)	N = 1,829 (%)	N = 2,885 (%)	N = 1,656 (%)
Furosemide	616 (9.7)	98 (5.4)	274 (9.5)	244 (14.7)
Ramipril	488 (7.7)	145 (7.9)	221 (7.66)	122 (7.4)
Bisoprolol	327 (5.1)	85 (4.7)	134 (4.6)	108 (6.5)
Digoxin	270 (4.2)	—	121 (4.2)	149 (9.0)
Amiodarone	259 (4.1)	65 (3.6)	139 (4.8)	55 (3.3)
Amlodipine	223 (3.5)	96 (5.3)	127 (4.4)	—
Enalapril	213 (3.3)	57 (3.1)	101 (3.5)	55 (3.3)
Doxazosin	151 (2.4)	71 (3.9)	80 (2.8)	—
Atenolol	139 (2.2)	65 (3.6)	74 (2.6)	—
Metoprolol	110 (1.7)	44 (2.4)	66 (2.3)	—
Hydrochlorothiazide	61 (1.0)	—	—	61 (3.7)
Spironolactone	47 (0.7)	—	—	47 (2.8)
Canrenone	46 (0.7)	—	—	46 (2.8)
Valsartan and diuretic	46 (0.7)	—	—	46 (2.8)
Carvedilol	43 (0.7)	43 (2.4)	—	—

ATC, anatomical therapeutic chemical.

Furthermore, adjusted multivariate logistic regression indicated that the risk of hospitalization was significantly higher for all elderly age groups compared to young adults as the number of suspected and concomitant drugs, and the number of concomitant conditions increases (**Figure 1**).

Table 3 reports the most frequently reported suspected drugs among CV medications leading to ED visit. The total number of suspected drugs analyzed was 20,070, of which 13,700 (3,586 youngest-old; 6,587 middle-old; 3,527 oldest-old) belonging to the ATC class B and 6,370 (1829 youngest-old; 2,885 middle-old; 1,656 oldest-old) to the ATC class C. Although with different percentages within the individual elderly age groups, ATC class B was mostly represented by warfarin (39.7%), acetylsalicylic acid (24.4%), clopidogrel (5.4%), acenocumarol (4.5%), and dabigatran (3.0%). Similarly, in terms of reported frequencies for each elderly age group, ATC class C was mostly represented by furosemide (9.7%), ramipril (7.7%), bisoprolol (5.1%), digoxin (4.2%), and amiodarone (4.1%).

Table 4 reports ADEs associated with the most frequently reported suspected CV medication groups leading to ED visit. The total number of PT analyzed was 27,497, of which 18,251 (4,517 youngest-old; 8,710 middle-old; 5,024 oldest-old) belonging to the ATC class B and 9,246 (2,733 youngest-old; 4,151 middle-old; 2,362 oldest-old) to the ATC class C. Although with different percentages within the individual elderly age groups, ATC class B was mostly associated to epistaxis (17.0%), gastrointestinal bleedings (13.2%), alterations of the international normalized ratio (8.1%), central nervous system hemorrhages (6.1%), and genitourinary bleedings (5.7). Similarly, ATC class C was mostly associated to hypotension, syncope and pre-syncope (16.7%), electrolyte imbalance (13.2%), bradycardia (6.4%), asthenia and muscular weakness (5.2%), and dermatologic reactions (4.4%).

DISCUSSION

This active pharmacovigilance study was carried out to define the clinical and pharmacological characteristics of outpatients' ADEs associated with CV medications leading to ED visits in the elderly Italian population. To our knowledge, this is the first analysis of its kind conducted in several Italian EDs to calculate the risk of hospitalization related to CV medications in different elderly age groups compared to young adults.

From an in-depth literature search, numerous investigations have been reported on ADEs leading to ED visits and hospitalizations in European high-income countries (Lombardi et al., 2020b). A French survey (Queneau et al., 2007), performed over two periods of 1 week each, in EDs of five university hospitals and five general hospitals throughout France, reported that 21% of patients needed a clinical consultation

TABLE 4 | Adverse drug events among cardiovascular medications (ATC classes B and C) leading to emergency department visit.

Adverse drug event	Elderly overall	Youngest-old	Middle-old	Oldest-old
		65–74 years	75–84 years	>85 years
ATC class B, blood and blood forming organs	N = 18,251 (%)	N = 4,517 (%)	N = 8,710 (%)	N = 5,024 (%)
Haemorrhage	9,131 (50.0)	2,450 (54.2)	4,243 (48.7)	2,438 (48.5)
Epistaxis	3,108 (17.0)	905 (20.0)	1,436 (16.5)	767 (15.3)
Gastrointestinal	2,414 (13.2)	683 (15.1)	1,026 (11.8)	705 (14.0)
Central nervous system	1,106 (6.1)	202 (4.5)	605 (6.9)	299 (6.0)
Genitourinary	1,043 (5.7)	254 (5.6)	499 (5.7)	290 (5.8)
Dermatologic	743 (4.1)	186 (4.1)	335 (3.8)	222 (4.4)
Ophthalmic	330 (1.8)	102 (2.3)	148 (1.7)	80 (1.6)
Pulmonary	191 (1.0)	52 (1.1)	107 (1.2)	32 (0.6)
Not specified	196 (1.1)	66 (1.5)	87 (1.0)	43 (0.9)
Altered international normalized ratio	1,482 (8.1)	283 (6.3)	635 (7.3)	564 (11.2)
Anaemia	1,011 (5.5)	199 (4.4)	446 (5.1)	366 (7.3)
Unintentional or intentional overdose	342 (1.9)	79 (1.7)	138 (1.6)	125 (2.5)
ATC class C, cardiovascular system	N = 9,246 (%)	N = 2,733 (%)	N = 4,151 (%)	N = 2,362 (%)
Hypotension, syncope and pre-syncope	1,541 (16.7)	430 (15.7)	748 (18.0)	363 (15.4)
Electrolyte imbalance	1,219 (13.2)	265 (9.7)	561 (13.5)	393 (16.6)
Hyponatremia	529 (5.7)	109 (4.0)	248 (6.0)	172 (7.3)
Hyperkalaemia	365 (3.9)	66 (2.4)	163 (3.9)	136 (5.8)
Hypokalaemia	325 (3.5)	90 (3.3)	150 (3.6)	85 (3.6)
Bradycardia	590 (6.4)	144 (5.3)	276 (6.6)	170 (7.2)
Asthenia and muscular weakness	477 (5.2)	137 (5.0)	216 (5.2)	124 (5.2)
Dermatologic reaction	403 (4.4)	164 (6.0)	169 (4.1)	70 (3.0)
Erythema	201 (2.2)	67 (2.5)	91 (2.2)	43 (1.8)
Localized or general pruritus	106 (1.1)	45 (1.6)	47 (1.1)	14 (0.6)
Urticaria	96 (1.0)	52 (1.9)	31 (0.7)	13 (0.6)
Localized or peripheral edema	399 (4.3)	161 (5.9)	175 (4.2)	63 (2.7)
Dizziness	252 (2.7)	85 (3.1)	120 (2.9)	47 (2.0)

ATC, anatomical therapeutic chemical.

after experiencing an ADE. The authors included all patients aged ≥15 years, without performing age subgroup analyses. Noteworthy, their multivariate logistic regression analysis found that age and number of concomitant medications were significantly associated with the ADE. In particular, the most frequently incriminated drug classes included diuretics (11.7%), anticoagulants (9.3%) and other CV drugs (15.4%).

Another prospective study performed in France (four non-consecutive weeks in 2002–2003) aimed to assess the incidence of adverse drug reactions (ADRs) and to identify the factors associated to hospital admissions in the elderly population (Olivier et al., 2009). Authors compared the characteristics of patients admitted for a suspected ADR with those of patients admitted for other reasons. They found that the number of drugs being taken (OR 1.18, 95% CI [1.08, 1.29]) and the use of antithrombotic agents (2.26, [1.33, 3.88]) were the factors most frequently related to ADRs.

Rodenburg and colleagues conducted a nationwide study of all hospital admissions between 2000 and 2005 with data from the Dutch National Medical Register with the aim of studying the differences between men and women in hospital admissions for ADRs due to CV drugs (Rodenburg et al., 2012). Overall, 34% of all ADR-related admissions were attributed to CV drugs, with a prevalence of female sex (54%). Similarly, to our study, the authors found that anticoagulants and antiplatelets, particularly salicylates, diuretics, and cardiotonic glycosides were responsible for the majority of the ADR-related hospital admissions.

A small prospective cross-sectional diagnostic study (30-days follow-up) was performed in the ED of the University Hospital of Basel (Switzerland) to identify the frequency of drug-related problems (DRPs) among elderly patients presenting to the ED with non-specific complaints (NSC), and to evaluate responsible drug classes (Nickel et al., 2013). During the study period, 633 NSC patients were included. Their median age was 81 years (IQR 72–87), and authors reported a mean Charlson comorbidity index of 2.5 (IQR 1–4). DRPs were identified in 12.2% of cases. Polypharmacy and diuretics, in particular thiazides, were most frequently associated with DRPs.

In four large German hospitals, the percentage of suspected ADR cases among all adult patients presenting to the ED was determined during a 30 days period study (Schurig et al., 2018). The authors analyzed a total of 10,174 emergency room visits, 665 of which were potentially associated with a suspected ADR. The median age of the study population was 74.5 years, and 264 patients (75%) were 65 years old or older, and 55% were women. Patients with ADR were found to be taking a median of seven different drugs simultaneously and, similarly to our study, antithrombotic agents, beta-blockers, renin-angiotensin system inhibitors, and diuretics were the most commonly suspected cause of ADR.

Through a review of observational studies, Bouvy and colleagues underlined that the occurrence of ADEs within the

European hospital setting is still significant (Bouvy et al., 2015). However, the still low number of studies performed in outpatients, such as the investigations on ADEs leading to ED visits and hospitalisations, particularly those performed on a large sample, identify a scarcity of information on ADEs epidemiology in this setting.

In Italy, in a retrospective cohort study of data from an active pharmacovigilance project at 32 EDs in the Lombardy region collected between January 1, 2010 and December 31, 2011, Perrone and co-workers assessed the preventability, seriousness, and economic burden of ADRs as cause of ED admission (Perrone et al., 2014). During the study period, the authors analyzed 8,862 ADRs and found that B (blood and blood-forming organs) was one of the most frequently reported ATC class leading to ED admissions. Furthermore, older age and polypharmacy were associated with a higher risk of hospitalization. These findings have already been confirmed in our large nationwide multicentre study published in 2020 (Lombardi et al., 2020b).

Comparing our results with those obtained from the American and Asian high-income countries, it seems quite clear that important differences exist both in terms of study methods and study population. Nevertheless, most of the evidence published from these studies on the safety of CV medications in the elderly visiting the ED are quite comparable to those reported in our analysis, in particular in terms of suspected drug classes and other risk factors (i.e., high number of concomitant drugs and/or concomitant conditions).

A cross sectional study, aimed to address the association between inappropriate prescribing in elderly Medicare/Medicaid dual enrolees and injury-related ED visit (Blackwell et al., 2009), found that CV agents had the lowest proportion of ED-related fills for injuries compared to the other drug categories. However, among CV agents, clonidine and doxazosin had higher associations with injury than nifedipine. Additionally, based on cost, doxazosin was associated with the most expensive injury-related ED visits in the category of CV medications.

Between 2004–2005, a nationally representative, public health surveillance of ADEs and a cross-sectional survey of outpatient medical visits were performed to estimate the number of and risk for ED visits for ADEs involving Beers criteria medications compared with other medications (Budnitz et al., 2007). Among elderly U.S. patients, an estimated 177,504 ED visits for ADEs occurred both years. An estimated 3.6% of these visits were caused by adverse events related to medications considered to be always potentially inappropriate, according to the Beers criteria, and 33.3% of visits were for adverse events from three other medications, including warfarin (17.3%) and digoxin (3.2%). The authors also concluded that performance measurements and interventions targeting warfarin and digoxin use could prevent multiple ED visits for ADE.

Budnitz and colleagues performed another nationally representative study, using the adverse-event data from the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project to estimate the frequency and rates of hospitalization after ED visits for ADEs in older Americans and to assess the contribution of specific medications (Budnitz et al., 2011). On the basis of 5,077 cases identified in their sample, there were an estimated 99,628 emergency hospitalizations for ADEs each year from 2007 through 2009. Nearly half of these hospitalizations were among middle-old and oldest-old patients (48.1%). Medications or medication classes most frequently implicated alone or in combination in 67.0% of hospitalizations were warfarin (33.3%) and oral antiplatelet agents (13.3%). Budnitz reported that the majority of emergency hospitalizations for recognized ADEs in older Americans resulted from a few commonly used medications, concluding that better management of antithrombotic therapies could have the potential to reduce ADE-related hospitalizations in the elderly.

In a relevant publication, Budnitz and colleagues also described the characteristics of ED visits for ADEs in the United States in 2013–2014, performing an active, nationally representative, public health surveillance in 58 EDs participating in the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project (Shehab et al., 2016). Based on data from 42,585 cases, an estimated 34.5% of ED visits for ADEs occurred among adults aged 65 years or older in 2013–2014 compared with an estimated 25.6% in 2005–2006. Of note, older adults experienced the highest hospitalization rates (43.6%). Anticoagulants, with other two medication classes, were implicated in an estimated 46.9% of ED visits, which included clinically significant ADEs, such as haemorrhages. The authors reported that, since 2005–2006, the proportion of ED visits for ADEs from anticoagulants increased. Among older adults, three drug classes, including anticoagulants, were implicated in an estimated 59.9% of ED visits for ADEs. Furthermore, four anticoagulants (warfarin, rivaroxaban, dabigatran, and enoxaparin) were the most common drugs implicated in the ADEs.

A one-year retrospective chart review was conducted to determine the prevalence and severity of ADEs in patients presenting at EDs in two university-hospitals in the Canadian province of Newfoundland and Labrador (Sikdar et al., 2010). Of the 1,458 patients presenting to the EDs, 55 were determined to have an ADE. After a sample-weight adjustment, the prevalence of ADEs was found to be 2.4%. Prevalence increased with age (7.8%, ≥65 years) and the mean age for patients with ADEs was higher than for those with no ADEs ($p < 0.01$). A higher number of comorbidities and medications was associated with drug-related visits. CV agents (37.4%) were among the most common drug class associated with ADEs.

A cross-sectional study was performed in Canada to identify medications with a higher risk of ADEs among subjects aged ≥65 years, using public administrative data (Bayoumi et al., 2014). During the study period (2006–2008), among elderly patients in Ontario EDs, the NACRS (National Ambulatory Care Reporting System) identified more than 23,000 ADEs, which represented 0.8% of the sample (21.5% of them were hospitalised). Anticoagulants were among the drugs most frequently implicated in the ADEs of ED visits (14.2%).

In Asia, a prospective observational cohort study of patients aged 18 years and older presenting to the ED of an urban, tertiary medical center in Taiwan (Chen et al., 2012), was conducted to

determine the incidence, risk and patient outcomes of ADE in an ED population. Of 58,569 ED visits, 452 patients (0.77%) had physician-documented ADE. CV agents accounted for the most ADE (25.8%) and consisted of 65.3% of ADE in patients aged 65 years and older. Elderly age resulted to be the main risk factor for ADE-related hospitalization (OR 1.9, 95% CI [1.1–3.4]).

Cheng and collaborators performed another prospective case-control study on elderly patients presenting to the ED in Taiwan (Chen et al., 2014). Out of 20,628 visits, physician documented a total of 295 ADEs in older adults. The number of administered drugs was identified as an independent risk factor for ADEs (OR 4.1, 95% CI [2.4–6.9] for 3–7 drugs; OR 6.4, 95% CI [3.7–11.0] for eight or more drugs). Moreover, diuretics, CV agents, and anticoagulants were the medications most commonly related to ADEs occurrence. In addition, a subsequent investigation revealed that the majority of older patients were males, reporting fatigue or altered mental status, with cardiovascular, renal, and respiratory complications, with a higher Charlson comorbidity index scores, and with a higher number of concomitant medications. Chen and colleagues reported that, among elderly, antithrombotic and CV agents were the drug groups most commonly associated ADEs (Chen et al., 2015).

In 2017, Oscanoa and co-workers performed a systematic review and meta-analysis of ADR-induced hospital admissions focusing on the elderly population (Oscanoa et al., 2017). They searched the literature from 1988 to 2015, identifying a total of 42 included articles, of which only 12 were conducted in the ED setting and none were focused on CV medications. Of note, the authors found that among the classes most frequently related to hospital admissions in the elderly were beta-blockers (1.8–66.7%), oral anticoagulants (3.3–55.6%), digoxin (1.6–18.8%), angiotensin-converting enzyme (ACE) inhibitors (5.5–23.4%), and calcium entry blockers (1.0–8.3%). Interestingly, as we observed in our sample, the majority of symptoms resulting in hospital admissions were: 1) hypotension, caused by beta-blockers, ACE inhibitors or calcium antagonists, 2) bleeding, due to oral anticoagulants utilization, or 3) bradycardia associated to the use of digoxin.

Considering the above comparison between our data and those published in other high-income countries, the relevant differences in standard of care and ED visit management policy need to be taken into account. In particular, differences in health care and ED payment system, ED crowding, and practices or plans to mitigate ED crowding must be considered (Pines et al., 2011). It has already been demonstrated that many patients living in high-income countries with good primary care and health insurance coverage, independently from the characteristics of each health care system, choose the ED over primary care, even for non-life-threatening conditions (Pines et al., 2011). Italy, such as many other high-income countries (i.e., Canada, Denmark, Finland, France, Saudi Arabia, Spain, Sweden, United Kingdom), presents a universal publicly funded health care system which is trying to prevent ED visits, and related crowding, for chronic conditions and adverse events associated to their pharmacological treatments.

Recently, a model for better understanding ADE-related ED visits was settled by Jatau and colleagues (Jatau et al., 2019). Authors identified a lack in knowledge and clinical practice, as well as targeted interventions to improve strategies for the prevention of ADEs. Their study underlined the need for a "proactive" role of healthcare professionals, in particular of clinical pharmacist expert in pharmacovigilance, to guarantee an optimal use of medications and to reduce the burden of ADEs as cause of ED visits. We believe that the active pharmacovigilance approach proposed in our study represents a first step toward Jatau's suggestions, especially for elderly patients exposed to CV medications.

In summary, based on the evidence described in the present analysis and available in the scientific literature, Italian doctors should be aware that, among elderly outpatients exposed to CV medications, middle-old (75–84 years) and oldest-old (≥85 years) subjects, women, Caucasians, and subjects exposed to polypharmacy and suffering from one or more comorbidities represent the subgroups at higher risk of hospitalization. Considering the suspected drugs among CV medications, antiarrhythmics, beta-blocking agents, renin-angiotensin system inhibitors, antiplatelets, and anticoagulants are the classes most frequently involved in the ADE and associated to ED visits and hospitalization. Taking into consideration all these characteristics could be useful for general practitioners and specialists working in EDs to avoid and oversee CV medications-related ADEs in clinical practice involving the elderly.

Strengths and Limitations

Like any retrospective analysis, this study also has some limitations. First, it contains only ADEs recognized and managed in ED. Second, since not all elderly patients experiencing an ADE, even if serious, go to the ED or spontaneously report the adverse event, an underestimation of ADEs could not be completely ruled out. This issue, is particularly relevant when we consider out-of-hospital mortality (i.e., home, nursing residence, etc.), especially sudden death which in the elderly can also be related to CV medications. Second, a selection bias of more clinically relevant cases (i.e., patients who referred to the ED after a contact with their general practitioner) could not be completely excluded. However, since we considered all serious and non-serious ADEs leading to the ED, the impact of this bias could be considered of relatively low relevance. Third, ADE reports may also be affected by inherent limitations, such as the quality of reported clinical data, which can sometimes be inaccurate or incomplete. Therefore, the absence of such data in the ADE reports may have impacted their clinical evaluation. For example, the lack of information regarding the level of consciousness (i.e., mental status) and eyesight, especially in the elderly where the risk of medication errors is higher as compared to younger population (i.e., medication with a narrow therapeutic window), could partially explain the risk of hospitalization observed in our sample. Moreover, since elderly patients suffering from CV diseases are certainly over represented in our sample, this evidence may not represent the entire elderly

Italian population. However, in order to reduce this issue, comorbidities collected throughout the pharmacovigilance report forms were considered as covariates for adjustment in the multivariate logistic regression. Finally, we observed that the total number of participating centers was reached starting from 2011 (active monitoring at full capacity) (**Supplementary Figures S1, S2**). For this reason, during the first 4 years period, considering that we included only elderly patients treated with CV medications, we identified a small number of ADE reports. On the contrary, in the second (n = 8,762) and third (n = 8,124) 4 years period, the high number of ADE reports showed more homogeneous and representative results in terms of ED visits and risk of hospitalization. Nevertheless, since we aimed to perform an overall analysis of the data collected in ED throughout the active pharmacovigilance monitoring during the entire study period, we did not exclude, even if few, the data collected between 2007–2010.

Despite these limitations, this is the first analysis of its kind conducted in several Italian EDs and for a long period of time. The use of electronic ED medical records with high quality information on elderly population allowed us to adjust our analysis for important confounding variables, such as patients' demographic characteristics, polytherapy, and comorbidities. In addition, the data we analyzed come from a large number of Italian EDs equally distributed throughout the five regions involved, which makes these evidences characteristic of and comparable to the whole elderly Italian population visiting the ED due to an ADE.

CONCLUSION

Our real-world findings underline relevant safety aspects of CV medications in the elderly Italian population. ED clinicians must always consider the higher risk of hospitalization related to the use of CV drugs in elderly, particularly in oldest-old ones, for antiarrhythmics, beta-blocking agents, renin-angiotensin system inhibitors, antiplatelets, and anticoagulants.

Furthermore, our study confirms that the risk of hospitalization is significantly higher for all elderly age groups compared to young adults as the number of suspected and concomitant drugs, and the number of concomitant conditions increases.

Referring to the elderly, further analysis should be performed to evaluate the possible association between therapeutics guidelines changing over time and frequency/characteristics of ED visits and/or hospitalization due to ADEs.

In conclusion, we believe that in the elderly population there is still a need to increase the availability of evidence concerning potential ADEs due to inappropriate self-medication and ADEs due to drug-drug interactions and polytherapy. In our opinion, increasing the awareness of the risk of CV medications related ADEs is particularly important, especially for the general practitioner, who is frequently the first prescriber. In clinical practice, further active pharmacovigilance studies are needed to evaluate all safety aspects of drug use in the elderly.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

Study design was contributed by GC, AB, AV and NL, with assistance from the rest of the authors. AB took the lead in data analysis, assisted by RB, GC and NL. Data interpretation was performed by GC, AV and NL, with assistance from the other authors. The manuscript was written primarily by GC and NL, with assistance from the other authors, and revised by SP, GS, MT, MR, AC, MV, GV and GM. All authors approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2020.611102/full#supplementary-material.

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UGT1A1 rs4148323 A Allele is Associated With Increased 2-Hydroxy Atorvastatin Formation and Higher Death Risk in Chinese Patients With Coronary Artery Disease

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It is widely accepted that genetic polymorphisms impact atorvastatin (ATV) metabolism, clinical efficacy, and adverse events. The objectives of this study were to identify novel genetic variants influencing ATV metabolism and outcomes in Chinese patients with coronary artery disease (CAD). A total of 1079 CAD patients were enrolled and followed for 5 years. DNA from the blood and human liver tissue samples were genotyped using either Global Screening Array-24 v1.0 BeadChip or HumanOmniZhongHua-8 BeadChip. Concentrations of ATV and its metabolites in plasma and liver samples were determined using a verified ultra-performance liquid chromatography mass spectrometry (UPLC-MS/MS) method. The patients carrying A allele for the rs4148323 polymorphism (*UGT1A1*) showed an increase in 2-hydroxy ATV/ATV ratio (p = 1.69E–07, false discovery rate [FDR] = 8.66E–03) relative to the value in individuals without the variant allele. The result was further validated by an independent cohort comprising an additional 222 CAD patients (p = 1.08E–07). Moreover, the rs4148323 A allele was associated with an increased risk of death (hazard ratio [HR] 1.774; 95% confidence interval [CI], 1.031–3.052; p = 0.0198). In conclusion, our results suggested that the *UGT1A1* rs4148323 A allele was associated with increased 2-hydroxy ATV formation and was a significant death risk factor in Chinese patients with CAD.

Keywords: atorvastatin, coronary artery disease, *UGT1A16, polymorphisms, ADME genes, clinical outcomes**

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INTRODUCTION

Atorvastatin (ATV), which reduces low-density lipoprotein cholesterol (LDL-C) by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, is among the most widely prescribed drugs for treating and preventing atherosclerotic disease events (Rosenson, 2006). The beneficial effects of ATV therapy in reducing the risk of cardiovascular morbidity and mortality have been well documented (Sever et al., 2003; Arca, 2007; Sillesen et al., 2008).

ATV is orally administered in the active acid form and is extensively metabolized by cytochrome P450 (CYP) 3A4 to form two major active metabolites, 2-hydroxy (2-OH) ATV and 4-hydroxy (4-OH) ATV (Park et al., 2008). Both metabolites are pharmacologically equivalent to parent ATV and significantly contribute to the circulating inhibitory activity for HMG-CoA reductase (Lennernas 2003). Glucuronidation, mediated via the enzymes UDP-glucuronosyltransferase (UGT) 1A1 and 1A3 (UGT1A1/3) in the liver, is the critical step in facilitating the conversion of the acid forms of ATV to the corresponding lactones (Prueksaritanont et al., 2002; Schirris et al., 2015). Thus, variations in the activities of drug metabolizing enzymes may result in lower or greater exposure to ATV.

Pharmacogenetic studies have shown that single-nucleotide polymorphisms (SNP) in genes related to absorption, distribution, metabolism and excretion (ADME) of drugs contribute to interindividual variability in drug efficacy and adverse effects (Lauschke et al., 2017; Guan et al., 2019). Failure to recognize these variants could lead to high systemic drug concentrations, which may increase rates of adverse events (Roden et al., 2019).

In this study, we focused particularly on the genes involved in ADME to identify novel genetic polymorphisms affecting plasma ATV and its metabolites concentrations and clinical outcomes of patients with coronary artery disease (CAD). Subsequently, we aimed to identify specific SNP associated with ATV metabolism in human liver microsomes (HLM).

METHODS

Ethics Statement

This study was approved by the Medical Ethical Review Committee of Guangdong Provincial People's Hospital (Approval number GDREC2010137H) and Sun Yat-sen Memorial Hospital (Approval number CS07095) (Guangzhou, China), and conducted in accordance with the basic principles of the Declaration of Helsinki. All patients provided written informed consent.

Study Population

A schematic diagram of this study was exposited in **Figure 1**. A total of 1079 CAD patients were categorized into two cohorts to discover and validate the effects of genetic variants on ATV metabolism and the risk of all-cause death. Thereafter, 55 HLM were enrolled to verify the effect of enzyme activity of *UGT1A1* on ATV metabolism and the correlation between *UGT1A1**6* and the formation rate of 2-OH ATV. All patients were sequentially enrolled in Guangdong Provincial People's Hospital between January 2010 and December 2013 according to the inclusion and exclusion criteria. Patients were followed up for all-cause death up to 5 years. CAD was defined as the presence of ≥50% stenosis in at least one major coronary artery based on coronary angiography. The inclusion criteria were patients with CAD aged 18–80 years who underwent percutaneous coronary intervention (PCI) and received ATV therapy. Exclusion criteria included renal impairment (serum creatinine >3 times the upper limit of normal (ULN), renal transplantation or dialysis); liver impairment (serum transaminase >3 times the ULN, or a diagnosis of cirrhosis); pregnancy or lactation; malignant disease; uncontrolled infection; worsening of any chronic disease; use of lipid-lowering drugs other than ATV.

All patients received ATV for at least seven consecutive days at a dose of 10–40 mg/day before blood samples were collected. The dose of ATV was chosen based on the discretion of the physician. Steady-state ATV concentrations could be reached after approximately 3 days (Cilla et al., 1996). Baseline medical information was collected from the hospital medical records, including demographics, medical history, biochemical measurements, and comedications. Drug compliance was monitored by contacting with the patients at hospitalization or hospital visit. Patients were contacted every 6 months via telephone for surveillance of all-cause death. Individuals who could not be contacted despite several attempts were considered as lost to follow-up.

Blood Sampling

Fasting venous blood (4 ml) was drawn into ethylenediaminetetraacetic acid (EDTA)-containing tubes 10–12 h after the last ATV dose. Samples were centrifuged 1900 *g* for 10 min at 4°C; plasma was collected and stored at −80°C until analysis.

HLM Preparation

The tumor resection margin of patients with liver cancer or the liver tissues of patients with benign liver diseases undergoing hepatectomy were collected at Sun Yat-Sen Memorial Hospital (Guangzhou, China) from September 2012 to May 2015 ($n = 55$). Specimens for microsome extraction were quickly prepared using the GENMED A Solution (GENMED Scientific Inc., Arlington, TX, United States) and stored in liquid nitrogen until use. HLM were prepared according to our previously published protocol (Liu et al., 2016). Protein concentration was determined by the Bradford protein assay kit (Bio-Rad, Hercules, CA, United States) with bovine serum albumin as standard.

Genotyping

Genomic DNA was extracted from blood samples using the TIANamp Genomic DNA Kit (Cat. no. DP304; TIANGEN Biotech, Beijing, China) per manufacturer's instructions. DNA quality and quantity were assessed using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, United States) and agarose gel electrophoresis, respectively.

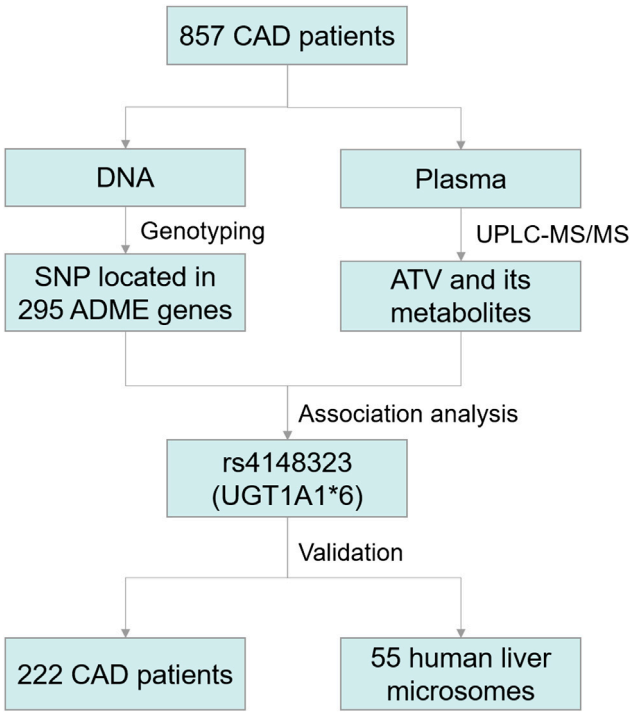

FIGURE 1 | Schematic diagram of the Trial Protocol. CAD, coronary artery disease; ATV, atorvastatin; UGT1A1, UDP-glucuronosyltransferase 1A1; SNP, single-nucleotide polymorphisms; ADME, absorption, distribution, metabolism, and excretion.

In the discovery cohort, genotyping was performed for 857 DNA samples from patients with CAD on the Global Screening Array-24 v1.0 (GSA) BeadChip (Illumina Inc., San Diego, CA, United States) comprising 700,078 SNP. Genotyping procedures followed the Infinium HTS Assay protocol, and intensity data were normalized using Illumina's GenomeStudio software and calling algorithm. In the validation cohort comprising the other 222 patients with CAD, genotyping of *UGT1A1* c.211G > A (rs4148323) was performed by TaqMan assay (Applied Biosystems, California, United States). DNA from the human liver samples (n = 55) were genotyped using the HumanOmniZhongHua-8 BeadChip (Illumina Inc., San Diego, CA, United States) comprising 900,015 SNP.

A standard quality control procedure was applied to the raw genotyping data to filter both unqualified SNP and samples prior to association analysis. Samples with call rates <95% were removed. SNP were excluded if they 1) did not map on autosomal chromosomes; 2) had a call rate <95%; 3) had a minor allele frequency (MAF) < 5%; and 4) were deviated from Hardy–Weinberg equilibrium (p-value < 1.0E−06). After quality control, 291194 SNP in the GSA BeadChip and 695778 SNP in the HumanOmniZhongHua-8 BeadChip were retained for analysis.

Determination of ATV and Its Metabolites Concentrations

Concentrations of ATV and its acid (2-OH ATV and 4-OH ATV) and lactone metabolites (ATV lactone [ATV L], 2-OH ATV L and 4-OH ATV L) in plasma were measured by ultra-performance liquid chromatography mass spectrometry (UPLC-MS/MS). Our previous report has established the accuracy and reproducibility of this method (Cai et al., 2017).

Activity Determination of UGT1A1

The UGT1A1 activity in HLM was determined using the known substrate SN-38. The procedure was carried out based on our previously validated approach (Zhong et al., 2017).

ATV Metabolism in HLM

A typical phase I and II enzymes mixing incubation system contains potassium phosphate buffer (50 mM, pH = 7.4), phase I Solution A and B, HLM (final concentration 0.35 mg/ml), ATV (final concentration 1.5 μg/ml), phase II Solution A and B in a total volume of 400 μL. Incubations were carried out for 60 min at 37°C in a shaking water bath. After the incubation, 60 μL ice-cold acetonitrile containing internal standard carbamazepine (100 ng/ml) were added to terminate the enzyme activity. All experiments were performed in triplicate. The samples were centrifuged at 15,000 *g* for 30 min at 4°C, and then ATV and its major metabolites in supernatant was analyzed by UPLC-MS/MS method as previously described (Cai et al., 2017).

Statistical Analyses

Demographic and clinical characteristics were described as follows: continuous variables are presented as mean ± standard deviation (SD) and categorical variables are presented as counts (percentages). Normality was evaluated by the Shapiro–Wilk test. Natural-log transformation was performed prior to statistical analysis since the raw ATV analyte concentrations did not follow a normal distribution. Univariate linear regression analysis was used to assess the relationships between the baseline characteristics and plasma ATV concentration, and the significant characteristics (p-value < 0.05) were included into multivariate linear regression analysis.

In the discovery stage, SNP located in 295 candidate ADME genes from the PharmaADME website (http://www.pharmaadme.org/) were employed to association analysis. Chi-square test was used to estimate the Hardy-Weinberg equilibrium. Linear regression analysis under the additive mode was used to identify the associations between the candidate SNP and the concentrations of ATV, five metabolites (2-OH ATV, 4-OH ATV, ATV L, 2-OH ATV L and 4-OH ATV L) and five concentration ratios (2-OH ATV/ATV, 4-OH ATV/ATV, ATV L/ATV, 2-OH ATV L/ATV, 4-OH ATV L/ATV). In addition to sex, age and ATV dose, aspartate aminotransferase (AST) and creatinine (CREA) levels were also included for adjustment since they were significantly associated with plasma ATV concentration (**Table 1**). The linkage disequilibrium (LD) analyses were conducted to identify independent SNP between SNP pairs located in same chromosome and the r^2 of two SNP exceeding 0.5 was considered in LD. The false discovery rate (FDR) was used to correct the number of SNP and association analyses for multiple hypothesis testing. The significant correlation (*FDR* < 0.05)

TABLE 1 | 1,079 patient characteristics and their effects on plasma concentration of ATV.

Characteristics		Value *N* (%) or mean ± SD	Plasma ATV concentration, ng/mL			
			Univariable analysis		Multivariable analysis	
			Estimate	*p*-value	Estimate	*p*-value
Demographic data						
Total number		1,079				
Age (years)		62.95 ± 10.07	0.010	1.02E–02		
Sex	Female	218 (20.20)	0.029	7.63E–01		
	Male	861 (79.80)				
Dosage (mg)	10	19 (1.76)	0.017	2.13E–03	0.014	2.69E–02
	20	924 (85.63)				
	40	136 (12.60)				
Medical history						
Arrhythmia	No	984 (91.38)	–0.158	2.43E–01		
	Yes	93 (8.62)				
Diabetes	No	779 (72.33)	–0.014	8.70E–01		
	Yes	298 (27.67)				
Heart failure	No	986 (91.55)	–0.182	1.82E–01		
	Yes	91 (8.45)				
Hypertension	No	432 (40.07)	0.044	5.73E–01		
	Yes	646 (59.93)				
Hyperlipidemia	No	956 (88.68)	0.054	6.51E–01		
	Yes	122 (11.32)				
Biochemical measurements						
ALT, U/L		27.50 ± 13.37	0.010	1.13E–03		
AST, U/L		26.77 ± 11.29	0.020	6.44E–09	0.021	1.80E–04
CREA, umol/L		86.37 ± 24.87	0.006	2.99E–04	0.004	3.47E–04
eGFR, ml/min/1.73m^2		94.24 ± 72.49	–0.001	8.50E–02		
CK, U/L		111.95 ± 110.51	0.000	4.07E–01		
CKMB, U/L		7.55 ± 6.03	0.001	9.20E–01		
CHOL, mmol/L		4.29 ± 1.13	0.093	6.44E–03		
LDL-C, mmol/L		2.59 ± 0.93	0.133	1.26E–03		
HDL-C, mmol/L		0.96 ± 0.26	–0.314	3.67E–02		
TRIG, mmol/L		1.61 ± 1.11	0.042	2.23E–01		
GLUC, mmol/L		6.73 ± 2.74	0.015	2.90E–01		
Lpa, mmol/L		303.24 ± 324.14	0.000	1.89E–01		
Apo (a), g/L		1.04 ± 0.27	–0.451	3.34E–03		
Medication						
β-blockers	No	114 (10.58)	0.023	8.52E–01		
	Yes	963 (89.42)				
ACEIs	No	390 (36.21)	–0.081	3.07E–01		
	Yes	687 (63.79)				
CCBs	No	775 (71.96)	0.096	2.56E–01		
	Yes	302 (28.04)				
PPI	No	552 (51.25)	0.085	2.65E–01		
	Yes	525 (48.75)				

Estimates were calculated by applying a linear regression model. Variables with $p < 0.05$ *were included into the multivariable analysis. SD = standard deviation; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; eGFR = estimated glomerular filtration rate; CKMB = creatine kinase MB; CHOL = cholesterol; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; TRIG = triglyceride; GLUC = glucose; Lpa = lipoprotein (a); Apo (a) = apolipoprotein (a); ACEIs = angiotensin converting enzyme inhibitors; CCBs = calcium channel blockers; PPIs = proton pump inhibitors.*

between SNP and metabolite concentration ratio was repeatedly investigated in the validation cohort. For SNP pairs in LD, only the SNP with the most significant *p* value was selected.

Spearman correlation analysis was used to study the correlation between the UGT1A1 enzyme activity and the reduction of ATV as well as the formation rate of its five metabolites. To examine relations between the candidate SNP and the reduction of ATV as well as the formation of metabolites from ATV in 55 HLM, the independent sample *t* test or one-way ANOVA test was used for data conforming to normal distribution, whereas the nonparametric Mann–Whitney *U* or Kruskal–Wallis *H* test was used for data conforming to skewed distribution. Cox regression analysis was utilized to assess the association of SNP with all-cause death with results presented as hazard ratio (HR) and 95% confidence interval (CI). Cumulative event rates were estimated with the Kaplan–Meier method. A two-sided *p*-value < 0.05 was considered statistically significant.

All statistical analyses were carried out using PLINK (version 1.07, http://zzz.bwh.harvard.edu/plink/), R (version 3.4.3, https://www.r-project.org/) and GraphPad Prism 8 (GraphPad Software, San Diego, CA, United States).

TABLE 2 | Ten SNPs significantly associated with the concentration ratio of 2-OH ATV to ATV in 857 patients with CAD.

SNP	CHR	BP	Change	Gene symble	Ref	Alt	2-OH ATV/ATV		
							Beta	*P*	FDR
rs4148323	2	234669144	Exonic	UGT1A1	G	A	0.184	1.69E−07	8.66E−03
rs15524	7	99245914	UTR3	CYP3A5	A	G	0.129	8.52E−07	1.09E−02
rs10242455	7	99240179	Intergenic	ZSCAN25, CYP3A5	A	G	0.129	8.52E−07	1.09E−02
rs4646457	7	99245080	Downstream	CYP3A5	A	C	0.129	8.52E−07	1.09E−02
rs2687136	7	99325882	Intronic	CYP3A7, CYP3A7-CYP3A51P	C	T	0.125	2.23E−06	1.63E−02
rs2687134	7	99331042	Intronic	CYP3A7, CYP3A7-CYP3A51P	T	G	0.124	2.29E−06	1.63E−02
rs4646450	7	99266318	Intronic	CYP3A5	G	A	0.124	2.60E−06	1.63E−02
rs776746	7	99270539	Splicing	CYP3A5	C	T	0.124	2.86E−06	1.63E−02
rs4646458	7	99245013	Downstream	CYP3A5	T	G	0.124	5.27E−06	2.70E−02
rs3806598	2	234579892	Intronic	UGT1A10, UGT1A8	A	C	0.151	7.2E−06	3.35E−02

Ref reference allele, Alt alternate allele, UTR untranslated region, SNP, single-nucleotide polymorphisms; ATV, atorvastatin; 2-OH ATV, 2-hydroxy atorvastatin; CHR, chromosome; BP, base position; FDR, false discovery rate.

The p-values were calculated based on the linear regression analysis under the additive mode. The FDR were calculated on the basis of Benjaminiand Hochberg method. The SNPs are annotated to the nearest gene if identified in this study (marked by asterisk symbol) or to previously known gene if in linkage disequilibrium with the known loci for any lipid measure. Chromosomal positions are based on hg19 reference sequence.

RESULTS

Patient Characteristics and Their Effects on Plasma ATV Concentrations

Patients' demographic and clinical characteristics and their impact on the plasma ATV concentrations are presented in **Table 1**. In total, 1,079 Chinese patients with CAD who had received ATV therapy were sequentially recruited in the study and followed for 5 years. Univariate linear regression analysis indicated that patients with older age, higher ATV dose, higher levels of alanine aminotransferase (ALT), AST, CREA, CHOL and LDL-C tended to have a higher plasma ATV concentration, while patients with higher levels of high-density lipoprotein cholesterol (HDL-C) and apolipoprotein (a) [Apo (a)] tended to have a lower plasma ATV concentration. In the multivariate model, only ATV dose, AST and CREA levels remained independent predictors of plasma ATV concentrations (p = 2.69E−02, 1.80E−04 and 3.47E−04, respectively) in CAD patients (**Table 1**).

rs4148323 was Associated With Higher Concentration Ratio of 2-OH ATV to ATV

Ten SNP were found to have a significant effect on the concentration ratio of 2-ATV to ATV (*FDR* < 0.05, **Table 2**). Among these SNP, an exonic variant of rs4148323 in *UGT1A1* was most strongly associated with an increase in the 2-OH ATV/ATV ratio. Five SNP (rs15524, rs4646457, rs4646450, rs776746 and rs4646458) in *CYP3A5* also showed significant positive correlations with the formation of 2-OH ATV. Furthermore, an intergenic variant (rs10242455 between *ZSCAN25* and *CYP3A5*) and three intronic variants (rs2687136 and rs2687134 in *CYP3A7*; rs3806598 in *UGT1A10*) were also significantly associated with 2-OH ATV/ATV ratio (**Table 2**). Further analysis indicated that rs4148323 was in strong LD with rs3806598, and rs15524 was in strong LD with the remaining seven loci located in chromosome 7 (r^2 > 0.5). Finally, rs4148323 was further verified to be significantly correlated with 2-OH ATV/ATV ratio in an independent cohort comprising an additional 222 CAD patients (p = 1.08E−07, **Figure 2A**).

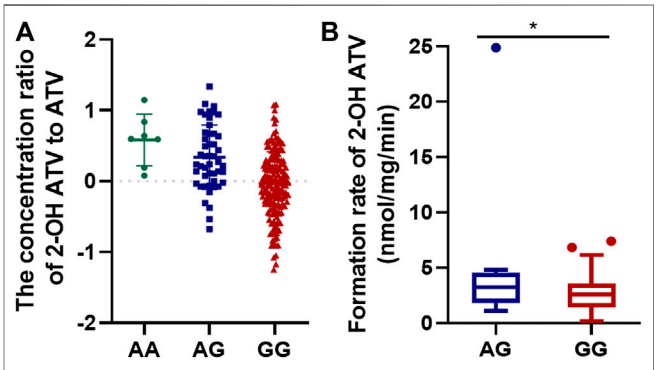

FIGURE 2 | The effect of genotype of rs4148323 on the formation of 2-OH ATV in the 222 patients with CAD **(A)** and 55 HLM **(B)**. ATV, atorvastatin; CAD, coronary artery disease; HLM, human liver microsomes.

Influence of the Genotype of rs4148323 on the Formation Rate of 2-OH ATV in HLM

To verify the effect of rs4148323 on the rates of formation of 2-OH ATV from ATV, the association between genotypes and 2-OH ATV formation rate was investigated in 55 HLM. The results showed that SNP rs4148323 in *UGT1A1* was associated with changes in 2-OH ATV levels (5.30 ± 7.44 and 2.71 ± 1.68 nmol/mg/min for AG and GG, respectively; p = 0.026, **Figure 2B**).

The Correlation Between UGT1A1 Activity and the Metabolism of ATV in HLM

Correlation between UGT1A1 activity and rates of microsomal metabolism of ATV and its metabolites are detailed in **Figure 3**. Higher UGT1A1 activity was associated with a markedly increased formation rates of 2-OH ATV, 4-OH ATV, 2-OH ATV L and 4-OH ATV L (r = 0.4208, p = 0.0026; r = 0.4285, p = 0.0021; r = 0.3476, p = 0.0144; r = 0.3512, p = 0.0133). In

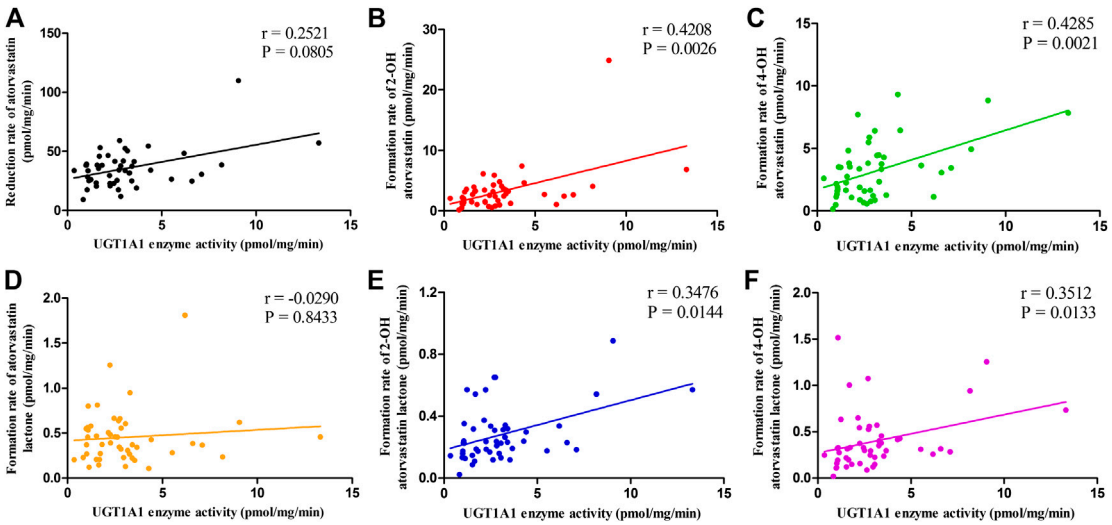

FIGURE 3 | The correlations between UGT1A1 activity and the rates of microsomal metabolism of ATV **(A)**, 2-OH ATV **(B)**, 4-OH ATV **(C)**, ATV L **(D)**, 2-OH ATV L **(E)** and 4-OH ATV L **(F)**. UGT1A1, UDP-glucuronosyltransferase 1A1; ATV, atorvastatin; ATV L, atorvastatin lactone.

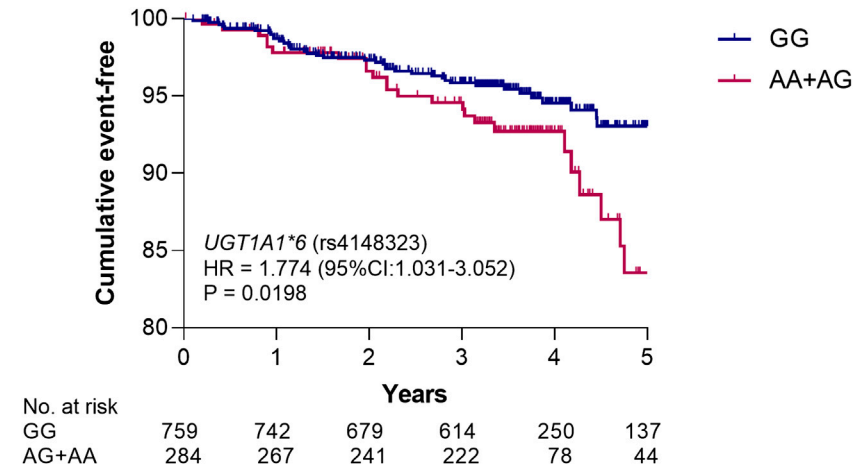

FIGURE 4 | Kaplan–Meier analysis of rs4148323 for all-cause death risk. The *p* value was calculated by log-rank test. UGT1A1, UDP-glucuronosyltransferase 1A1; HR, hazard ratio; 95% CI, 95% confidence interval.

contrast, the activity of UGT1A1 was not correlated with the reduction rate of ATV and the formation rate of ATV L (p = 0.0805 and 0.8433, respectively) (**Figure 3**).

Impact of Genetic Polymorphisms on the Clinical Endpoint

In order to illustrate the genotype of rs4148323 whether has an effect on the poor prognosis of patients with CAD, we merged the discovery and validation cohorts to assess the association between genotypes and death risk. Due to the small number of patients with the AA genotype of rs4148323 (n = 16), the AG and AA individuals were grouped together into the AG + AA genotype group (the A allele carriers), for analysis. Kaplan-Meier survival analysis showed that the carriers of rs4148323 A allele have a higher risk of death than non-carriers (HR 1.774, 95% CI, 1.031–3.052; p = 0.0198) (**Figure 4**).

DISCUSSION

Our result showed that a variant of rs4148323, located in an *UGT1A1* exon, increased the plasma ATV's active metabolite 2-OH ATV formation. This finding was further validated by an independent cohort comprising an additional 222 CAD patients and by the human liver microsome systems. Furthermore, the

UGT1A1 rs4148323 A allele has a significantly higher risk of death in Chinese patients with CAD. Consequently, genotyping of rs4148323 might be useful for tailoring both the ATV dose and safety monitoring of CAD patients.

Despite tremendous progress due to lifestyle interventions and drug treatments, CAD remains one of the most significant cause of death worldwide (Georgia Karanasiou et al., 2018). ATV is a life-saving drug which leads to reduce cardiovascular events in patients with cardiovascular disease, providing substantial public health benefits (Crouch 2001). ATV exists in both the acid and lactone forms *in vivo*. The acid form is pharmacologically active, whereas the lactone form is inactive toward HMG-CoA reductase and has been associated with muscle-related adverse effects (Hermann et al., 2006; Skottheim et al., 2008). ATV-induced liver injury can be caused during ATV therapy. The higher hepatocellular concentration of ATV was found to increase the risk of hepatotoxicity since ATV induced cytotoxicity in HepaRG cells in a concentration-dependent manner (Fukunaga et al., 2016). We have previously shown that high plasma exposure of statins was associated with an increased risk of contrast-induced acute kidney injury in patients with CAD; therefore, statins should be used with caution in these patients (Cai et al., 2018). We also found that a higher plasma exposure of ATV and metabolites was linked to increased risk of death in CAD patients (Zhou et al., 2020).

Interindividual differences in efficacy of ATV may be caused not only by nongenetic factors, but also by genetic polymorphisms in drug metabolizing enzymes and transporters involved in ATV metabolism and elimination (Kivisto et al., 2004; Cho et al., 2012; Wei and Zhang 2015; Peng et al., 2018). UGT1A1 is an important member of the UGT1A family responsible for the conjugation and detoxification of numerous endogenous and exogenous compounds (Levesque et al., 2007). Defects in this enzyme result in unconjugated hyperbilirubinemia, such as Gilbert syndrome and Crigler–Najjar syndrome (Kadakol et al., 2000). The genetic polymorphism *UGT1A1*6* (rs4148323, c.211G > A, Arg71Gly) is an exonic variant of the *UGT1A1* gene on chromosome 2q37 and associated with reduced UGT1A1 activity (Bai et al., 2019). *UGT1A1*6* is highly prevalent in East Asian populations but is absent in European and African populations (Dai et al., 2013). It has allele frequencies of 23%, 23%, 13%, and 0% among Chinese, Korean, Japanese, and German populations, respectively (Akaba et al., 1998). It was reported that one of the metabolic pathways of ATV is through UGT1A1-mediated glucuronidation (Schirris et al., 2015) and the A allele in *UGT1A1* rs4148323 is associated with decreased UGT1A1 activity (Bai et al., 2019). Therefore, we speculated that the rs4148323 A allele might decrease glucuronidation activity for ATV and corresponding increase in 2-OH ATV production.

Many studies have reported genetic variants were associated with CAD pathogenesis (McPherson and Tybjaerg-Hansen 2016; Miao et al., 2018). Despite an enormous amount of research that has been done on the biological effect of *UGT1A1* gene (Goon et al., 2016), few studies have assessed whether the rs4148323 SNP has a prognostic value on all-cause death among CAD patients. To our knowledge, we are the first to demonstrate that the rs4148323 A allele was associated with increased risk of death in CAD patients.

CYP3A5 is an important hepatic drug-metabolizing enzyme. Willrich *et al.* found that the CYP3A5*3A allele was associated with reduced cholesterol-lowering response to ATV in 139 non-African individuals with hypercholesterolemia (Willrich et al., 2008). In the present study, positive correlations were found between SNP (rs15524, rs4646457, rs4646450, rs776746 and rs4646458) in the *CYP3A5* gene and the formation of 2-OH ATV. ATV and its active metabolites are subject to cellular membrane transport by organic anion-transporting polypeptide (OATP) transporters and P-glycoprotein (P-gp) (Bogman et al., 2001; Chen et al., 2005). Despite evidence that drug transporter polymorphisms could influence ATV metabolism (Lee et al., 2010; Wang et al., 2017), we did not observe such an association *in vivo* and the reason for this result is unclear.

Our study had two limitations. First, the study subjects were primarily Han ethnic Chinese, and that caution may be warranted in extrapolating our results to other populations. Second, the sample size was relatively small. In order to minimize the finding of false positive statistical associations, the *p* values were adjusted using the FDR.

In summary, the *UGT1A1* rs4148323 A allele was found to be significantly associated with elevated 2-OH ATV formation, and might increase the risk of death in Chinese patients with CAD. The present study provides suggestive data, and genotyping large cohorts of CAD patients for rs4148323 in *UGT1A1* gene will be required to unambiguously prove these findings.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: EMBL-EBI [Project: PRJEB42554; Analyses: ERZ1714343].

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethical Review Committee of Guangdong Provincial People's Hospital and Sun Yat-sen Memorial Hospital (Guangzhou, China). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

H-PL, S-LZ, Y-ZZ, and HW wrote manuscript. S-LZ, Y-ZZ, H-PL, L-YC, LT, and MY designed research. MQ, L-YC, J-EL, H-PL, HW, C-YD, Y-BL, and QZ performed research. H-PL, MQ, QZ, L-YC, WH, and Y-BL analyzed data.

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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.

GLOSSARY

ATV atorvastatin
GLUC glucose
TRIG triglycerides
CHOL cholesterol
HDL-C high-density lipoprotein cholesterol
LDL-C low-density lipoprotein cholesterol
CREA creatinine
ALT alanine aminotransferase
AST aspartate aminotransferase
CK creatine kinase
CKMB creatine kinase MB
Lp (a) lipoprotein (a)
Apo (a) apolipoprotein (a)
CAD coronary artery disease
FDR false discovery rate
ADME absorption, distribution, metabolism, and excretion
CYP cytochrome P450
HLM human liver microsomes
HR hazard ratio
OR odds ratio
CI confidence interval
eGFR estimated glomerular filtration rate
MAF minor allele frequency
PCI percutaneous coronary intervention
CCB calcium channel blocker
ACEI angiotensin-converting enzyme inhibitor
PPI proton pump inhibitor
SNP single-nucleotide polymorphisms
LD linkage disequilibrium
UGT UDP-glucuronosyltransferase
ULN upper limit of normal
SD standard deviation
UPLC-MS/MS ultra-performance liquid chromatography mass spectrometry
HMG-CoA 3-hydroxy-3-methylglutaryl-coenzyme A
OATP organic anion transporting polypeptide
P-gp P-glycoprotein

frontiers in Pharmacology

ORIGINAL RESEARCH
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Ten-Year Trends in the Use of Oral Anticoagulants in Australian General Practice Patients With Atrial Fibrillation

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Objective: Appropriate use of oral anticoagulants (OACs) reduces the risk of stroke in patients with atrial fibrillation (AF). The study characterized the prescribing of OACs in people with AF in the Australian primary care setting over 10 years.

Design: Retrospective population study.

Setting and Participants: We performed 10 sequential cross-sectional analyses of patients with a recorded diagnosis of AF between 2009 and 2018 using national general practice data. The proportion of patients with AF who were prescribed an OAC based on their stroke risk was examined.

Primary and secondary outcomes: The primary outcome was the proportion of high stroke risk patients who were prescribed an OAC over a decade. The secondary outcome was variation in OAC prescribing among general practices.

Results: The sample size of patients with AF ranged from 9,874 in 2009 to 41,751 in 2018. The proportion who were prescribed an OAC increased from 39.5% (95% CI 38.6–40.5%) in 2009 to 52.0% (95% CI 51.5–52.4%) in 2018 (p for trend < 0.001). During this time, the proportion of patients with AF and high stroke risk who were prescribed an OAC rose from 41.7% (95% CI 40.7–42.8%) to 55.2% (95% CI 54.7–55.8%; p for trend < 0.001) with the direct-acting oral anticoagulants accounting for over three-quarters of usage by 2018. There was substantial variation in OAC prescribing between general practices. In 2018, the proportion of moderate to high stroke risk patients who were prescribed an OAC was 38.6% (95% CI 37.2–40.1%) in the lowest practice site quintiles and 65.6% (95% CI 64.5–66.7%) in the highest practice site quintiles.

Conclusions: Over the 10 years, OAC prescribing in high stroke risk patients with AF increased by one-third. There was considerable variation in OAC prescribing between general practices.

Keywords: trends, anticoagulants, atrial fibrillation, general practice, primary care, Australia

BACKGROUND

Appropriate utilization of oral anticoagulants reduces stroke risk in patients with atrial fibrillation (Aguilar and Hart, 2005). The vitamin K antagonist, warfarin, has been the mainstay of anticoagulation in AF for over 2 decades. It decreases the risk of stroke by almost two-thirds (Aguilar and Hart, 2005). However, it has a narrow therapeutic index and is associated with problematic drug and food interactions that require monitoring and dose adjustments. The direct-acting oral anticoagulants (DOACs) are at least non-inferior to warfarin in efficacy and safety (Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011). In Australia, three DOACs (rivaroxaban, dabigatran, and apixaban) were listed for Commonwealth subsidy under the Pharmaceutical Benefits Scheme (PBS) for non-valvular AF in 2013; since then their overall use has markedly increased (Drug Utilisation Sub-Committee (DUSC), 2016; Admassie et al., 2017; Alamneh et al., 2017; Pol et al., 2018). In contrast, the prescribing of warfarin has declined (Drug Utilisation Sub-Committee (DUSC), 2016; Admassie et al., 2017; Alamneh et al., 2017; Pol et al., 2018).

Recent studies on the utilization of OAC have highlighted both underuse and overuse in patients with AF in Australia (Admassie et al., 2017; Alamneh et al., 2017; Schaffer et al., 2019). The Tasmanian AF Study observed prescribing practice from 2011 to 2015, and reported that 55 and 63% of eligible AF patients with a high stroke risk were prescribed an OAC before and after DOACs were listed on the PBS, respectively (Admassie et al., 2017). This study, however, involved only hospitalized patients, who might have been more co-morbid than those managed in primary care; the results therefore may not have reflected OAC prescribing rates in general practices nationally. The current AF prescribing patterns, in relation to stroke risk, in the Australian primary care setting remain unknown.

The primary objective of this study was to investigate the proportion of Australian primary care patients with AF prescribed an OAC according to their stroke risk, and temporal trends in prescribing patterns over a 10 year period. The secondary objective was to examine variation in OAC prescribing between general practices.

METHODS

Data for this study was obtained from NPS MedicineWise's dataset, MedicineInsight. This is the largest and the most representative (in terms of gender, age, socioeconomic status) general practice dataset available to researchers in Australia (Busingye et al., 2019; MedicineInsight, 2020). A total of 429 practices sites contributed data for this study.

MedicineInsight uses a third-party tool that extracts, de-identifies and securely transmits patient data each week to its secure data repository. The extraction tool allows developing a longitudinal database of patients in general practices. The data that MedicineInsight collects from general practices include patient demographics, diagnoses, pathology test results, prescribed medications, and reasons for encounter. However, specific patient identifiers, such as patient name, address, and date of birth, are not included in this dataset (MedicineInsight, 2020).

We performed 10 sequential cross-sectional analyses of data on 1 September every year (census date) from September 01, 2009 to September 01, 2018. Patients with a recorded diagnosis of non-valvular AF were included in each analysis if 1) they were aged 18 years or older and not deceased on or before the census date, 2) they had had three or more recorded general practice visits in the previous two years and at least one of these visits was in the last six months, and 2) they had been registered in the general practice's electronic records at least one year before the census date. We excluded patient who had a recorded OAC prescription before the diagnosis of AF. We defined patients with AF as being prescribed an OAC (warfarin, dabigatran, rivaroxaban or apixaban) or antiplatelet agent (clopidogrel, ticagrelor, aspirin, ticlopidine, prasugrel, dipyridamole, abciximab, eptifibatide or tirofiban) when they had at least one recorded prescription, dated within 365 days before the census date. The prescriptions recorded in this dataset were only those prescribed by general practitioners (GPs). Aspirin is available without a prescription, but we could only capture prescribed data.

For most of our study period, guidelines recommended using the CHA_2DS_2-VASc score (congestive heart failure (1 point), hypertension (1 point), age ≥75 years (2 points), diabetes mellitus (1 point), stroke/transient ischaemic attack (TIA) (2 points), vascular disease (1 point), age 65–74 years (1 point) and sex female (1 point)) for assessing stroke risk and treatment eligibility in patients with AF (Steffel et al., 2018). Current comorbidities and age at the census date were used to calculate CHA_2DS_2-VASc score. Current comorbidities were defined as those diagnosed and recorded on or before the census date. Patients with AF were stratified as low risk when CHA_2DS_2-VASc was 0 and male or one and female, moderate risk with CHA_2DS_2-VASc = 1 and male, and high risk with CHA_2DS_2-VASc ≥2 (Steffel et al., 2018). The proportion of patients who were prescribed an OAC, antiplatelet alone, or neither were calculated with 95% confidence interval (CI) each year on 1 September from September 01, 2009 through September 01, 2018. Temporal trends were shown using graphs and a Cochran-Armitage test for trend (Lachin, 2011) was used to determine if any observed trends were statistically significant.

Similarly, the proportion of patients with moderate to high stroke risk (CHA_2DS_2-VASc ≥ 1 and male or CHA_2DS_2-VASc ≥ 2) or low stroke risk (CHA_2DS_2-VASc = 0 for male or CHA_2DS_2-VASc = 1 for female) who were prescribed an OAC was calculated each year for each practice site. Potentially appropriate prescribing was defined as prescribing of an OAC to patients with a medium to high stroke risk. Potentially inappropriate prescribing was defined as prescribing an OAC to patients with low stroke risk. All practice sites that contributed data at least for a year were included. Prescribing rates were ranked into quintiles and used as an indicator of general practice sites' prescribing performance. The variation between the highest- and lowest-prescribing practice quintiles each year was calculated as a prescribing gap. We calculated linear-weighted kappa coefficients for ordered categories to determine whether

TABLE 1 | Demographic characteristics of patients with atrial fibrillation, 2009–2018.

Year	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Sample (n)	9,874	13,723	17,807	22,510	26,777	32,285	35,641	38,804	41,338	41,751
Age (mean (SD)	75.1 (11.6)	75.3 (11.7)	75.3 (11.8)	75.7 (11.9)	75.3 (11.9)	75.3 (12.0)	75.5 (11.9)	75.6 (11.8)	75.7 (11.8)	76.0 (11.6)
Sex—male (%)	5,076 (51.4)	7,146 (52.1)	9,363 (52.6)	11,758 (52.2)	14,251 (53.2)	17,226 (53.4)	19,119 (53.6)	20,903 (53.9)	22,301 (54.0)	22,700 (54.4)
Indigenous status (%)										
ATSI	69 (0.7)	119 (0.9)	178 (1.0)	230 (1.0)	277 (1.0)	343 (0.6)	398 (1.1)	452 (1.2)	509 (1.2)	540 (1.3)
Non-ATSI	6,359 (64.4)	9,030 (65.8)	12,549 (70.5)	16,313 (72.5)	20,732 (77.4)	25,530 (79.1)	28,974 (81.3)	32,190 (83.0)	34,777 (84.1)	35,442 (84.9)
Missing	3,446 (34.9)	4,574 (33.3)	5,080 (28.5)	5,967 (26.5)	5,768 (21.5)	6,412 (19.9)	6,269 (17.6)	6,162 (15.9)	6,052 (14.6)	5,769 (13.8)
State (%)										
NSW	4,031 (40.8)	5,523 (40.3)	7,564 (42.5)	9,472 (42.1)	10,944 (40.9)	13,201 (40.9)	14,267 (40.0)	15,328 (39.5)	16,245 (39.3)	16,497 (39.5)
VIC	2,060 (20.9)	3,191 (23.3)	4,117 (23.1)	5,442 (24.2)	5,996 (22.4)	7,067 (21.9)	7,672 (21.5)	8,260 (21.3)	8,533 (20.6)	8,000 (19.2)
QLD	1,350 (13.7)	1,885 (13.7)	2,306 (13.0)	2,897 (12.9)	3,869 (14.5)	4,705 (14.6)	5,487 (15.4)	5,992 (15.4)	6,701 (16.2)	7,030 (16.8)
WA	878 (8.9)	1,054 (7.7)	1,188 (6.7)	1,348 (6.0)	2,055 (7.7)	2,765 (8.6)	3,163 (8.9)	3,659 (9.4)	4,002 (9.7)	4,102 (9.8)
TAS	1,208 (12.2)	1,511 (11.0)	1,729 (9.7)	2,156 (9.6)	2,311 (8.6)	2,727 (8.5)	2,937 (8.2)	3,064 (7.9)	3,209 (7.8)	3,454 (8.3)
SA	230 (12.2)	319 (2.3)	534 (3.0)	774 (3.4)	1,054 (3.9)	1,183 (3.7)	1,294 (3.6)	1,345 (3.5)	1,393 (3.4)	1,421 (3.4)
ACT	42 (0.4)	100 (0.7)	126 (0.7)	147 (0.7)	272 (1.0)	351 (1.1)	493 (1.4)	812 (2.1)	874 (2.1)	884 (2.1)
NT	75 (0.8)	140 (1.0)	243 (1.4)	274 (1.2)	276 (1.0)	286 (0.9)	328 (0.9)	344 (0.9)	381 (0.9)	363 (0.9)
Rurality (%)										
Major cities	5,189 (52.6)	7,355 (53.6)	9,460 (53.1)	12,237 (54.4)	15,167 (56.6)	18,469 (57.2)	20,528 (57.6)	22,581 (58.2)	24, 251 (58.7)	23,918 (57.3)
Inner regional	3,178 (32.2)	4,156 (30.3)	5,599 (31.4)	7,027 (31.2)	8,014 (29.9)	9,669 (30.0)	10,583 (29.7)	11,414 (29.4)	12,002 (29.0)	12,686 (30.4)
Outer regional	1,340 (13.6)	1,968 (14.3)	2,465 (13.8)	2,917 (13.0)	3,228 (12.1)	3,624 (11.2)	3,928 (11.0)	4,123 (10.6)	4,307 (10.4)	4,317 (10.3)
Remote/very remote	86 (0.9)	137 (1.0)	171 (1.0)	190 (0.8)	221 (0.8)	340 (1.1)	413 (1.2)	481 (1.2)	585 (1.4)	642 (1.5)
Missing	81 (0.8)	107 (0.8)	112 (0.6)	139 (0.6)	147 (0.6)	183 (0.6)	189 (0.5)	205 (0.5)	193 (0.5)	188 (0.5)
SEIFA quintiles (%)										
1	2,177 (22.1)	3,030 (22.1)	3,810 (21.4)	4,500 (20.0)	5,020 (18.8)	5,828 (18.1)	6,375 (17.9)	6,847 (17.7)	7,113 (17.2)	7,022 (16.8)
2	1,702 (17.2)	2,238 (16.3)	3,233 (18.2)	4,183 (18.6)	5,032 (18.8)	6,213 (19.2)	7,027 (19.7)	7,690 (19.8)	8,227 (19.9)	8,376 (20.1)
3	2,622 (26.6)	3,571 (26.0)	4,613 (25.9)	5,839 (25.9)	6,911 (25.8)	8,287 (25.7)	8,991 (25.2)	9,560 (24.6)	10,231 (24.8)	10,498 (25.1)
4	1,466 (14.9)	2,014 (14.7)	2,612 (14.7)	3,332 (14.8)	4,177 (15.6)	5,085 (15.8)	5,731 (16.1)	6,410 (16.5)	7,010 (17.0)	7,177 (17.2)
5	1,815 (18.4)	2,747 (20.0)	3,398 (19.1)	4,480 (19.9)	5,446 (20.3)	6,622 (20.5)	7,254 (20.4)	8,017 (20.7)	8,489 (20.5)	8,414 (20.2)
Missing	92 (0.9)	123 (0.9)	141 (0.8)	176 (0.8)	191 (0.7)	250 (0.8)	263 (0.7)	280 (0.7)	268 (0.7)	264 (0.6)
CHA_2DS_2-VASc score (%)										
Low (0 males, 1 in females)	548 (5.6)	805 (5.9)	1,072 (6.0)	1,349 (6.0)	1,753 (6.6)	2,155 (6.7)	2,345 (6.6)	2,569 (6.6)	2,713 (6.6)	2,548 (6.1)
Moderate (1 in males)	619 (6.3)	863 (6.3)	1,115 (6.3)	1,360 (6.0)	1,847 (6.9)	2,196 (6.8)	2,400 (6.7)	2,603 (6.7)	2,852 (6.9)	2,918 (7.0)
High (≥2)	8,707 (88.2)	12,055 (87.9)	15,620 (87.7)	19,801 (88.0)	23,177 (86.6)	27,934 (86.5)	30,896 (86.7)	33, 632 (86.7)	35,773 (86.5)	36,285 (87.0)

ATSI, Aboriginal and Torres Strait Islander; SD, standard deviation; SEIFA, socioeconomic indexes for areas.

practice performance remained constant over the study period (Vanbelle and Albert, 2009).

Socio-economic indexes for areas (SEIFA) quintile is an index developed by the Australian Bureau of Statistics (ABS) and ranks areas in Australia from 1 (most disadvantaged area) to 5 (most advantaged area) (Australian Bureau of Statistics, 2018). The ABS categorize rurality into five categories using the Accessibility/Remoteness Index of Australia (ARIA) score. These categories are major cities (ARIA 0–0.20), inner regional (0.21–2.40), outer regional (2.41–5.92), remote (5.93–10.53), and very remote (10.54–15) (Australian Statistical Geography Standard (ASGS), 2017); we collapsed remote and very remote areas into one group. SAS software (SAS version 9.4, SAS Institute Inc., Cary, NC, United States) was used for all data analyses, and a two-sided p-value < 0.05 was considered statistically significant.

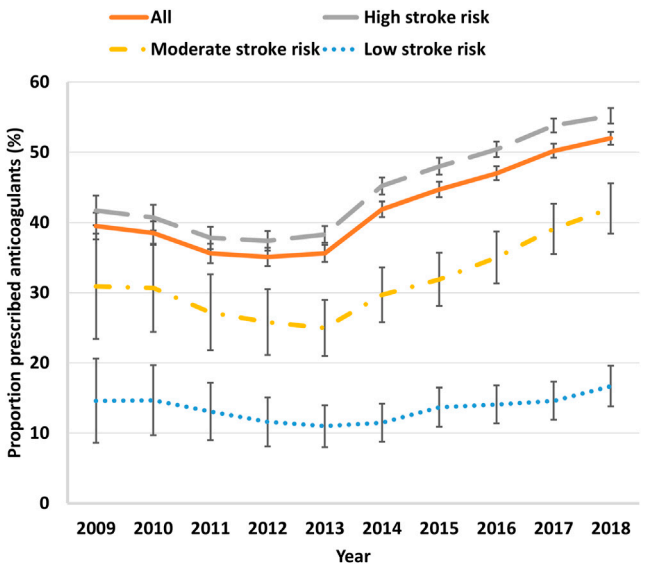

FIGURE 1 | Trends of oral anticoagulant prescribing in Australian general practice patients with atrial fibrillation stratified by CHA2DS2-VASc score, 2009–2018. Error bars indicate 95% confidence intervals.

Ethics approval was obtained from the Tasmanian Health and Medical Human Research Ethics Committee (H0017648). We also obtained approval to conduct this study from MedicineInsight's independent Data Governance Committee (2018–033). Patients were not identifiable, and individual patient consent was waived for our ethics application.

Patient and Public Involvement

No patient involved.

RESULTS

Baseline Characteristics

The total number of patients with AF included in our consecutive cross-sectional analyses ranged from 9,874 from 169 practice sites in 2009 to 41,751 from 429 practice sites in 2018. The mean age (standard deviation) of patients with AF increased slightly from 75.1 (11.6) years in 2009 to 76.0 (11.6) years in 2018 (p for trend < 0.001). The proportion of male patients increased from 51.4% (95% CI 50.4–52.4%) in 2009 to 54.5% (95% CI 54.0–55.0%) in 2018 (p for trend <0.001; **Table 1**).

Oral Anticoagulant Prescribing

The proportion of patients with AF and an OAC prescription recorded decreased from 39.5% (95% CI 38.6–40.5%) in 2009 to 35.1% (95% CI 34.5–35.8%) in 2011 and then increased to 52.0% (95% CI 51.5–52.4%) by 2018 ($p < 0.001$; **Figure 1**). In all patients with AF, lone antiplatelet prescribing dropped steadily from 17.6% (95% CI 16.8–18.3%) in 2009 to 2.9% (95% CI 2.7–3.0%) in 2018 (p for decrease over time <0.001; **Supplementary Table S1**). However, these latter data are unreliable as patients can obtain aspirin without a prescription. The proportion of people who had no record of a prescription for either treatment to prevent stroke increased from 42.9% (95% CI 41.9–43.9%) to 51.1% (95% CI 50.5–51.7%) in 2013 and plateaued around 47.0% between 2014 and 2016, and then declined to 45.2% (95% CI 44.7–45.7%) in 2018 (p for increase over time <0.001; **Supplementary Table S1**).

In high-risk patients (CHA_2DS_2-VASc≥2), the proportion with an OAC prescription recorded increased from 41.7% (95% CI 40.7–42.8%) in 2009 to 55.2% (95% CI 54.7–55.8%) in 2018 ($p < 0.001$). In moderate stroke risk patients (CHA_2DS_2-VASc = 1 and male), the proportion who were receiving an OAC increased from 30.9% (95% CI 27.2–34.7%) in 2009 to 42.0% (95% CI 40.2–43.8%) in 2018 ($p < 0.001$). In low stroke risk patients with AF (CHA_2DS_2-VASc = 1 and female, 0 and male), the proportion who were prescribed an OAC decreased from 14.6% (95% CI 11.8–17.8%) in 2009 to 11.0% (95% CI 9.6–12.6%) in 2013 and then increased to 16.7% (95% CI 15.3–18.2%) in 2018 ($p < 0.001$; **Figure 1**).

General Practices' Prescribing Performance Gap Over Time

In 2009, the proportion of moderate to high stroke risk patients (CHA_2DS_2-VASc ≥ 1 and male or CHA_2DS_2-VASc ≥ 2 and female) with AF and an OAC prescription recorded among the lowest prescribing practice quintile was 24.7% (95% CI 22.3–27.4%), compared with 54.7% (95% CI 52.6–56.9%) in the highest quintile. By 2018, prescribing had increased to 38.6% (95% CI 37.2–40.1%) and 65.6% (95% CI 64.5–66.7%) in the lowest and highest practice quintiles, respectively. The gap between the highest- and lowest-prescribing practice quintiles in OAC prescribing for patients with moderate to high stroke risk

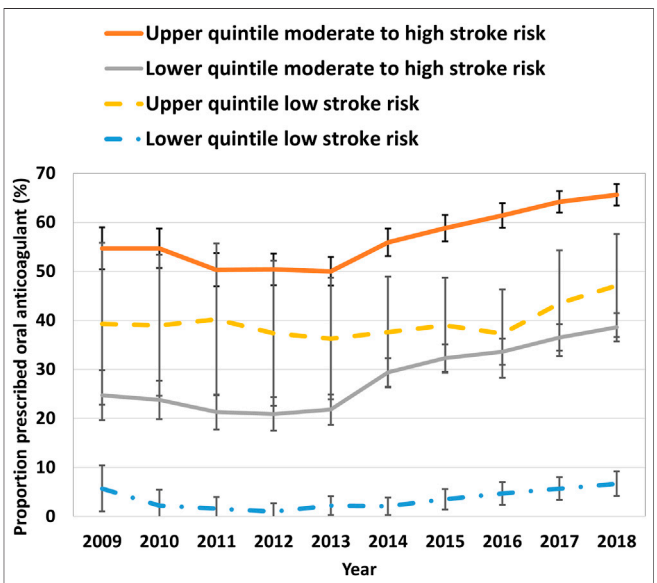

FIGURE 2 | Practice site prescribing-performance quintile in moderate to high stroke risk patients with atrial fibrillation, 2009–2018. Error bars indicate 95% confidence intervals.

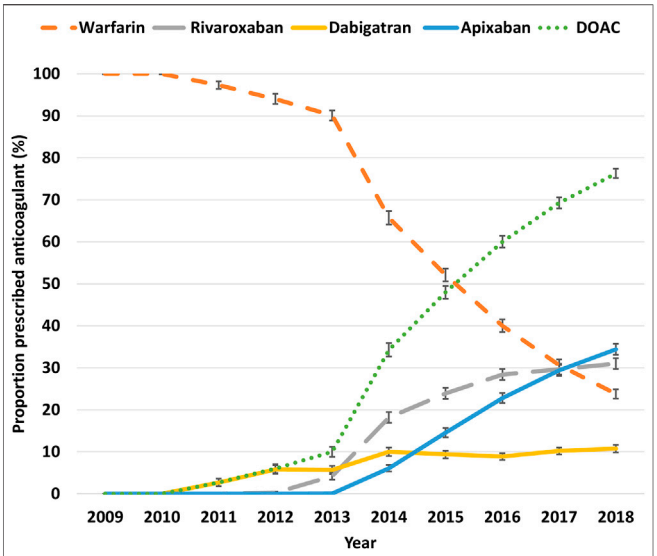

FIGURE 3 | The proportion of patients with atrial fibrillation receiving an oral anticoagulant, 2009–2018. Error bars indicate 95% confidence intervals.

remained wide, falling slightly from 30.0% in 2009 to 25.9% in 2018 (**Figure 2**).

A total of 429 practice sites contributed data in 2018. Of these, 169 (39.4%) had provided data since 2009, of which 64 (37.9%) of practice sites' OAC prescribing quintile did not change, and 120 (71.0%) practice sites continued in the same or closest prescribing quintile. There was reasonable agreement in practices sites' prescribing quintile between 2009 and 2018, weighted kappa = 0.34 (95% CI 0.24–0.45) (McHugh, 2012).

In 2009, the proportion of patients with AF who were prescribed an OAC while potentially not recommended (CHA_2DS_2-VASc = 0 and male or CHA_2DS_2-VASc = 1 and female) in the lowest- and highest-prescribing quintiles were 5.7% (95% CI 3.7–8.4%) and 39.3% (95% CI 31.3–47.8%), respectively. At the end of the study period, the proportion of potentially inappropriate prescribing in the lowest- and highest-prescribing quintiles had increased to 6.7% (95% CI 5.5–8.0%) and 47.1% (95% CI 41.9–52.4%), respectively (**Figure 2**).

Trends in the Use of Warfarin and DOACs

Among all patients with an OAC prescription recorded, the proportion who were prescribed a DOAC increased rapidly from 2.7% (95% CI 2.4–3.3%) in 2011 to 76.3% (95% CI 75.7–76.8%) in 2018, while the proportion of those prescribed warfarin correspondingly decreased from 97.3% (95% CI 96.8% 97.7%) to 23.8% (95% CI 23.2–24.3%) (**Figure 3**; **Supplementary Table S2**).

DISCUSSION

The analyses of this large and nationally representative data suggest changing practice trends in the rate and type of OAC prescribing over the 10 year period. The proportion of patients with moderate to high stroke risk who were prescribed an OAC increased steadily by one-third from 2009 to 2018. This increase in the proportion patients with moderate to high stroke risk who were prescribed an OAC was significantly higher from 2013 onwards, corresponding with the PBS listing of DOACs for Australian government subsidization (rivaroxaban in August 2013, and apixaban and dabigatran in September 2013) (Drug Utilisation Sub-Committee (DUSC), 2016). In 2010, the European Society of Cardiology (ESC) guidelines recommended prescribing of an OAC for all AF patients at moderate-high risk of stroke, (i.e., CHA_2DS_2-VASc score ≥1) instead of antiplatelet therapy (Camm et al., 2010). This was followed by the 2012 ESC's updated recommendation to avoid prescribing of aspirin in low-stroke risk patients (Camm et al., 2012). These changes may also explain the surge in OAC prescribing during the study period (Camm et al., 2012). Similar trends of an increase in OAC use, with a slow initial uptake after the introduction of DOACs, have been reported by studies from the United Kingdom and Denmark (Gadsbøll et al., 2017; Loo et al., 2017).

In 2018, just over half of the high-risk patients were prescribed an OAC. This rate is low compared with the rates reported from previous studies. The Tasmanian AF study found 63% of high-risk patients were prescribed an OAC. However, that study involved hospitalized patients who might have been more comorbid than general practice patients and it excluded patients with known OAC contraindications. A study in the United Kingdom using general practice data found that over three-quarters of high-risk patients with AF were prescribed an OAC (Adderley et al., 2018). Another study from Denmark found that two-thirds of patients were prescribed an OAC (Gadsbøll et al., 2017).

Despite an overall increase in OAC prescribing over the study period, there remained wide gaps between the highest- and lowest-performing practices in both appropriate (for moderate to high stroke risk) and potentially inappropriate (for low stroke risk) prescribing. One possible reason for the observed gaps in the appropriate use of an OAC might be the absence of regular reassessment of CHA_2DS_2-VASc scores. A study by Yoon et al. (Yoon et al., 2018) found that 46.6% of low-risk and 72% of moderate-risk patients at baseline were reclassified as being at high stroke risk within 10 years of follow-up. Increasing GPs' awareness of the need for annual stroke risk assessment may improve OAC prescribing.

STRENGTHS AND LIMITATIONS

This was the first AF study conducted using MedicineInsight dataset, which provided a large and national study population and thus enabled a comprehensive description of GP prescribing of OACs in Australia (González-Chica et al., 2018; Radford et al., 2018; MedicineInsight, 2020). Furthermore, 10 years sequential cross-sectional analyses enabled characterizing the longitudinal trends in OAC prescribing.

The study has several limitations. The MedicineInsight dataset contains only records of medications prescribed by GPs.

However, GPs in Australia typically continue those medications prescribed by cardiologists and so the trends described in this study may still be considered accurate and useful with regard to overall OAC prescribing. We did not account for medication contraindications and adverse drug reactions, that may have prevented GPs from prescribing an OAC.

In this study, we used the guidelines retrospectively. For instance, before 2012, OAC treatment was recommended for patients at moderate to high stroke risk, and aspirin was widely used for patients at low stroke risk (Camm et al., 2010). However, the guidelines used for this analysis were in use for most of the study period and are appropriate to evaluate the trends.

CONCLUSION

Over the 10 years, overall OAC prescribing increased by one-third. By 2018, 55.2% of the patients with a high stroke risk had an OAC prescription recorded, with the proportion varying substantially between practices. There remains scope to improve OAC prescribing for AF in the primary care setting, and the reasons for withholding OAC therapy in eligible patients need to be investigated.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the data analyzed in this study was obtained from MedicineInsight with the restriction of not sharing the data publicly. Requests to access these datasets should be directed to MedicineInsight, DataGovernance@nps.org.au. Requests to access the datasets should be directed to DataGovernance@nps.org.au.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Tasmanian Health and Medical Human Research Ethics Committee, University of Tasmania; and the MedicineInsight independent Data Governance Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

WB participated in the study design, data preparation and manipulation, analysis and interpretation of the data and drafting and revising of the manuscript. GP, LB, JR, and BW participated in the study concept and design. GP, LB, JR, BW, MS, and CC participated in the critical revision of the manuscript.

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We are grateful to the general practices and general practitioners that participate in MedicineInsight, and their patients who allow the use of de-identified information for MedicineInsight.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.586370/full#supplementary-material.

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REVIEW
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Effect of Liraglutide on Cardiometabolic Risk Profile in People with Coronary Artery Disease with or without Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background: Whether liraglutide use improves cardiometabolic risk factors in different subsets of subjects with coronary artery disease (CAD) remains unclear. In a systematic review and meta-analysis, we quantified the effects of liraglutide on cardiometabolic risk profile in subjects with CAD with or without type 2 diabetes mellitus (T2D).

Methods: Online database searches were conducted in PubMed, Scopus, EMBASE, Web of Science, Cochrane library, and Google Scholar from incept up to 15th January 2021. We identified randomized controlled trials (RCTs) assessing the effects of liraglutide compared to placebo on cardiometabolic risk profile. We used the random- or fixed-effect models to pool the weighted mean differences (WMDs) and 95% confidence intervals (CIs).

Results: Out of a total of 7,320 citations, six articles (seven RCTs) with 294 subjects with CAD (mean age, 61.21 years; 19% women) were included. Our findings presented as WMD and 95% CI showed a statistical significant decrease in hemoglobin A1c (HbA1c) [−0.36%; −0.47; −0.26, $p < 0.001$; $I^2 = 0.0\%$ (with 6 RCTs)], body mass index (BMI) [−0.61 kg/m^2; −1.21; −0.01, $p = 0.047$; $I^2 = 72.2\%$ (with five RCTs)], and waist circumference [−2.41 cm; −3.47; −1.36, $p < 0.001$; $I^2 = 0.0\%$ (with three RCTs)]. Through a set of subgroup analyses, we found a significant reduction in BMI in CAD patients with T2D [WMD = −1.06; 95% CI, −1.42, −0.70, $p < 0.001$; $I^2 = 0.0\%$ (with three RCTs)] compared to CAD only patients [WMD = −0.08; 95% CI, −0.45, 0.29, $p = 0.66$; $I^2 = 0.0\%$ (with two RCTs)] in the liraglutide group compared with the placebo group. No significant changes in heart rate, blood pressure, and lipid profiles were observed.

Conclusions: Among people with established CAD, liraglutide significantly improved HbA1c, BMI, and waist circumference values. The effect of liraglutide on BMI was more robust in individuals with T2D compared to those without.

Keywords: liraglutide, cardiometabolic profiles, coronary artery disease, systematic review, meta-analysis

INTRODUCTION

Liraglutide is an analog of human native incretin hormone with 97% similarity and is known as a long-acting glucagon-like peptide 1 receptor agonist (GLP1-RA) (Howell et al., 2019). Liraglutide is used as a dual therapy option after first-line metformin therapy in type 2 diabetes mellitus (T2D)patients with established CVD (Cosentino et al., 2019; Buse et al., 2020). Liraglutide can also be considered inT2D patients aged 55 years or older and high risk of CVD, even without established atherosclerotic cardiovascular disease (ASCVD), to reduce the risk of major adverse cardiovascular events (MACE) (Buse et al., 2020). The results of a recent meta-analysis revealed that GLP1-RAs reduce the risk of myocardial infarction (MI), stroke, and cardiovascular death by approximately 14% in T2D patients with known ASCVD (Zelniker et al., 2019). The multifaceted mechanism of liraglutide's action induces increased insulin secretion, decreased glucagon secretion, and delayed gastric emptying (Howell et al., 2019).

Coronary artery disease (CAD) involves blood flow impairment through the coronary arteries. Silent ischemia and angina pectoris are among the most common CAD clinical presentation. Most importantly, CAD is a predominant risk factor for sudden cardiac death and heart failure progression (Velagaleti & Vasan, 2007; Malavolta et al., 2017). Optimal treatment of CAD leads to improve patients' survival rates for many years and decrease the disease progression and complications (Malavolta et al., 2017).

Liraglutide has favorable effects on cardiometabolic risk factors in T2D patients (Davies et al., 2015; Sun et al., 2015; Sun et al., 2015; Liakos et al., 2019; Matikainen et al., 2019). Whether this medication improves cardiometabolic risk profiles in CAD patients remains unclear. Therefore, we conducted a systematic review and meta-analysis of randomized controlled trials (RCT) to assess and quantify the effect of liraglutide on cardiometabolic traits including glycemic traits, body mass index (BMI), waist circumference (WC), blood pressure, heart rate, and lipids traits in patients with established CAD. Whether coincidence of CAD with T2D can influence the effect of liraglutide on cardiometabolic risk profile was also evaluated.

MATERIALS AND METHODS

The current systematic review and meta-analysis was performed and reported according to the items in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

Search Strategy

Online database searches were conducted in PubMed, Scopus, EMBASE, Web of Science, the Cochrane library, and an additional search in Google Scholar from inception to the 15th of January 2021. To increase our searches' sensitivity, we manually checked the reference lists of relevant studies and previous reviews. The search strategy was performed using the following pattern: (Key terms for liraglutide)AND (Key terms for population/ interested outcomes) AND (Key terms for study design). Scopus search trips as an example are provided in **Supplementary Appendix 1**.

Inclusion and Exclusion Criteria

Two authors (MSh-B and FJ) independently evaluated all retrieved citations using the inclusion criteria. Discrepancies were resolved through consensus or discussion with a third author (RT or PN-S). We included all published RCTs in English (either with parallel or cross-over design) that investigated the effect of liraglutide use on cardiometabolic profile in CAD patients with or without T2D. No date limitations were on the studies' identification.

Data Extraction

Two independent authors (MSh-B and FJ) extracted the following information from the selected studies: first author, year of publication, study design, the mean age of participants, study population, mean (SD) changes of cardiometabolic traits including hemoglobin A1c (HbA1c), BMI, WC, systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL)-cholesterol, and high-density lipoprotein (HDL)-cholesterol), the number of participants in total and each group (intervention and control), type of intervention, type of placebo, and duration of intervention. In case of disagreement between the two authors, the consensus was reached by a third author (F.A).

Quality Assessment

The quality of the selected studies was critically assessed using the Cochrane Collaboration Risk of Bias tool. The quality items included "randomization generation, allocation concealment, blinding of subjects and outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias." The results of the quality assessment of included studies are presented in **Figure 1**.

Statistical Analysis

All statistical analyses were performed using STATA version 12.0 (Stata Corp., College Station, TX) and RevMan software (Cochrane Review Manager, version 5.2). The effect of liraglutide on cardiometabolic traits was reported as mean (SD) change in the intervention and the placebo groups. Once included RCTc did not report mean (SD) change, we

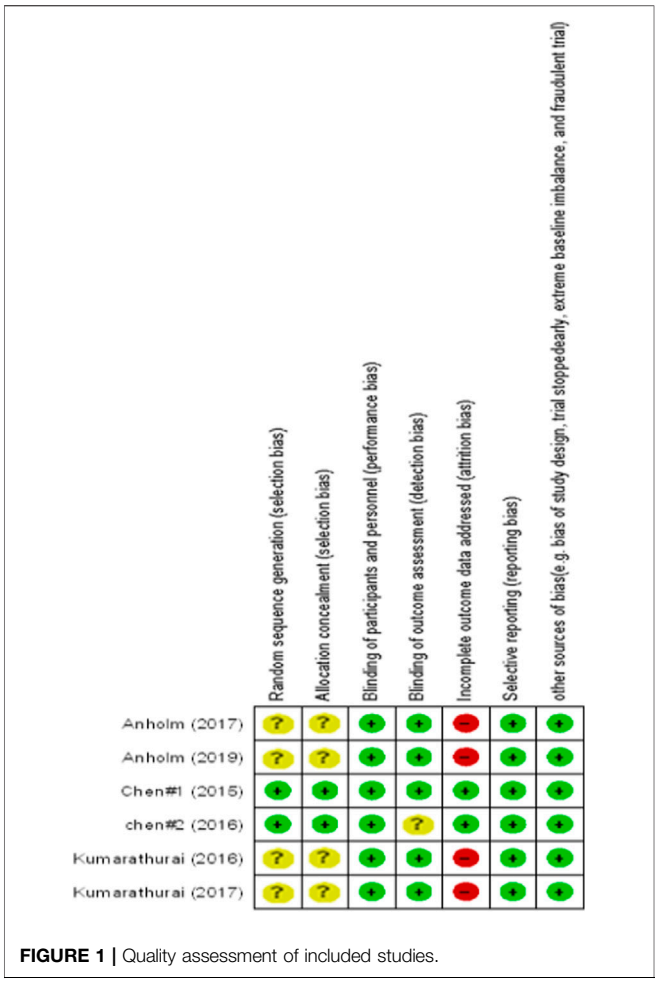

FIGURE 1 | Quality assessment of included studies.

calculated the mean changes, and their corresponding SDs using the following formula: [$mean_{post}$ − $mean_{pre}$] and [$\sqrt{([SD_{pre}^2 + SD_{post}^2] - [2 \times R \times SD_{pre} \times SD_{post}])}$] (Borenstein et al., 2011), respectively. The correlation coefficient (R) was calculated based on the study conducted by Kumarathurai et al. (2017) using an appropriate formula proposed by Cochrane guidelines for systematic reviews and meta-analysis (Higgins, 2011). In Chen et al. (2016) study, CIs for mean changes for each group (intervention/control) were used to calculate their SDs by the following formula: [SD = $\sqrt{N}$ × (upper limit − lower limit)/2 × a value from a t distribution]; t value for a 95% CI from a sample size of 45 subjects (per each group) was obtained as 2.02. Statistical heterogeneity across selected trials was determined using Cochrane's Q test and the I^2 statistic with I^2 > 50% and Cochrane's Q test as p < 0.1, indicating the existence of significant heterogeneity across included studies. We used the random-effects model [with DerSimonian–Laird method] to pool the weighted mean differences (WMDs) and 95% confidence intervals (CIs); otherwise, the fixed-effect model [with inverse variance method] was applied. In a set of subgroup analyses, we assessed liraglutide's effect on the cardiometabolic risk profile, in patients with CAD comparing those with and without T2D. To assess our findings' robustness, a series of sensitivity analyses were conducted with the leave-one-out method to assess the impact of each included study on the pooled WMDs. We assessed the presence of potential evidence of publication bias using the Egger regression and Begg's rank correlation tests, with p < 0.05 suggesting publication bias.

RESULTS

A total of 7,320 citations were identified through electronic database searches. Of these, 3,231 were duplicate reports. After screening titles and abstracts, 456 full texts were retrieved for assessment. Finally, six articles (including seven RCTs, as some articles contained more than one study) (Chen et al., 2015; Chen et al., 2016; Kumarathurai et al., 2016; Anholm et al., 2017; Kumarathurai et al., 2017; Anholm et al., 2019) were included in our meta-analysis. The process of study identification and selection is presented in **Figure 2**.

The design of four included studies was cross-over (Kumarathurai et al., 2016; Anholm et al., 2017; Kumarathurai et al., 2017; Anholm et al., 2019) while two had a parallel design (Chen et al., 2015; Chen et al., 2016). Six RCTs had reported data for calculating changes in HbA1c; five had data on BMI, SPB, DBP, four on heart rate, three on WC, LDL-cholesterol, and two on TG, TC, HDL-cholesterol. The characteristics of RCTs included in the meta-analysis are summarized in **Table 1**.

The Effects of Liraglutide Use on Cardiometabolic Traits

The effects of liraglutide on cardiometabolic traits among patients with CAD are shown in **Figures 3A–M**.

Using fixed-effect model, our meta-analyses showed a significant decrease in the WMD of HbA1c [WMD = −0.36%; 95% CI, −0.47; −0.26, p < 0.001; I^2 = 0.0% (with six RCTs)], and WC [WMD = −2.41 cm; 95% CI, -3.47; - 1.36, p < 0.001; I^2 = 0.0% (with three RCTs)], and according to random-effects model, a significant decrease in the WMD of BMI [WMD = −0.61 kg/m^2; 95% CI, −1.21; −0.01, p = 0.047; I^2 = 72.2% (with five RCTs)] in the liraglutide group compared with the placebo group.

Liraglutide had no significant effect on lipid traits, including TG [WMD = −2.09 mg/dl; 95% CI, −12.06; 7.88, p = 0.681; I^2 = 0.0% (with two RCTs)], TC [WMD = −10.66 mg/dl; 95% CI, −26.62; 5.30, p = 0.190; I^2 = 0.0% (with two RCTs)], LDL-cholesterol [WMD = −3.56 mg/dl; 95% CI, −12.68; 5.55, p = 0.444; I^2 = 0.0% (with three RCTs)], and HDL-cholesterol [WMD = −1.50 mg/dl; 95% CI, −5.86; 2.85, p = 0.499; I^2 = 50.3% (with two RCTs)].

No significant changes in SBP [WMD = −2.36%; 95% CI, −5.45; 0.72, p = 0.133; I^2 = 0.0% (with five RCTs)], DBP [WMD = 1.51%; 95% CI, −1.32; 4.35, p = 0.295; I^2 = 0.0% (with five RCTs)],

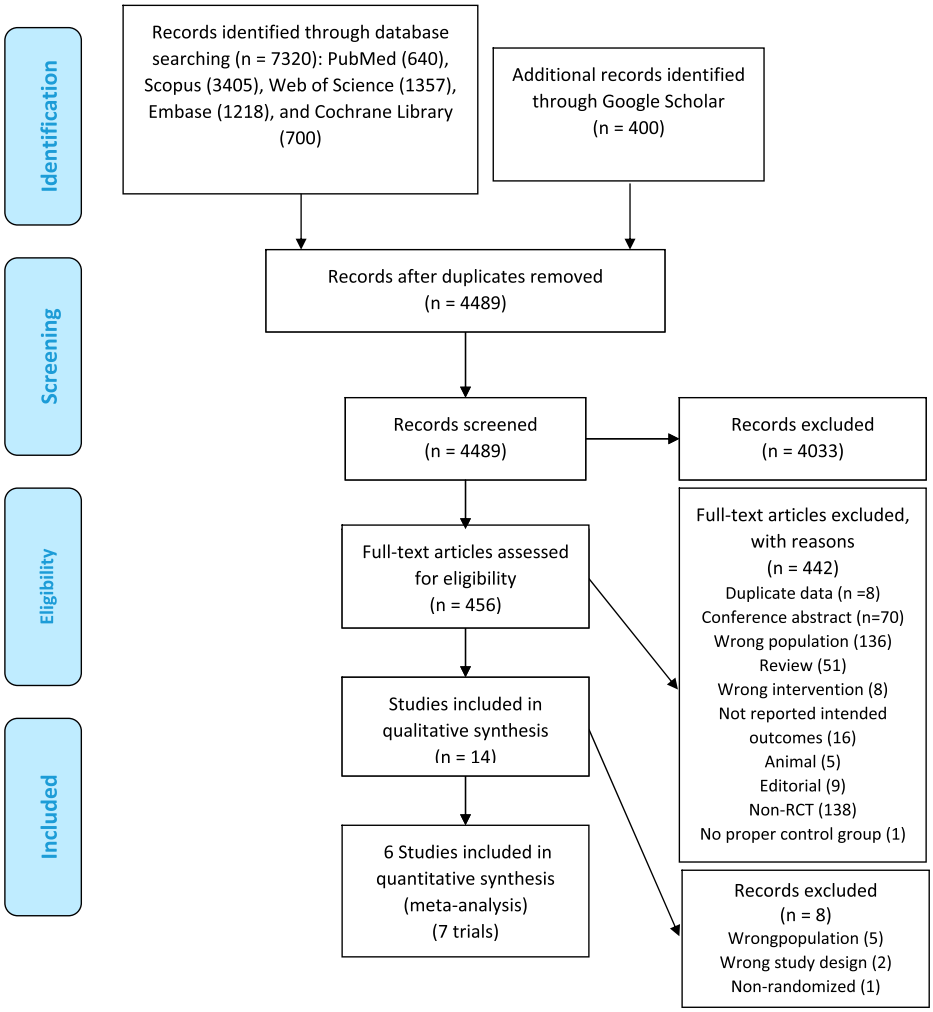

FIGURE 2 | Flowchart of the identification studies and selection process.

and heart rate [WMD = 1.83 bpm (beat per minute); 95% CI, −2.14; 5.80, p = 0.366; I^2 = 62.8% (with four RCTs)] were observed.

Subgroup Analysis

As shown in **Supplementary Table S1**, Liraglutide effects in CAD patients with and without T2D were analyzed and compared through a set of subgroup analyses. We found a significant difference between the two groups in whichCAD patients with T2D had significantly more reduction in BMI [WMD = −1.06 kg/m^2; 95% CI, v1.42; −0.70, $p < 0.001$; I^2 = 0.0% (with three RCTs)] compared to CAD only patients [WMD = −0.08 kg/m^2; 95% CI, −0.45; 0.29, p = 0.660; I^2 = 0.0% (with two RCTs)]. In CAD patients with T2D, HDL-cholesterol decreased significantly compared to their comparator. No significant differences between CAD patients with and without T2D have been observed for the effect of liraglutide on the other cardiometabolic traits.

Sensitivity Analysis

Our sensitivity analyses showed no significant differences between the pre-and post-sensitivity WMDs after excluding each included RCT for HbA1c, WC, DBP, heart rate, and LDL-cholesterol. However, there was a significant change in the pooled WMD of the BMI and SBP in the liraglutide compared to the placebo group after removing Anholm et al. study (WMD = −0.41 kg/m^2; 95% CI, −1.14; 0.30) (Anholm et al., 2017) and Kumarathurai et al. study (WMD = −3.77%; 95% CI, −7.34; −0.20) (Kumarathurai et al., 2017) , respectively (**Table 2**).

Publication Bias

Egger regression and Begg's rank correlation tests indicated no significant evidence of potential publication bias for cardiometabolic traits including, HbA1C (P_{Eg} = 0.53, P_{Be} = 0.26), BMI (P_{Eg} = 0.97, P_{Be} = 0.62), WC (P_{Eg} = 0.47, P_{Be} = 0.60), SBP (P_{Eg} = 0.63, P_{Be} = 0.33), DBP (P_{Eg} = 0.71, P_{Be} = 0.62), heart rate (P_{Eg} = 0.81, P_{Be} = 0.17), and LDL-cholesterol (P_{Eg} =

TABLE 1 | Characteristics of included studies.

Authors (ref)	Publication year	Sample size (control/ intervention)	Country/ population	Intervention group	Duration of treartment	Duration of follow-up	Study design	Age (control, intervention)	Presented data
Chen et al. (2015)	2015	7/9	China/DM acute ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI	Liraglutide (0.6 mg once daily for 2 days (1.6 pmol/kg per minute), 1.2 mg for another 2 days (3.2 pmol/kg per minute), and 1.8 mg for 3 days (4.8 pmol/kg per minute))	1 week[a]	12 weeks	Single-center, randomized, double-blind, placebo, controlled trial	59.2 ± 14.4 57.7 ± 11.3	BMI, HbA1C, SBP, DBP, and HR
Chen et al. (2015)	2015	40/36	China/NDM acute ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI	Liraglutide (0.6 mg once daily for 2 days (1.6 pmol/kg per minute), 1.2 mg for another 2 days (3.2 pmol/kg per minute), and 1.8 mg for 3 days (4.8 pmol/kg per minute))	1 week[a]	12 weeks	Single-center, randomized, double-blind, placebo, controlled trial	59.2 ± 14.4 57.7 ± 11.3	BMI, HbA1C, SBP, DBP, and HR
Chen et al. (2016)	2016	45/45	China/Non-STsegment elevation myocardial infarction (NSTEMI)	Liraglutide (0.6 mg once daily for 2 days, 1.2 mg liraglutide for another 2 days, followed by 1.8 mg liraglutide for 3 days) injection	1 week[a]	12 weeks	Single-center, randomized, double-blind, placebo, controlled trial	59.0 ± 12.1 58.0 ± 11.7	BMI, HbA1C, SBP, DBP, HR, TG, TC, HDL-C, and LDL-C
Kumarathurai et al. (2016)	2016	30	Denmark/ Patients with CAD and T2D	0.6 mg liraglutide (injection) od + 500 mg metformin (tablet) bid was increased after 14 days to 1.2 mg od + (1,000 mg + 500 mg) daily and to 1.8 mg od + 1,000 mg bid after 28 days	12 weeks	12 weeks	Randomized, double-blind, placebo-controlled 12 plus 12 weeks crossover study	61.8 ± 7.6	BMI, WC, HbA1C, SBP, DBP, HR, and LDL-C
Kumarathurai et al. (2017)	2017	24	Denmark/ Overweight patients with newly diagnosed T2D and stable CAD	0.6 mg liraglutide once daily (o.d.) + 500 mg metformin twice daily (b.i.d.) was increased after 14 days to liraglutide 1.2 mg o.d.+ metformin (1000 mgþ500 mg) and to 1.8 mg o.d. + 1000 mg **B**.i.d. after 28 days	12 weeks	12 weeks	Randomized, double-blind, placebo-controlled, crossover study	62.5 + 7.2	WC, HbA1C, SBP, and DBP
Anholm et al. (2017)	2017	30	Denmark/ Overweight patients with CAD and newly diagnosed T2D	Liraglutide (1.8 mg once daily (titrated from 0.6 to 1.8 mg during 4 weeks)) + metformin (1 g twice daily (titrated from 500 mg to 1 g during 4 weeks))	12 weeks	12 weeks	Investigator-initiated, double-blinded, randomized, placebo-controlled, crossover trial	62.3 ± 7.6	BMI, WC, and HbA1C
Anholm et al. (2019)	2019	28	Denmark/ Patients with CAD and newly diagnosed T2D	Liraglutide once daily was titrated from 0.6 to 1.8 mg within 4 weeks and metformin was titrated from 500 mg twice daily to 1 g twice daily in 4 weeks	12 weeks	12 weeks	Investigator-initiated, double-blind, randomized, placebo-controlled, cross-over trial	62.3 ± 7.6	TG, TC, HDL-C, and LDL-C

Abbreviations: CAD, coronary artery disease; Non-DM, Non-diabetes mellitus; DM, diabetes mellitus; T2D, type 2 diabetes; PCI, percutaneous coronary intervention; BMI, body mass index; WC, waist circumference; HR, heart rate; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; TG, triglycerides; TC, total cholesterol; HbA1C, hemoglobin A1C; SBP, systolic blood pressure; DBP, diastolic blood pressure.

[a]*Duration of the follow-up was 12 weeks.*

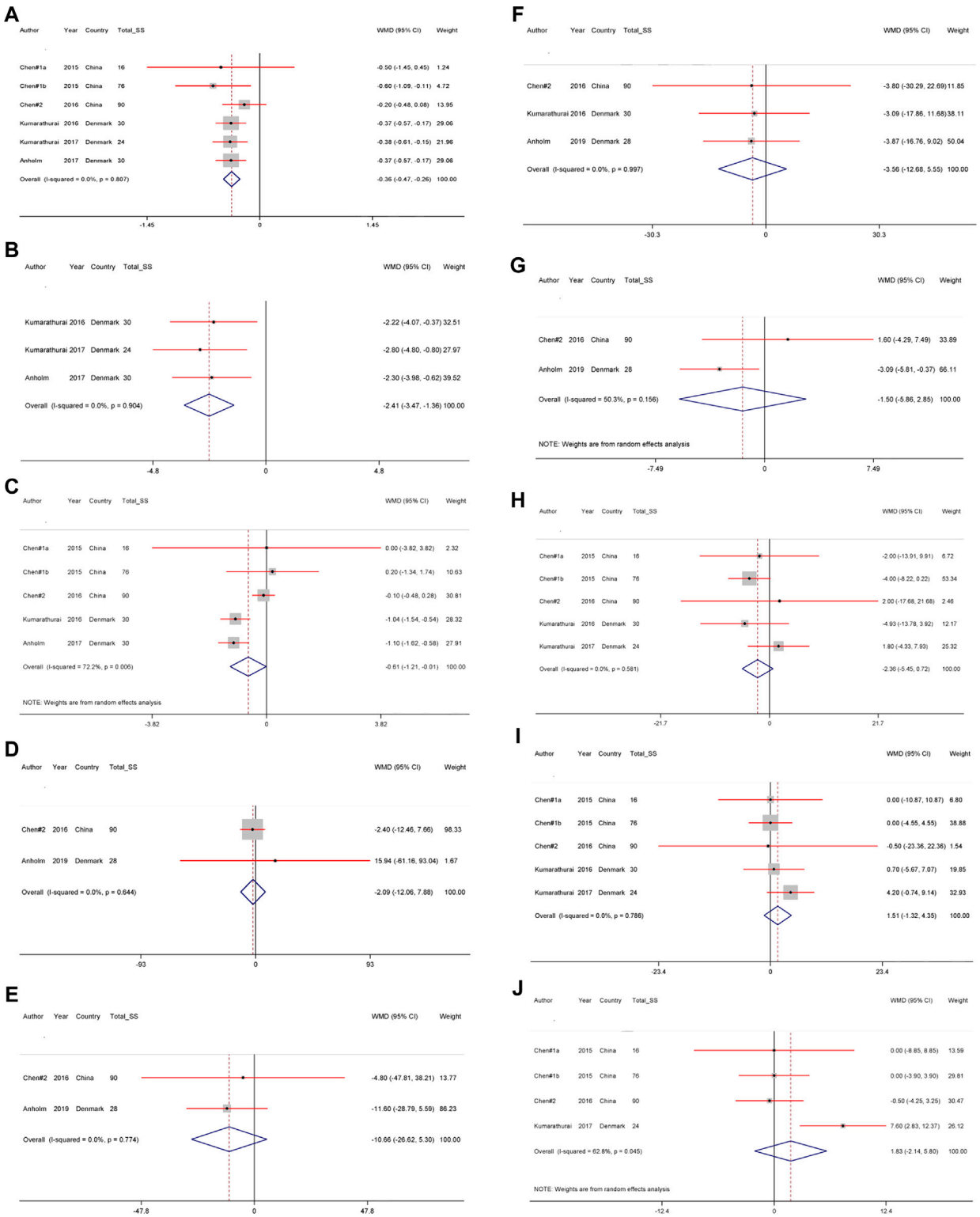

FIGURE 3 | A)–(J) The effect of liraglutide use on **(A)** hemoglobin A1c, **(B)** body mass index **(C)** waist circumference, **(D)** triglycerides **(E)** total-cholesterol, **(F)** low-density lipoprotein–cholesterol **(G)** high-density lipoprotein–cholesterol, **(H)** systolic blood pressure, **(I)** diastolic blood pressure and **(J)** Heart rate levels.

TABLE 2 | The effect of one by one trial in the association between liraglutide use and cardiometabolic profiles using sensitivity analysis.

Variable	Pre-sensitivity analysis			Upper and lower of effect size	Post-sensitivity analysis		
	No. of studies included	Pooled WMD	95% CI		Pooled WMD	95% CI	Excluded studies
HbA1C	6	−0.36	−0.47, −0.26	Upper	−0.34	−0.45, −0.24	Chen et al. (2015)
				Lower	−0.38	−0.50, −0.27	Chen et al. (2016)
BMI	5	−0.61	−1.21, −0.01	Upper	−0.41	−1.14, 0.30	Anholm et al. (2017)
				Lower	−0.99	−1.34, −0.64	Chen et al. (2016)
WC	3	−2.41	−3.47, −1.36	Upper	−2.26	−3.50, −1.01	Kumarathurai et al. (2017)
				Lower	−2.50	−3.79, −1.22	Kumarathurai et al. (2016)
SBP	5	−2.36	−5.45, 0.72	Upper	−0.49	−5.00, 4.02	Chen et al. (2015)
				Lower	−3.77	−7.34, −0.20	Kumarathurai et al. (2017)
DBP	5	1.51	−1.32, 4.35	Upper	2.47	−1.15, 6.10	Chen et al. (2015)
				Lower	0.19	−3.26, 3.65	Kumarathurai et al. (2017)
Heart rate	4	1.83	−2.14, 5.80	Upper	2.81	−2.74, 8.37	Chen et al. (2016)
				Lower	−0.23	−2.82, 2.34	Kumarathurai et al. (2017)
LDL-cholesterol	3	−3.56	−12.68, 5.55	Upper	−3.26	−16.16, 9.63	Anholm et al. (2019)
				Lower	−3.85	−15.44, 7.73	Kumarathurai et al. (2016)

Abbreviations: HbA1c, hemoglobin A1c; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TG, triglycerides; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein-cholesterol.

0.98, P_{Be} = 0.60). For traits assessed through meta-analysis with lower than three studies, it was impossible to assess the evidence of publication bias.

DISCUSSION

To our best knowledge, this is the first meta-analysis focused on RCTs that assessed the effect of liraglutide on various cardiometabolic traits in subjects with established CAD. To date, the cardioprotective mechanism of liraglutide has not been elucidated. The suggested conventional explanations are favorable improvements in cardiometabolic risk factors (HbA1c, body weight, SBP, and lipids) or direct action on heart and blood vessels as probable mechanisms (Nauck et al., 2017). Our meta-analysis of seven RCTs included 294 patients with established CAD and revealed that liraglutide treatment significantly decreases HbA1c levels and anthropometric measurements of BMI and WC. We also showed that the positive effect of liraglutide on BMI was more robust in CAD patients with T2D compared to those without.

Since, the CAD is more prevalent among older adults (Rodgers et al., 2019), our target population from the included RCTs, and subsequently study findings were narrowed down to the older population. There is a growing body of evidence suggesting that GLP1-RA may reduce mortality and cardiovascular outcomes, including fatal or non-fatal MI and stroke in T2D patients, beyond their beneficial effect on glycemic control (Kristensen et al., 2019). The LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial was the major RCT evaluating the efficacy and safety of liraglutide and revealed that T2D patients on liraglutide therapy had 13% lower MACE rates compared to placebo (Marso et al., 2016). The most recent LEADER post hoc analysis proves the efficacy of liraglutide treatment in patients with T2D and high risk of CVD, associated with a reduced risk of first and recurrence MACE (Verma et al., 2019). These cardio-protective effects of liraglutide might be derived from its effects on cardiometabolic traits that eventually influence cardiovascular events risk; however, the exact underlying mechanism remains uncertain. LEADER study may only reveal the potential beneficial effect of liraglutide in patients with T2D at high risk of CVD events, while our study included all RCTs performed in patients with known CAD, regardless of diabetes status.

Concerning the effect of liraglutide on glycemic traits, we found that in patients with liraglutide treatment compared to the placebo group, HbA1c levels decreased by approximately 0.36% with no significant difference between CAD subjects with and without T2D. This finding was concordant with 0.40% reduced HbA1c reported in the previous RCT among T2D patients (Marso et al., 2016).

Our finding showed BMI was reduced by 0.61 kg/m^2 in patients on liraglutide use compared to the placebo group. Moreover, in a subgroup analysis liraglutide significantly reduced BMI only in CAD patients with T2D. Liraglutide induces weight loss in obese non-diabetic patients by reduction of appetite and energy intake rather than the increase of energy expenditure (van Can et al., 2014). A recent meta-analysis indicates that liraglutide can be considered as an effective and safe treatment for obesity in non-diabetic individuals (Zhang et al., 2019). However, this effect is dose-dependent up to 3.0 mg once daily, with consistent therapy for at least 12 weeks (Zhang et al., 2019). This might explain our observation of a significant reduction in BMI only in CAD patients with T2D. However, we also think that the difference in RCTs' treatment duration from one week to a maximum of 12 weeks possibly impacted the potential effect on these markers over time. Our finding also suggests that liraglutide affects abdominal obesity, as estimated by WC, in which WC measures were reduced by 2.41 cm in the liraglutide group compared to the placebo group. This effect was consistent with a previous study demonstrating the beneficial effect of GLP1-RAs agents on

WC in T2D patients, especially in liraglutide users (Sun et al., 2015). It is well known that improvements in abdominal obesity and visceral fat accumulation are associated with reduced insulin resistance and a reduction in major cardiovascular risk factors (Ross and Janiszewski, 2008). Decreased BMI and WC by liraglutide partly explain the beneficial effect of liraglutide on CVD outcomes (Ross and Janiszewski, 2008). Our results showed no significant effect of liraglutide on heart rate, blood pressure, and lipid traits when compared with the placebo effects,which is discordant with previous studies conducted in T2D patients (Sun et al., 2015). These results might be due to the different responses of patients without diabetes to liraglutide treatment by different mechanisms such as attenuation of gastric lipid production or delayed gastric emptying rather than insulin resistance reduction in T2D patients (Hermansen et al., 2013; Madsbad, 2019).

This study has some limitations that should be acknowledged. First, our analysis was based on only six RCTs, including seven studies with a relatively small sample size ($n < 100$) in each trial and short follow-up; thus, caution should be applied while interpreting the results of our study. All of the studies included were performed among patients in two countries of Denmark and China. It is worth mentioning that the process of patient recruitment in two trials by Chen et al. (2015) and Chen et al. (2016) was performed in the hospital settings, while the remaining RCTs used the out-patients data with documented established CAD, according to their inclusion criteria (Kumarathurai et al., 2016; Anholm et al., 2017; Kumarathurai et al., 2017; Anholm et al., 2019). Hospital admitted patients in the acute phase of their CAD conditions might develop worse baseline health measurements and cardiometabolic profiles compared to stable out-patients. Therefore, long-term RCTs with a larger sample size in a more homogeneous target populations, within different ethnic backgrounds should be conducted to confirm our findings. Besides, as it can be argued that the inclusion of patients without diabetes with few major metabolic disorders might reduce the potential effect of liraglutide treatment, we suggest future RCTs in CAD patients with and without diabetes in separated groups.

CONCLUSION

Among the population with established coronary artery disease, liraglutide treatment compared with placebo was associated with improved glycemic control and anthropometric measurements, where the effect on BMI was more robust in patients with T2D compared to those without.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding or first author.

AUTHOR CONTRIBUTIONS

PN-S and RT contributed to conception. The databases were searched by MH-B. MS-B and FJ contributed significantly to screening and data collection; The data accuracy was checked by SR. All discrepancies among them were resolved through consensus or discussion with a third author (PN-S, RT, or FA). RT contributed significantly to data analysis, data interpretation and manuscript preparation. Author NS, RT, BS and MvH and FA contributed significantly to, data interpretation and manuscript preparation. FA contributed to supervising and final approval of the manuscript. All authors read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.618208/full#supplementary-material.

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Blood Pressure Changes Following Antihypertensive Medication Reduction, by Drug Class and Dose Chosen for Withdrawal: Exploratory Analysis of Data From the OPTiMISE Trial

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Aims: Deprescribing of antihypertensive drugs is recommended for some older patients with polypharmacy, but there is little evidence to inform which drug (or dose) should be withdrawn. This study used data from the OPTiMISE trial to examine whether short-term outcomes of deprescribing vary by drug class and dose of medication withdrawn.

Methods: The OPTiMISE trial included patients aged ≥80 years with controlled systolic blood pressure (SBP; <150 mmHg), receiving ≥2 antihypertensive medications. This study compared SBP control, mean change in SBP and frequency of adverse events after 12 weeks in participants stopping one medication vs. usual care, by drug class and equivalent dose of medication withdrawn. Equivalent dose was determined according to the defined daily dose (DDD) of each medication type. Drugs prescribed below the DDD were classed as low dose and those prescribed at ≥DDD were described as higher dose. Outcomes were examined by generalized linear mixed effects models.

Results: A total of 569 participants were randomized, aged 85 ± 3 years with controlled blood pressure (mean 130/69 mmHg). Within patients prescribed calcium channel blockers, higher dose medications were more commonly selected for withdrawal (90 vs. 10%). In those prescribed beta-blockers, low dose medications were more commonly chosen (87 vs. 13%). Withdrawal of calcium channel blockers was associated with an increase in SBP (5 mmHg, 95%CI 0–10 mmHg) and reduced SBP control (adjusted RR 0.89, 95%CI 0.80–0.998) compared to usual care. In contrast, withdrawal of beta-blockers was associated with no change in SBP (–4 mmHg, 95%CI –10 to 2 mmHg) and no difference in SBP control (adjusted RR 1.15, 95%CI 0.96–1.37). Similarly, withdrawal of higher dose medications was associated with an increase in SBP but no

change in BP control. Withdrawal of lower dose medications was not associated with a difference in SBP or SBP control. There was no association between withdrawal of specific drug classes and adverse events.

Conclusion: These exploratory data suggest withdrawal of higher dose calcium channel blockers should be avoided if the goal is to maintain BP control. However, low dose beta-blockers may be removed with little impact on blood pressure over 12-weeks of follow-up. Larger studies are needed to confirm these associations.

Keywords: deprescribing, older adults, hypertension, polypharmacy, Multi-morbidity, beta-blockers, calcium channel blockers, defined daily dose

INTRODUCTION

Antihypertensive treatment is effective at preventing stroke and cardiovascular disease in older high-risk patients with hypertension (Beckett et al., 2008; SPRINT Investigators et al., 2015; Thomopoulos et al., 2018) and many individuals aged 80 years or older are prescribed therapy (Sheppard et al., 2012). Such patients are also more likely to live with multiple long-term conditions (Barnett et al., 2012) leading to polypharmacy, which increases an individual's likelihood of hospitalization due to adverse events (Pirmohamed et al., 2004; Sato and Akazawa, 2013). It is unclear whether intensive blood pressure lowering is safe and effective in older patients with multi-morbidity and frailty. Previous trials have found that frailty has no modifying effect on the efficacy of blood pressure lowering in older patients (Warwick et al., 2015; Williamson et al., 2016), however, such trials may not have included very frail patients seen in the general population (Sheppard et al., 2020a; Sheppard et al., 2020b). In contrast, evidence from meta-analyses of randomized controlled trials (Bejan-Angoulvant et al., 2010; Thomopoulos et al., 2016) and observational studies (Tinetti et al., 2014; Benetos et al., 2015; Mansfield et al., 2016) suggests that aggressive lowering of systolic blood pressure (i.e. to less than 130 mm Hg) and multiple antihypertensive prescriptions may be harmful, particularly in older patients with polypharmacy and multi-morbidity (Tinetti et al., 2014; Thomopoulos et al., 2016).

Guidelines therefore recommend using clinical judgment when prescribing in frail older patients (National Heart Foundation of Australia, 2016; National Guideline Centre, 2019; Liu et al., 2020), emphasizing a personalized approach to care which might include attempts to improve quality of life through deprescribing (Benetos et al., 2016; National Guideline Centre, 2016). The Optimizing Treatment for MIld Systolic hypertension in the Elderly (OPTiMISE) trial (Sheppard et al., 2020c) examined a structured approach to antihypertensive medication reduction in older patients with multi-morbidity and controlled systolic hypertension, prescribed two or more antihypertensives. The overarching aim of the OPTiMISE trial was to reduce polypharmacy without blood pressure becoming uncontrolled. The trial showed that a strategy of medication reduction results in similar proportions of patients with controlled systolic blood pressure (<150 mm Hg) at 12 weeks when compared to continuing antihypertensives. No differences were observed in serious adverse events or quality of life, although systolic/diastolic blood pressure did increase modestly by 3/2 mm Hg in the medication reduction group (Sheppard et al., 2020c).

There is little evidence to guide antihypertensive deprescribing (Krishnaswami et al., 2019), and therefore physicians participating in the trial were instructed to decide which antihypertensive should be removed based on advice from a medication reduction algorithm (**Figure 1**). The present study aimed to examine whether this choice was associated with blood pressure changes and adverse events in the trial.

METHODS

Design

This was a post-hoc exploratory analysis of data from the OPTiMISE trial of antihypertensive medication reduction (Sheppard et al., 2020c). All participants randomized in the trial, who did not withdraw consent, were included in the analysis. The trial was approved by an NHS Research Ethics Committee (South Central - Oxford A; ref 16/SC/0628) and the Medicines and Healthcare products Regulatory Agency (MHRA; ref 21,584/0371/001-0001). All participants gave written informed consent. Details of patient recruitment and data collection are described in detail elsewhere (Sheppard et al., 2018; Sheppard et al., 2020c).

Study Population

Individuals were eligible if they were aged ≥80 years, with systolic blood pressure at baseline <150 mm Hg (based on the mean of the second and third readings taken, after 5 min of rest) and prescribed two or more antihypertensive treatments for at least 12 months. Recruiting primary care physicians were asked to only enroll patients whom in their opinion might potentially benefit from medication reduction due to existing polypharmacy, co-morbidity, non-adherence or dislike of medicines, and/or frailty. This clinical judgment was considered important given the current lack of evidence as to who should be targeted for such an intervention. Patients with a history of heart failure due to left ventricular dysfunction or myocardial infarction/stroke in the preceding 12 months, secondary hypertension or lacking in capacity to consent were excluded.

Potentially eligible patients were identified from searches of electronic health records in participating sites and sent letters of

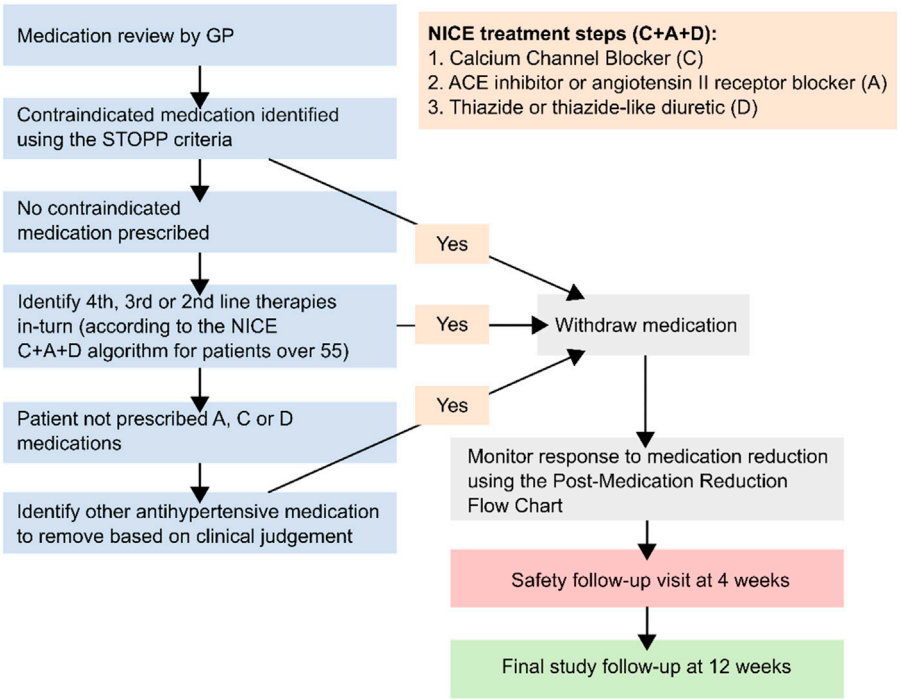

FIGURE 1 | Medication reduction algorithm given to general practitioners participating in the Optimize trial NICE = National Institute for Health and Care Excellence. Contraindicated medications described in the STOPP START criteria (Gallagher et al., 2008). Figure adapted from previous publications about this trial (Sheppard et al., 2018; Sheppard et al., 2020c).

invitation. Those expressing an interest attended a screening appointment.

Randomization and Blinding

Participants were allocated (1:1 allocation ratio) to one of the two study groups using a non-deterministic minimization algorithm, with minimization designed to balance site and baseline systolic blood pressure, via a fully validated, web-based, password protected system. Investigators and participants were unaware of the treatment allocation prior to consent and baseline assessments. The trial used an unblinded design with patients and investigators not masked to randomization group.

Medication Reduction Intervention

Participating primary care physicians reviewed each participant's medication regimen before randomization and decided which antihypertensive would be removed if they were allocated to medication reduction, using a pre-specified algorithm (**Figure 1**). This algorithm recommended reducing medications in reverse of the C + A + D NICE treatment algorithm. Following an adverse event possibly related to abrupt discontinuation of a beta-blocker, gradual withdrawal of these medications was encouraged to avoid rebound adrenergic hypersensitivity. For individuals randomized to medication reduction, physicians were asked to monitor blood pressure at a 4 week follow-up visit and reinstate treatment if it consistently rose above 150 (systolic) or 90 (diastolic) mm Hg, or in the case of adverse events or accelerated hypertension. Patients in the control group were given usual care and no medication changes were mandated.

Outcomes

Outcomes examined in this analysis were not pre-specified before the end of the trial and should be treated as exploratory. Outcomes included between group differences in systolic blood pressure control, adverse events and change in systolic and diastolic blood pressure at follow-up by drug class and dose of medication chosen for withdrawal. Adverse events were defined as any clinical event occurring during follow-up, regardless of whether it was deemed to be possibly, probably or definitely related to the intervention by the treating physician. Systolic and diastolic blood pressure were defined as the mean of the second and third consecutive readings taken at 1 min intervals. Measurements were taken in the seated position, using the clinically validated BpTRU blood pressure monitor (Mattu et al., 2004) after a period of 5 min of rest.

Definition of Subgroups

For each analysis by drug class, groups were determined according to drug classifications in the British National Formulary (BNF) (Royal Pharmaceutical Society, 2020). Equivalent dose of medication was determined by converting the doses of each drug chosen for withdrawal into a common unit of measure using the World Health Organisation (WHO) defined daily dose (DDD) for each medication type (World Health Organisation (WHO) Collaborating Centre for Drug Statistics

Methodology, 2020). For example, the DDD for Ramipril is 2.5 mg (World Health Organisation (WHO) Collaborating Centre for Drug Statistics Methodology, 2020), so if a drug was prescribed at 1.25 mg, it would be classified in the present analysis as having a medication equivalent dose of 0.5. For the purposes of these analyses, participants were divided into two groups according to the equivalent dose of medication chosen for withdrawal; low dose medications were those prescribed at less than the DDD (i.e. an equivalent medication dose of <1). Higher dose medications were those prescribed at the DDD or higher doses (i.e. an equivalent medication dose of ≥1).

Covariates

Data relating to participant demographics, body mass index, blood pressure, cognition (Montreal Cognitive Assessment [MoCA] Score) (Nasreddine et al., 2005), functional independence (modified Rankin score) (Sulter et al., 1999), frailty (electronic/Searle Frailty Index) (Searle et al., 2008; Clegg et al., 2016), past medical history and treatment prescriptions were collected at baseline via participant questionnaires and review of the electronic health record. Predictors of physician drug choice were selected to reflect trial guidance provided on medication reduction. This included the number of pre-existing medication prescriptions, concurrent morbidities, frailty (defined using the electronic frailty index) (Clegg et al., 2016), age, sex and systolic blood pressure at baseline. Multivariate models examining the association between medication withdrawal and outcomes were adjusted for factors found to be predictive of medication choice for withdrawal and missing follow-up data, including baseline systolic blood pressure, gender, MoCA score (Nasreddine et al., 2005), EQ-5D-5L Index (Herdman et al., 2011), Searle Frailty Index (Searle et al., 2008) and primary care site.

Statistical Analysis

Descriptive statistics were used to describe the study population, the proportion of participants maintaining medication reduction and the proportion experiencing no increase in systolic blood pressure in the intervention group at follow-up. These were estimated by drug class and dose of medication chosen for withdrawal. Since the choice of drug to withdraw was not fixed, but rather at the discretion for the treating physician, multivariable logistic regression was used to examine predictors of physician drug choice. Statistically significant predictors were included as factors for adjustment in the main analysis.

Data from participants examining outcomes of medication reduction by drug class and medication dose were analyzed according to the groups to which they were allocated (i.e. by intention to treat). The relative risk (RR) for blood pressure control and adverse events between groups were examined by drug class and medication dose chosen for withdrawal using a robust Poisson regression model. Each model was adjusted for baseline systolic blood pressure, covariates predictive of drug choice for medication withdrawal and those predictive of missing blood pressure data at follow-up (identified in the preparatory analyses). Since the treating physician's choice of medication to withdraw was made prior to consent and randomization, data were available for all randomized participants, even though only half went on to have the medication withdrawn. Therefore, models compared patients withdrawing specific drugs (the intervention group) to patients where the same drug was selected for withdrawal, but treatment was actually continued (usual care). Separate models were fitted according to the drug class and medication dose chosen for withdrawal. Adjusted mean difference in change in blood pressure was analyzed by means of generalized linear mixed model with binomial error and log link, with factors predictive of physician choice of drug to withdraw and baseline systolic blood pressure, gender, cognitive function (MoCA Score), EQ-5D-5L Index and Searle Frailty Index as fixed effects and primary care site as a random effect.

All data were analyzed using Stata statistical software (version 16.0, College Station TSL, StataCorp, 2019). Data are presented as means, medians and proportions with 95% confidence intervals (CI) unless otherwise stated.

RESULTS

A total 569 patients were recruited to the trial from 69 general practices in Central, Eastern and Southern England. The characteristics of participants in the trial were broadly comparable to those of a similar age group in the general population (**Supplementary Table S1**). Two hundred and eighty-two participants (49.6%) were randomized to the medication reduction intervention and 287 participants (50.4%) were randomized to usual care. A total of 534 (93.8%) participants attended 12-week follow-up and provided valid blood pressure readings. Participants were well matched for all variables at baseline, with a mean age of 85 years, multi-morbidity (mean 5.8 morbidities; 98.4% participants had ≥2 morbidities including hypertension) and polypharmacy (median four medications; **Table 1**). Mean blood pressure at baseline was 130/69 mm Hg and individuals were taking a median of 2 (IQR 2–3) antihypertensive medications.

The most commonly prescribed medications at baseline were calcium channel blockers (390 participants, 68.5%), ACE inhibitors (267 participants, 46.9%) and beta-blockers (228 participants, 40.1%). Calcium channel blockers were typically prescribed in combination with ACE inhibitors (180 participants, 31.6%), angiotensin II receptor blockers (136 participants, 23.9%) or beta-blockers (131 participants, 23.0%) (**Supplementary Table S2**). Thiazide and thiazide-like diuretics were the most common drug class chosen by physicians for medication reduction (168 participants, 29.6%; 76.4% of those prescribed thiazide and thiazide-like diuretics) (**Table 2**). There were no between group differences in the drug classes chosen for medication reduction. Higher dose calcium channel blockers, thiazides and thiazide-like diuretics were more commonly selected for withdrawal than lower dose medications within these classes (higher dose 90–91% vs. low dose 9–10%; **Table 3** and **Supplementary Table S3**). In contrast, low dose beta-blockers were more commonly chosen for withdrawal than higher dose beta-blockers (higher dose 13% vs. low dose 87%; **Table 3**).

Association Between Medication Reduction and Outcomes by Drug Class

After adjusting for factors predictive of drug choice for medication reduction (**Supplementary Table S4**), participants

TABLE 1 | Baseline demographics and clinical characteristics.

	Medication reduction group (*n* = 282)	Usual care group (*n* = 287)
Participant characteristics		
Age (years), mean (SD)	84.6 (3.3)	85.0 (3.5)
Sex (% female)	131 (46.5%)	145 (50.5%)
Body mass index (mean [SD]; kg/m^2) (n = 534)	27.2 (4.2)	28.0 (4.3)
Ethnicity (% white)	278 (98.6%)	278 (96.9%)
Current smoker (%)	3 (1.1%)	5 (1.7%)
Alcohol consumption (% reporting drinking alcohol every week)	98 (34.8%)	108 (37.6%)
Montreal cognitive assessment score[a] (mean [SD]) (n = 562)	24.4 (3.6)	24.0 (4.1)
EQ-5d-5L index[b] (mean [SD]) (n = 563)	0.78 (0.17)	0.76 (0.17)
Modified rankin scale[c] (% score >2 [dependant]) (n = 540)	36 (12.8%)	42 (14.6%)
Electronic frailty index (eFI),[d] mean (SD)	0.14 (0.07)	0.15 (0.07)
Fit (eFI 0–0.12; %)	121 (42.9%)	109 (38.0%)
Mild (eFI >0.12–0.24; %)	132 (46.8%)	143 (49.8%)
Moderate (eFI >0.24–0.36; %)	27 (9.6%)	32 (11.1%)
Severe (eFI >0.36; %)	2 (0.7%)	3 (1.0%)
Systolic blood pressure (mmHg), mean (SD)	129.4 (13.1)	130.5 (12.3)
Diastolic blood pressure (mmHg), mean (SD)	68.4 (9.1)	70.1 (8.4)
Orthostatic hypotension (%), (*n* = 525)[e]	15 (5.7%)	10 (3.8%)
Medical history		
Chronic kidney disease (%)	83 (29.4%)	103 (35.9%)
Cancer (%)	67 (23.8%)	68 (23.7%)
Cardiac disease (%)[f]	61 (21.6%)	61 (21.3%)
Diabetes (%)	48 (17.0%)	53 (18.5%)
Atrial fibrillation (%)	45 (16.0%)	45 (15.7%)
Transient ischemic attack (%)	27 (9.6%)	22 (7.7%)
Stroke (%)	23 (8.2%)	22 (7.7%)
Peripheral vascular disease (%)	6 (2.1%)	9 (3.1%)
Number of morbidities, mean (SD)	5.7 (2.7)	6.0 (2.9)
% ≥2 morbidities (%)	278 (98.6%)	282 (98.3%)
Medication prescriptions		
Antihypertensive (%)[g]	282 (100.0%)	287 (100.0%)
ACE inhibitor (%)	139 (49.3%)	128 (44.8%)
Angiotensin II receptor blocker (%)	99 (35.2%)	115 (40.1%)
Calcium channel blockers (%)	199 (70.6%)	191 (66.6%)
Thiazide and related diuretics (%)	109 (38.7%)	111 (38.7%)
Beta-blockers (%)	112 (39.7%)	116 (40.4%)
Alpha-blockers (%)	41 (14.5%)	39 (13.6%)
Other antihypertensives (%)	19 (6.7%)	35 (12.3%)
Statin (%)	97 (34.4%)	92 (32.1%)
Antiplatelet (%)	58 (20.6%)	53 (18.5%)
Total prescribed medications, median (IQR)	4 (3–7)	4 (3–7)

[a]*Score ranges between 0 and 30 with lower scores representing greater impairment. A score of 26 and over is considered to be normal.*
[b]*The EQ-5D-5L assesses five aspects of health: mobility, self-care, activities, discomfort, and anxiety/depression. EQ-5D-5L index scores were generated using crosswalk approach which translates the scores for the five EQ-5D-5L items into a single index value. The index value ranges from -0.594 (worse than death) to 1 (full health).*
[c]*Modified Rankin scale ranges from 0 (no symptoms) to 5 (severe disability).*
[d]*The Electronic Frailty Index has 36 items and is estimated from electronic health records. The index ranges from 0 (fit) to 1 (frail).*
[e]*Orthostatic hypotension defined as a decrease in systolic blood pressure of at least 20 mm Hg within 3 min of standing.*
[f]*Cardiac disease defined as the presence of myocardial infarction, coronary heart disease, angina or heart failure.*
[g]*The sum of percentages for all antihypertensive medication classes may exceed 100%, since participants had to be taking more than one antihypertensive medication to be eligible for the trial.*
SD = standard deviation.

were less likely to have controlled systolic blood pressure at follow-up if reducing calcium channel blockers (adjusted RR 0.89 95% CI 0.80–0.998) (**Figure 2**). Withdrawal of calcium channel blockers was also associated with an increase in systolic and diastolic blood pressure (4.7 mm Hg, 95% CI −0.3–9.7 mm Hg [systolic]; 4.3 mm Hg, 95% CI 1.3–7.3 mm Hg [diastolic]) (**Figure 3**). Withdrawal of beta-blockers was associated with a non-significant reduction in systolic blood pressure (−4.0 mmHg, 95% CI −9.8 to 1.8 mmHg). There was no association between withdrawal of specific drug classes and adverse events (e.g. increased blood pressure, chest pain, infections, ankle swelling, headache and back pain, etc.).

TABLE 2 | Total proportion of medications prescribed and selected for medication reduction by randomized group.

Drug class	Medications prescribed			Medications selected for withdrawal			
	Total (%)	Intervention (%)	Control (%)	Total (%)	Proportion of total prescribed (%)	Intervention (withdrawal attempted) (%)	Control (withdrawal not attempted) (%)
Calcium channel blocker	390 (68.5%)	199 (70.6%)	191 (66.6%)	131 (23.1%)	33.6	64 (22.8%)	67 (23.4%)
ACE inhibitor	267 (47.0%)	139 (49.3%)	128 (44.8%)	68 (12.0%)	25.5	34 (12.1%)	34 (11.9%)
Angiotensin II receptor blocker	214 (37.7%)	99 (35.2%)	115 (40.1%)	55 (9.7%)	25.7	27 (9.6%)	28 (9.8%)
Thiazide or thiazide-like diuretic	220 (38.8%)	109 (38.8%)	111 (38.8%)	168 (29.6%)	76.4	88 (31.3%)	80 (27.8%)
Beta-blocker	228 (40.1%)	112 (39.7%)	116 (40.6%)	77 (13.6%)	33.8	36 (12.8%)	41 (14.3%)
Alpha-blocker	80 (14.1%)	41 (14.5%)	39 (13.6%)	43 (7.6%)	53.8	22 (7.8%)	21 (7.3%)
Other antihypertensive	54 (9.5%)	19 (6.7%)	35 (12.2%)	25 (4.4%)	46.3	10 (3.6%)	15 (5.2%)

ACE = angiotensin converting enzyme.

TABLE 3 | Antihypertensive medications chosen for withdrawal at baseline by drug class and medication dose.

Drug	Low dose medication withdrawal subgroup (<DDD)			Higher dose medication withdrawal subgroup (≥DDD)		
	Total (%)	Intervention (withdrawal attempted) (%)	Control (withdrawal not attempted) (%)	Total (%)	Intervention (withdrawal attempted) (%)	Control (withdrawal not attempted) (%)
Calcium channel blockers	13 (9.9%)	9 (6.9%)	4 (3.1%)	118 (90.1%)	55 (42.0%)	63 (48.1%)
ACE inhibitors	18 (26.5%)	11 (16.2%)	7 (10.3%)	50 (73.5%)	23 (33.8%)	27 (39.7%)
Angiotensin II receptor blockers	18 (32.7%)	6 (10.9%)	12 (21.8%)	37 (67.3%)	21 (38.2%)	16 (29.1%)
Thiazide and thiazide-like diuretics	15 (9.1%)	11 (6.7%)	4 (2.4%)	149 (90.9%)	74 (45.1%)	75 (45.7%)
Beta-blockers	66 (86.8%)	29 (38.2%)	37 (48.7%)	10 (13.2%)	6 (7.9%)	4 (5.3%)
Alpha-blockers	19 (44.2%)	10 (23.3%)	9 (20.9%)	24 (55.8%)	12 (27.9%)	12 (27.9%)
Other antihypertensives	22 (73.3%)	7 (23.3%)	15 (50.0%)	8 (26.7%)	4 (13.3%)	4 (13.3%)

ACE = angiotensin converting enzyme; DDD = defined daily dose.

Association Between Medication Reduction and Outcomes by Medication Dose

Withdrawal of higher dose medications was associated with an increase in systolic and diastolic blood pressure (4.7 mm Hg, 95% CI 1.8–7.5 mm Hg [systolic]; 2.4 mm Hg, 95% CI 0.7–4.0 mm Hg [diastolic]) but no difference in blood pressure control (adjusted RR 0.98 95% CI 0.92–1.46) (**Figure 4**). Withdrawal of low dose medications was not associated with any difference in systolic blood pressure (–0.5 mm Hg, 95% CI –5.0 to 4.1 mmHg) or blood pressure control (adjusted RR 1.00 95% CI 0.89–1.13) between groups. However, withdrawal of low dose medications was associated with an increased risk of adverse events (adjusted RR 1.56 95% CI 1.14–2.14).

Maintenance of Medication Reduction

All 282 patients randomized to the intervention arm of the trial attempted to withdraw the medication chosen by their primary care physician. Overall, 91 (32.4%) had their medication reintroduced and 101 (35.9%) experienced no increase in systolic blood pressure at 12 weeks follow-up (**Supplementary Table S5**). The highest proportion of participants maintaining medication reduction and experiencing no increase in systolic blood pressure were those reducing ACE inhibitors (79.4 and 44.1% respectively) and beta-blockers (80.6 and 55.6% respectively). There was no difference in the proportion maintaining medication reduction between those withdrawing higher dose medications and those withdrawing low dose medications (higher dose 66.3% vs. low dose 70.4%).

DISCUSSION

The OPTiMISE trial (Sheppard et al., 2020c) found that one antihypertensive medication could be withdrawn in the majority of participants without substantial change in blood pressure control at 12 weeks follow-up. This post-hoc exploratory analysis found some evidence to suggest that beta-blockers in particular, especially those prescribed at low doses, may be withdrawn with little or no increase in blood pressure. This makes them a potential target for deprescribing in older patients with no other compelling indication for therapy. Withdrawal of higher dose calcium channel blockers was associated with a reduced likelihood of blood pressure control at follow-up, despite these medications being less likely to be selected for medication reduction in participants with higher

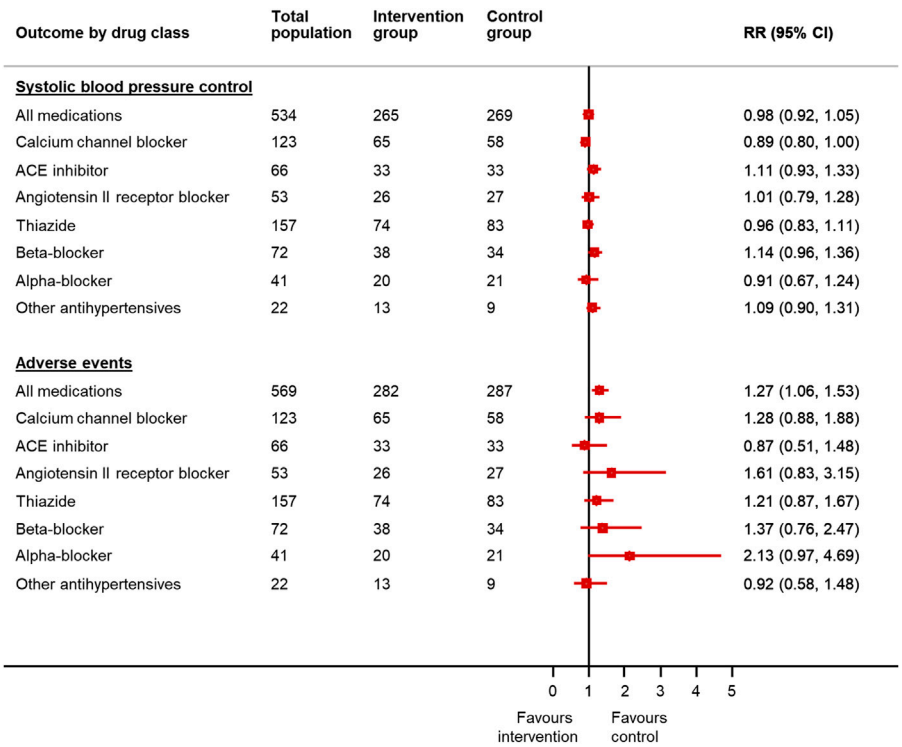

FIGURE 2 | Relative risk of blood pressure control and adverse events in patients reducing antihypertensive medication compared to usual care, by drug class chosen for withdrawal*. *Since the treating physician's choice of medication to withdraw was made prior to consent and randomization, data were available for all randomized participants, even though only half went on to have the medication withdrawn in the trial. RR = relative risk; CI = confidence interval. Generalized linear mixed model with binomial error and log link, with factors predictive of physician choice of drug to withdraw (see **Table 2**) and baseline systolic blood pressure, gender, cognitive function (MoCA Score), EQ-5D-5L Index and Searle Frailty Index as fixed effects.

baseline blood pressures. This supports recommendations for the use of calcium channel blockers as a first line therapy for hypertension in older patients and suggests these might be avoided as a target for deprescribing. These analyses were exploratory in nature and further larger, appropriately powered studies are needed to confirm these findings in older patients with multi-morbidity and polypharmacy.

Strengths and Limitations

This is the first analysis of medication reduction by antihypertensive drug class and medication dose using data from a randomized controlled trial (Sheppard et al., 2020c). The trial was successful in recruiting a mildly frail population with multi-morbidity and polypharmacy, representative of older patients attending primary care in England. This was a post-hoc, exploratory analysis, which may have been underpowered to show definitive associations between drug classes, particularly for alpha-blockers and 'other' antihypertensives that were chosen for withdrawal in less than 50 trial participants. Since multiple statistical analyses were conducted, the significant associations between withdrawal of calcium channel blockers, higher dose medications and blood pressure at follow-up may have been observed by chance and so these results should be interpreted with caution.

Although follow-up was achieved in 93.8% of participants, the period of follow-up was short, and so it was not possible to examine clinical endpoints such as hospitalization, cardiovascular disease or death at this stage, though the cohort will be followed up. In addition, although routine prescription of beta-blockers is often accompanied by monitoring of heart rate, we did not collect this or related outcomes (e.g. development of atrial fibrillation) during follow-up, precluding any analyses of these outcomes.

Comparison With Previous Literature

Previous trials of antihypertensive medication reduction have only attempted medication reduction in up to two thirds of participants (Moonen et al., 2015; Gulla et al., 2018; Luymes et al., 2018), had smaller sample sizes (Moonen et al., 2015; Gulla et al., 2018), examined younger populations (i.e. aged less than 80 years) (Luymes et al., 2018) and lacked comparisons with a control group to determine the effect of deprescribing on outcomes (Gulla et al., 2018). This is the first analysis of any previous trial examining deprescribing by drug class and medication dose, providing preliminary data which should be explored in future appropriately powered studies. This might involve attempting to pool data from previous trials (Moonen et al., 2015; Gulla et al., 2018; Luymes et al., 2018) to increase the power to detect effects.

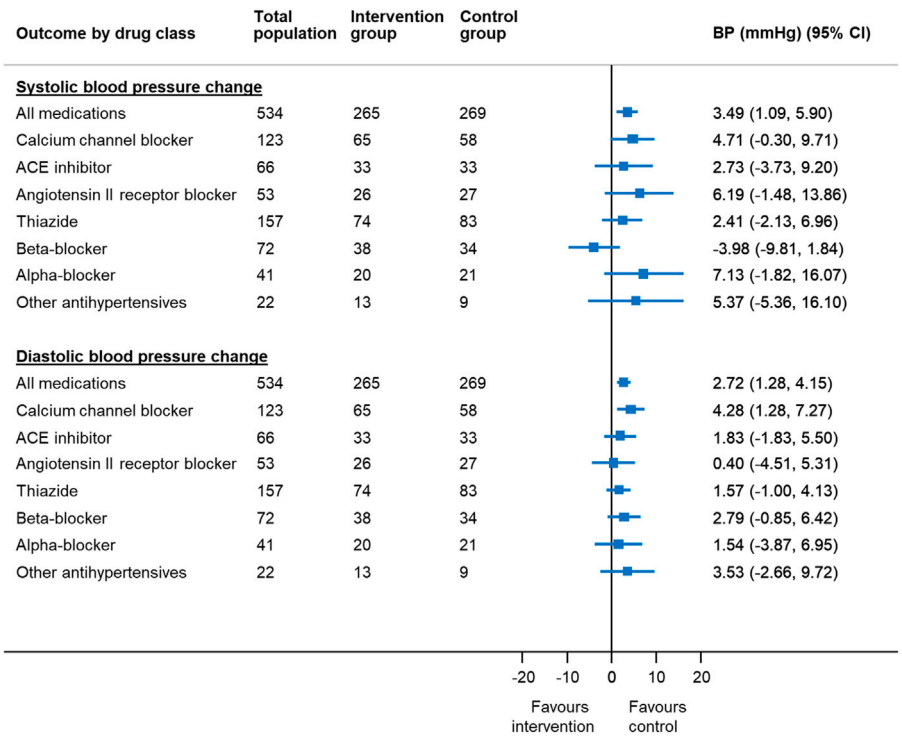

FIGURE 3 | Mean change in blood pressure in patients reducing antihypertensive medication compared to usual care, by drug class chosen for withdrawal* *Since the treating physician's choice of medication to withdraw was made prior to consent and randomization, data were available for all randomized participants, even though only half went on to have the medication withdrawn in the trial. BP = blood pressure; CI = confidence interval Generalized linear mixed model with binomial error and log link, with factors predictive of physician choice of drug to withdraw (see **Table 2**) and baseline systolic blood pressure, gender, cognitive function (MoCA Score), EQ-5D-5L Index and Searle Frailty Index as fixed effects and primary care site as a random effect.

Implications for Clinical Practice

Physicians participating in the OPTiMISE trial (Sheppard et al., 2020c) were given the freedom to choose which medication should be withdrawn if participants were randomized to the intervention arm of the trial. Advice was given in the form of a medication reduction algorithm which recommended reducing medications in reverse of the C + A + D NICE treatment algorithm (National Guideline Centre, 2019) i.e.; if a participant was prescribed three antihypertensive medications including a thiazide or thiazide-like diuretic, this was recommended to be removed instead of a renin-angiotensin system medication or a calcium channel blocker. In the present analysis, 3 out of 4 patients prescribed a thiazide and thiazide-like diuretic had this medication chosen for withdrawal and increasing number of antihypertensive medications prescribed was one of the strongest predictors of this choice, suggesting that the medication reduction algorithm was followed as suggested.

Calcium channel blockers were less likely to be chosen for medication reduction in patients with higher baseline systolic blood pressure and despite this, withdrawal of these medications was associated with a higher likelihood of uncontrolled blood pressure at follow-up. One explanation for this might be that these medications were predominantly prescribed at higher doses, where the blood pressure lowering effect might be expected to be greater. There is also evidence to suggest that calcium channel blockers are more effective in older individuals, leading to recommendations in clinical guidelines that these should be used as a first line therapy (Williams et al., 2018; National Guideline Centre, 2019). These findings reinforce recommendations in the medication withdrawal algorithm used in the trial, which suggested that these medications should be considered last for medication withdrawal.

The proportion of patients prescribed beta-blockers at baseline was relatively high, particularly since patients with a history of heart failure due to left ventricular dysfunction were excluded (Sheppard et al., 2018). Given that many participants had been diagnosed with hypertension for many years, it is possible that beta-blockers were originally prescribed at a time when they were recommended as a first line treatment for hypertension (Williams et al., 2004). Although subsequent guidelines have changed this recommendation (Mayor, 2006), many patients could have remained on the same treatment as originally prescribed.

These data show that a high proportion of patients withdrawing beta-blockers maintained medication reduction at follow-up and that withdrawal of such medications may be associated with no change or even a reduction in systolic blood pressure. Beta-blockers were more likely to be prescribed at lower doses for patients enrolled into the trial, and selected for medication reduction if participants were prescribed a higher number of

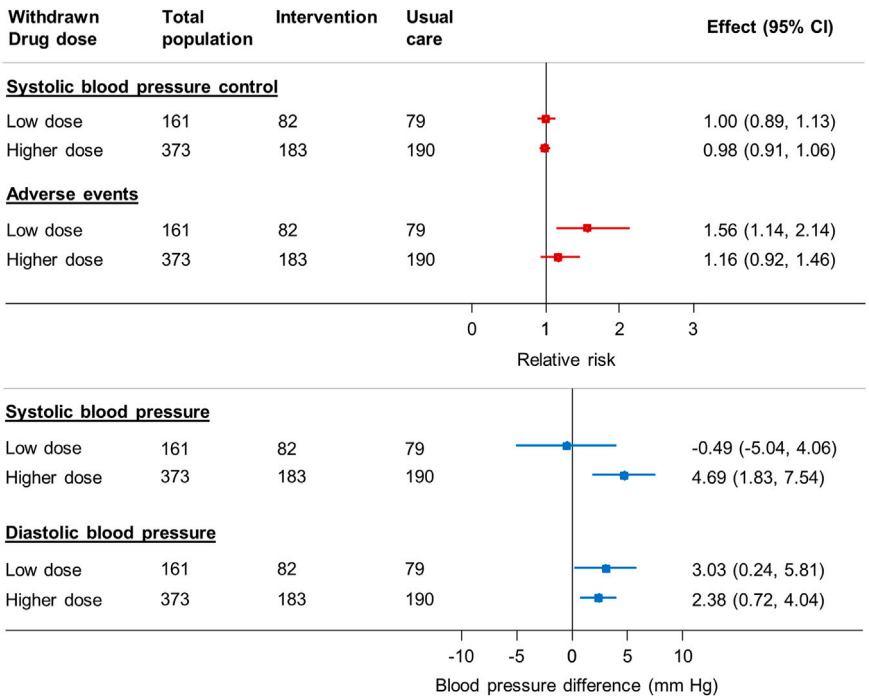

FIGURE 4 | Relative risk of blood pressure control, adverse events and mean change in blood pressure in patients reducing antihypertensive medication compared to usual care, by dose of medication chosen for withdrawal* *Since the treating physician's choice of medication to withdraw was made prior to consent and randomization, data were available for all randomized participants, even though only half went on to have the medication withdrawn in the trial. BP = blood pressure; CI = confidence interval Generalized linear mixed model with binomial error and log link, with factors predictive of physician choice of drug to withdraw (see table two) and baseline systolic blood pressure, gender, cognitive function (MoCA Score), EQ-5D-5L Index and Searle Frailty Index as fixed effects and primary care site as a random effect.

antihypertensive medications at baseline. Since polypharmacy is associated with reduced adherence to medications (Smaje et al., 2018), it is possible that withdrawal of beta-blockers may have increased an individual's adherence to their remaining medications causing blood pressure to be reduced at follow-up, although one might expect this to also be the case for withdrawal of any medication in patients taking multiple antihypertensives.

While withdrawing low-dose beta-blockers with no resulting increase in blood pressure maybe an appealing strategy for physicians, it is important to note that beta-blockers have other cardio-protective properties and may be indicated for other reasons beyond hypertension, such as ischemic heart disease, tachycardia and heart failure with reduced ejection fraction. There was also some evidence to suggest that withdrawal of low dose medications resulted in an increase in adverse events, although these varied widely in terms of severity (e.g. increased blood pressure, chest pain, infections, ankle swelling, headache and back pain). Only 23 participants (13 in the medication reduction group and 10 in the usual care group) experienced a serious adverse event resulting in hospitalization during the trial (Sheppard et al., 2020c). Until studies with long-term follow-up are conducted, it is difficult to draw firm conclusions regarding the choice of medication to withdraw first as part of a deprescribing intervention.

CONCLUSION

This exploratory analysis found some evidence to suggest that withdrawal of higher dose calcium channel blockers should be avoided if the goal is to maintain blood pressure control. However, low dose beta-blockers may be removed with little impact on blood pressure at follow-up. More appropriately powered studies are needed to determine whether withdrawal of certain drug classes and/or doses are preferable over others in older patients with multi-morbidity and polypharmacy.

OPTIMISE INVESTIGATORS

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DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion 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 South Central-Oxford A (ref 16/SC/0628). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JS and RM conceived, designed and secured funding for the study with JB, ML, GF, FH, PL, JM and RP. JS undertook the analysis and wrote the first draft. All authors reviewed and edited the manuscript. JS and RM are co-chief investigators and will act as guarantors for this work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.619088/full#supplementary-material.

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OPINION
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Implementing Clinical Decision Support Tools and Pharmacovigilance to Reduce the Use of Potentially Harmful Medications and Health Care Costs in Adults With Heart Failure

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Heart failure (HF) is associated with significant morbidity, mortality, compromised quality of life and socioeconomic burden worldwide. This chronic condition is becoming an increasingly important concern given the increased prevalence of HF among aging populations. Significant contributors toward escalating health care costs are emergency room visits and hospitalizations associated with HF. An important strategy to improve health care outcomes and reduce unnecessary costs is to identify and reduce the prescribing of potentially harmful medications (PHMs) among adults with HF. Previous studies in patients with HF found roughly 10–50% of them were prescribed at least one PHM in ambulatory care and inpatient health care settings. This opinion highlights recent findings from studies assessing prevalence of PHMs, associations between PHM prescribing and characteristics, and what can be done to improve patient outcomes and reduce the use of PHMs and associated health care costs in adults with HF.

Keywords: heart failure, potentially harmful medication, health care utilization, clinical decision support systems, medication therapy management, pharmacovigilance

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INTRODUCTION

Heart failure (HF) is associated with compromised quality of life, and significant morbidity, mortality, and socioeconomic burden worldwide. It is estimated that up to 7% of the population in some industrialized countries is diagnosed with HF (Savarese and Lund, 2017). A systematic review reported annual per patient cost of care ranged from $868 to $25,532 depending on the country (Lesyuk et al., 2018). Inpatient treatment of heart failure is estimated to comprise 44–96% of the overall cost of treatment (Lesyuk et al., 2018). Two-thirds of patients with HF experienced a rehospitalization within the first year hospital discharge in the US (Curtis et al., 2008). Reducing avoidable exacerbations of HF and optimizing medication regimens are necessary to mitigate avoidable health care utilization.

It is estimated that patients with HF utilize 7 prescriptions daily in addition to over-the-counter medications and supplements (Masoudi et al., 2005). Furthermore, one in two patients following a HF-related hospitalization utilized more than 10 prescriptions chronically (Unlu et al., 2019). It is estimated that 82% of patients using more than 7 medications may experience a significant drug-drug interaction (Goldberg et al., 1996). Additionally, medication related treatment failure and new medical problems may cost the US approximately $528.4 billion annually (Watanabe et al., 2018).

Medication related problems such as drug-drug interactions, drug-disease interactions, and suboptimal dosing of medications can occur in fragmented health care systems where patients utilize multiple health care providers. This is problematic among patients with HF in whom worsening disease control can quickly lead to avoidable emergency department (ED) visits and hospitalizations.

The American Heart Association (AHA) and the European Society of Cardiology (ESC) published statements detailing a list of potentially harmful medications (PHMs) known to exacerbate or cause HF and included a detailed description of their quality of evidence (Page et al., 2016; El Hadidi et al., 2020). Additionally, heart failure management guidelines published by the AHA in collaboration with the American College of Cardiology and the Heart Failure Society of America (Yancy et al., 2017), the ESC (Ponikowski et al., 2016), the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand (Atherton et al., 2018), and the Japanese Circulation Society in collaboration with the Japanese Heart Failure Society (Tsutsui et al., 2019) identified certain medications that should be avoided among patients with HF. Despite these publications, little has been done to reduce prescribing of these medications among patients with HF through a systematic approach. Recent research has demonstrated that dedicated clinical decision support systems (CDSS) can improve guideline directed prescribing for the treatment of HF in ambulatory care settings (McKie et al., 2020) and electronic engagement of patients can also positively improve prescribing (Allen et al., 2021). However, a review by Kao et al. (Kao et al., 2020) reported on the need for greater innovation within electronic health records (EHRs), such as triggered alerts within a CDSS to reduce prescribing of PHMs for optimal management of patients with HF. This opinion reviewed evidence describing the prevalence of PHM prescribing among patients with HF and has suggested strategies about how health care systems can reduce prescribing of PHMs through triggered alerts within a CDSS and pharmacovigilance programs to reduce medication burden, and potentially avoidable health care utilization.

POTENTIALLY HARMFUL MEDICATION PRESCRIBING

Since the publication of the AHA scientific statement, several studies have examined the prescribing of PHM among adults. Presently, the analysis of PHM prescribing among patients with HF can be divided into three settings: hospitalizations (Caughey et al., 2019; Alvarez et al., 2020; Goyal et al., 2020) administrative claims, (Alvarez et al., 2019; Silva Almodóvar and Nahata, 2020) and within an outpatient clinic (Brinker et al., 2020). These studies in large part assessed PHMs among patients in the United States (US) (Alvarez et al., 2019; Alvarez et al., 2020; Brinker et al., 2020; Goyal et al., 2020; Silva Almodóvar and Nahata, 2020) while one study assessed PHM prescribing in Australia (Caughey et al., 2019). Complete information on the studies assessed in this opinion can be found in **Table 1**.

Goyal et al. (Goyal et al., 2020) assessed the prescribing of PHMs among older adults participating in a nationally representative cohort before and after a HF-related hospitalization. This study found 41% of individuals hospitalized for HF were using a PHM (Goyal et al., 2020). Upon discharge, 36% of patients still utilized a PHM. Alvarez et al. (Alvarez et al., 2020) conducted a similar analysis among Medicare patients with reduced ejection fraction HF (HFrEF) at 90 and 365 days after discharge from a HF-related hospitalization. This study found 12% of patients were with PHM at 90 days after a HF-related hospitalization and the prevalence increased to 19% at 1 year (Alvarez et al., 2020). It is important to note this study limited their identification of PHMs to medications mentioned in the 2013 ACC/AHA HF guideline potentially resulting in an underestimation of PHM prescribing (Alvarez et al., 2020).

Caughey et al. (Caughey et al., 2019) assessed PHM prescribing at 120 days before and after a HF-related hospitalization utilizing an Australian Department of Veteran Affairs claims database. Authors found almost 60% of their cohort were prescribed PHMs at 120 days prior to a HF-related hospitalization while 56% continued to be prescribed a PHM after 120 days (Caughey et al., 2019). The most common medications identified as PHMs in these studies included albuterol, metformin, non-dihydropyridine calcium channel blockers (CCBs), tricyclic antidepressants, systemic corticosteroids, and tamsulosin (Caughey et al., 2019; Alvarez et al., 2020; Goyal et al., 2020). These medications have been associated with an increased risk of hospitalization, increased (ED) visits, or exacerbation or precipitation of HF (Page et al., 2016).

Two studies assessed PHM prescribing by analyzing administrative claims data (Alvarez et al., 2019; Silva Almodóvar and Nahata, 2020). Alvarez et al. (Alvarez et al., 2019) found 24% of adults under 65 years of age with HFrEF were prescribed a PHM (Alvarez et al., 2019). A separate study using claims for one Medicare insurance plan assessed patients with HF who were enrolled in Medicare and eligible for Medication Therapy Management (MTM) services (Silva Almodóvar and Nahata, 2020). This study assessed medication prescribing in a Medicare cohort with significant comorbidity burden which was at greater risk for drug-drug and drug-disease interactions (Silva Almodóvar and Nahata, 2020). This study found 53% of patients were prescribed a PHM (Silva Almodóvar and Nahata, 2020). These studies may have underestimated the prevalence of PHM in their populations given they limited their PHMs to only medications with evidence derived from randomized clinical trials, meta-analyses, single randomized trials, or nonrandomized studies (Alvarez et al., 2019; Silva Almodóvar and Nahata, 2020). The most common PHMs prescribed in these studies were NSAIDs, nondihydropyridine CCBs, dipeptidyl peptidase-4 inhibitors (DPP4i), citalopram, specific antiarrhythmics, and thiazolidinediones (Alvarez et al., 2019; Silva Almodóvar and Nahata, 2020). In addition to the previously mentioned medications, use of NSAIDs, DPP4is, citalopram, antiarrhythmics, and thiazolidinediones among patients with HF may lead to a potentially avoidable hospitalization or ED visit (Page et al., 2016).

TABLE 1 | Summary of studies reporting potentially harmful medication prescribing in patients with heart failure.

Study Authors (publication year)	Setting (study year/s)	Inclusion Criteria	Exclusion Criteria	Rule set utilized and applied in the study	Number of patients assessed (count, % with PHM)	Characteristics associated with PHM[a] (OR, 95% CI)	Most common medications reported as PHM[b] (n, %)
Goyal et al. (2020)	Inpatient Hospitalization during REGARDS study enrollment in the US (2003–2014)	Medicare Part A enrollment for 90 days following hospitalization, ≥65 years of age, participant of REGARDS study, hospitalized for HF	Hospice referral at discharge from hospital, without medication data at hospital admission or discharge	2016 AHA Scientific Statement Drugs That May Cause or Exacerbate heart failure (medications limited to those as having potentially life-threatening effects that could lead to a hospitalization or emergencydepartment visit)	558 (228, 41%)	Logistic regression assessing association with PHM prescribing after discharge: diabetes (1.80, 1.18–2.75) small hospital size (1.93, 1.18–3.16)	At hospital admission: Albuterol (92, 16%) Metformin (55, 10%) NSAIDS (50, 9%) Diltiazem (39, 7%) Thiazolidinediones (35, 6%) At hospital discharge: Albuterol (123, 22%) Metformin (41, 7%) NSAIDS (18, 3%) Diltiazem (42, 8%) Thiazolidinediones (20, 4%)
Alvarez et al. (2020)	90 days post discharge from hospitalization identified from CMS data files of a nationally representative 5% Medicare sample in the US (2013–2016)	Medicare enrollment, ≥66 years of age, HF discharge between April 2014–September 2016, with primary diagnosis of HFrEF, enrolled in Medicare Part D at hospital discharge, filled a prescription for an ACEi, ARB, or ARNi, and an HF-specific beta-blocker (metoprolol succinate, bisoprolol, or carvedilol) within 90 days from discharge	Not enrolled in Medicare Part D, diagnosis of metastatic cancer or malignant tumor, ESRD, death during the index hospitalization, not discharged home or left hospital against medical advice	2013 ACC/AHA HF guidelines: NSAIDs (diclofenac, ibuprofen, naproxen, meloxicam, indomethacin, celecoxib, ketorolac, etodolac, nabumetone, diflunisal, fenoprofen, flurbiprofen, ketoprofen, mefenamic oxaprozin, piroxicam, tolmetin), thiazolidinediones (pioglitazone and rosiglitazone), antiarrhythmics (flecainide, dronedarone), and non-dihydropyridine CCBs (diltiazem, verapamil)	90 days post discharge 8993 (1077, 12%) 365 days post discharge (1721, 19.14%)	Multivariate regression assessing association with PHM prescribing after discharge: Female (1.25, 1.08–1.46) Hispanic (1.49, 1.18–1.88) Severe Obesity (1.38, 1.10–1.74) Atrial Fibrillation (1.37, 1.18–1.59) Diabetes (1.37, 1.18–1.59) Chronic Lung Disease (1.44, 1.24–1.68) Pre-hospitalization PHD Exposure (14.99, 12.94–17.36) Ischemic heart disease (0.77, 0.66–0.90) Implantable Cardioverter Defibrillator (0.80, 0.63–0.999) Renal Failure (0.78, 0.67–0.93)	90 days post discharge NSAIDs (610, 6.7%) CCBs (426, 474%) 365 days post discharge NSAIDs (1185, 13.18%) CCBs (525, 5.84%)
Caughey et al. (2019)	Administrative health claims from Australian Government Department of Veteran Affairs (DVA) (2012)	Hospitalized with HF, eligible for all health services subsidized by the DVA in the 12 months before the start date of the study	Not reported	2016 AHA Scientific Statement Drugs That May Cause or Exacerbate Heart Failure, 2011 update to National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand Guidelines for the prevention, detection, and management of chronic heart failure in Australia, 2006 (omitted anesthesia medicines and dronedarone due to its unavailability in the dataset or country respectively)	4069 (2435, 59.8%)	Not reported	120 days prior to hospitalization Albuterol (832, 20.4%) Systemic corticosteroids (709, 17.4%) Tricyclic Antidepressants (380, 9.3%) Metformin (338, 8.3%) Tamsulosin (151, 7.3%) Non-selective COX Inhibitors (251, 6.2%) Topical B-Blockers (232, 5.7%) Diltiazem (210, 5.2%) 120 days after hospitalization Albuterol (832, 20.4%) Systemic corticosteroids (709, 17.4%) Tricyclic Antidepressants (380, 9.3%) Metformin (338, 8.3%) Tamsulosin (151, 7.3%) Non-selective COX Inhibitors (251, 6.2%) Topical B-Blockers (232, 5.7%) Diltiazem (210, 5.2%)

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TABLE 1 | (*Continued*) Summary of studies reporting potentially harmful medication prescribing in patients with heart failure.

Study Authors (publication year)	Setting (study year/s)	Inclusion Criteria	Exclusion Criteria	Rule set utilized and applied in the study	Number of patients assessed (count, % with PHM)	Characteristics associated with PHM[a] (OR, 95% CI)	Most common medications reported as PHM[b] (n, %)
Alvarez et al. (2019)	Outpatient pharmacy claims from Truvan Health Market Scan Claims database in the US (2011–2015)	Diagnosed with systolic HF, between 18–65 years of age	COPD on steroids, ESRD, malignant neoplasm with/ without metastatic disease, with less than 6 months of claims from enrollment date, no pharmacy coverage	2016 AHA Scientific Statement Drugs That May Cause or Exacerbate Heart Failure (oral medications with A or B level evidence with major potential for induction or precipitation of HF)	40,966 (9954, 24.3%)	Logistic regression assessing association with PHM prescribing: Female sex (1.16, 1.10–1.22) Osteoarthritis (1.70, 1.61–1.79) Hypertension (1.36, 1.25–1.47) Diabetes mellitus (1.52, 1.44–1.59) Atrial fibrillation (1.23, 1.17–1.29) Myocardial infarction (0.76, 0.72–0.80) Neurological and/or psychiatric Disorders (1.42, 1.35–1.50) Outpatient cardiology visit (1.74, 1.65–1.84) Polypharmacy (1.69, 1.59–1.79)	After HF diagnosis: NSAIDS (6710, 44%) Citalopram (1680, 11%) Diltiazem (1675, 11%) Sitagliptin (1438, 9.4%) Antiarrhythmics (1258, 8.3%)
Silva Almodóvar and Nahata (2020)	Outpatient pharmacy claims from Medicare insurance plan in the US (2018)	Medicare enrolled, MTM eligible, diagnosed with HF	Without evidence of prescription claims, only with a diagnosis code for HFpEF	2016 AHA Scientific Statement Drugs That May Cause or Exacerbate Heart Failure (oral or injectable medications with A or B level evidence with major potential for induction or precipitation of HF)	13,250 (7017, 53%)	Number of unique medications (1.05, 1.04–1.06) Female Sex (1.24, 1.15–1.33) Living in an area where more than 10% of individuals lived below the federal poverty line (1.25–1.36)	During study period: NSAIDs (3357, 25%) DPP4i (3117, 24%) Non-dihydropyridine CCBs (936, 7%)
Brinker et al. (2020)	Frankel Cardiovascular Center Heart Failure with Preserved Ejection Fraction Clinic in the US (2016–2019)	Participation in clinic	Not reported	2016 AHA Scientific Statement Drugs That May Cause or Exacerbate Heart Failure: medications that posed a major risk of causing or exacerbating HF	231 (119, 52%)	Not reported	During study period: Metformin (43.19%) Nondihydropyridine CCB (26, 11%) Citalopram or escitalopram (18.8%) Sulfonylurea (16.7%) NSAIDs (16.7%) Hydroxychloroquine (13.6%)

[a]*Only statistically significant associations were included.*

[b]*Medications included with greater than 5% prevalence.*

ACC, American college of cardiology; ACEi, angiotensin converting enzyme inhibitor; AHA, American heart association; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; CCB, calcium channel blockers; CMS, centers for medicare and medicaid services; COPD, chronic obstructive pulmonary disease; DPP4i, dipeptidyl peptidase-4 inhibitor; ESRD, end stage renal disease; HF, heart failure; HFpEF, heart failure preserved ejection fraction; HFrEF, heart failure reduced ejection fraction; ICD, international classification of diseases; MTM, medication therapy management; NSAIDS, nonsteroidal anti-inflammatory drugs; OR, odds ratio; PHM, potentially harmful medication; US, united states.

Finally, a study by Brinker et al. (Brinker et al., 2020) examined the prescribing of PHMs among a cohort with preserved ejection fraction HF (HFpEF) in one outpatient clinic. Approximately, 52% of patients were with a PHM. The most commonly prescribed PHMs in this study were metformin, non-dihydropyridine CCBs, and citalopram or escitalopram.

CHARACTERISTICS ASSOCIATED WITH PHM PRESCRIBING

Examining patient characteristics associated with the prescribing of PHM may inform which patient populations would likely benefit most from targeted interventions. Goyal et al. (Goyal et al., 2020) reported patients with diabetes and those admitted to small hospitals with PHM prescribing had greater odds of having a PHM at discharge. Among Medicare patients that were hospitalized with HF, patients with PHM prescribing prior to the hospitalization, female sex, atrial fibrillation, severe obesity, diabetes, and chronic lung disease were with higher odds of PHM after a HF-related discharge; patients with ischemic heart disease, implantable cardioverter defibrillator, and renal failure were with significantly lower odds of PHM prescribing after a HF-related discharge (Alvarez et al., 2020).

In adults under 65 years of age, polypharmacy, use of loop diuretics, an outpatient cardiology visit, female sex, and

diagnoses of osteoarthritis, hypertension, diabetes mellitus, atrial fibrillation, peripheral vascular disorder, neurological/psychiatric disorders, and chronic obstructive pulmonary disease were associated with prescribing of PHM; patients with history of a myocardial infarction were with lower odds of PHM prescribing (Alvarez et al., 2019). Among Medicare patients who were eligible for an MTM service, female sex, increasing number of prescriptions, residence in higher levels of poverty and greater number of prescribers and pharmacies were associated with PHM prescribing (Silva Almodóvar and Nahata, 2020). It is important to note the only characteristic of prescribers assessed was prescriber specialty. One study found that physician primary care providers prescribed the largest number of PHMs among MTM eligible patients with HF (Silva Almodóvar and Nahata, 2020).

DISCUSSION

Numerous studies have provided clear evidence for the prescribing of PHMs among patients with HF, which can lead to unnecessary health care utilization. Inpatient care represented 44–96% of the global cost of the management of HF; it is estimated to represent approximately 62–84% of the annual costs in the US. (Lesyuk et al., 2018) An obvious question is: what can be done to address this issue? One strategy would be to implement triggered alerts in an electronic health record's CDSS using rule sets adapted from the AHA scientific statement, ESC's position statement and heart failure prescribing guidelines to identify and prevent prescribing of PHMs in patients with HF. Smaller hospitals relative to larger hospitals may benefit more from this type of intervention given patients at these hospitals had greater odds of having a PHM (Goyal et al., 2020).

This type of triggered alert within a CDSS can draw the health care provider's attention to the patient's previously established diagnosis of HF, the offending drug's potential for harm, and suggest a safer medication. This would allow the provider to make the most educated therapeutic decision at the point of prescribing. To the authors' knowledge current electronic interventions are primarily focused on improving prescribing of medications meant to treat HF and research is needed to evaluate the use of these technologies to reduce rates of PHM prescribing. A previous systematic review found implementation of CDSS improved provider compliance with clinical practice related to the screening and treatment of cardiovascular related illnesses (Njie et al., 2015). McKie et al. (McKie et al., 2020) found CDSS significantly improved guideline recommended treatment of patients with HF in a primary care setting. However, another study in patients with HF in a hospital setting reported roughly 3.6 alerts per patient resulting in provider alert fatigue (Wadhwa et al., 2008). The risk for alert fatigue emphasizes the need to carefully design the triggered alerts with user feedback to ensure optimal uptake and efficacy.

In addition to the implementation of well-designed triggered alerts, dedicated pharmacovigilance programs need to be implemented to identify and resolve potential drug-drug interactions, drug-disease interactions, and adverse events. Targeted programs for PHMs among patients with heart failure can reduce prescribing of PHMs and thus reduce potentially avoidable health care utilization. As an example, the Centers for Medicare and Medicaid Services currently requires Medicare insurance plan providers to utilize MTM programs to optimize health outcomes and reduce the risk of medication related adverse events (Medication therapy management Centers for Medicare and Medicaid Services, 2020). MTM programs may incorporate automated algorithm driven electronic reviews and manual reviews of medication claims by health care providers to decrease and prevent prescribing of harmful medications.

It would be important for these programs to utilize health care providers with expertize in the comprehensive management of multiple concurrent medications as patients with heart failure and comorbidities such as diabetes, severe obesity, hypertension, atrial fibrillation, chronic lung disease, osteoarthritis, hypertension, peripheral vascular disorder, or neurological/psychiatric disorders had greater odds of using a PHM (Alvarez et al., 2019; Alvarez et al., 2020; Goyal et al., 2020). Presently, MTM services are largely provided by clinical pharmacists who evaluate medication regimens and communicate with patients and prescribers to improve medication use (Centers for Medicare and Medicaid Services, 2018). These programs can address medication use after prescribing, given they would have access to diagnostic and prescription claims data for patients that may have been siloed across different health care systems and pharmacies. These features are especially important as patients with multiple prescribers and with multiple pharmacies presented with greater odds of having a PHM (Silva Almodóvar and Nahata, 2020).

Wide adoption of these programs across health care systems and insurance plans can significantly improve their ability to reduce the prevalence of PHMs. Previous research found MTM programs to be especially helpful in improving medication adherence and prescribing of medications in patients with HF (Perloth et al., 2013). However, the effects of MTM programs on reducing contraindicated medications among patients with HF may depend on the type of insurance program (Buhl et al., 2017). Targeted reviews within these programs have been found effective in initiating a large number of medication changes to reduce adverse outcomes (Buhl et al., 2017; Ferries et al., 2019). Thus, implementation of targeted programs and adoption of MTM services among health care systems and payers such as insurance plans may reduce prevalence of PHMs, hospitalizations, and health care utilization among patients with HF.

The prevalence of HF is expected to increase by 46% by 2030 (Benjamin et al., 2017). Given 10–50% of patients with HF

utilized at least one PHM, there is an urgent need to develop and implement efficient and effective tools and programs to optimize medication management of patients with HF (Alvarez et al., 2019; Caughey et al., 2019; Alvarez et al., 2020; Brinker et al., 2020; Goyal et al., 2020; Silva Almodóvar and Nahata, 2020). The implementation of triggered alerts targeting PHM medications among patients with HF within the CDSSs across all health care systems and pharmacovigilance programs including MTM among insurance plan providers are likely to reduce the prescribing of PHMs, and thus improve health outcomes and reduce unnecessary health care utilization among adults with HF.

AUTHOR CONTRIBUTIONS

MN conceived of the idea. ASA conducted the literature review. ASA took lead in the writing of the manuscript. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Case Report: Spontaneous Intramural Hematoma of the Colon Secondary to Low Molecular Weight Heparin Therapy

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Background: Hematoma of the colon is a rare hemorrhagic complication that affects patients accepting low molecular weight heparin (LMWH) therapy. Only scarce cases of colon hematoma have been reported, usually in children or patients accepting warfarin therapy.

Case summary: A 76-year-old Chinese man was diagnosed with atrial fibrillation and heart failure, with cardiac function NYHA grade III on March 21, 2018. This patient was given LMWH for anticoagulation therapy and developed a colon hematoma on the third day of hospitalization. Abdominal computed tomography (CT) showed the thickening of areas of the colon up to 110 mm × 78 mm in thickness, which was a symptom of colon hematoma. The patient underwent conservative treatment successfully. On March 27, the patient's abdominal pain was alleviated, and a CT scan showed that the intestinal hematoma was absorbed.

Conclusions: The most frequent minor bleeding events of LMWH anticoagulation are hemorrhage and subcutaneous hematoma. This case demonstrated that bowel hematoma despite its low incidence should be considered as an ADR of LMWH therapy, especially among patients who present with gastrointestinal symptoms.

Keywords: anticoagulation, bowel, hematoma, low molecular weight heparin, case report

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INTRODUCTION

Low molecular weight heparin (LMWH) has become the preferred agent for the prophylaxis and treatment of thrombosis disease in patients as it has been shown to be safe and effective. It is also used as a bridging treatment of atrial fibrillation (AF) and then was switched to treatment with oral anticoagulants (Xia et al., 2018). As with any other anticoagulants, the main complication of LMWH therapy is bleeding. Most spontaneous gastrointestinal tract hematomas are caused by blunt abdominal trauma, which can also be secondary to anticoagulation therapy. Other risk factors for spontaneous gastrointestinal tract hematoma involve an endoscopic examination, coagulation disorder, and hemorrhagic disease (Zammit et al., 2013). Cases of spontaneous bowel hematoma associated with subcutaneous LMWH injection have been reported, while colon hematoma cases are very rare, usually in children or patients undergoing warfarin therapy (Chung, 2016; Choi et al., 2018). We herein present a novel case of spontaneous intramural hematoma of the colon associated with subcutaneous LMWH therapy.

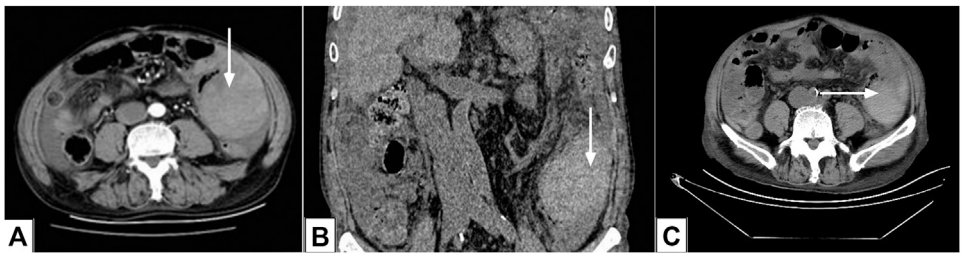

FIGURE1 | Abdominal computed tomography images. **(A, B)** Contrast-enhanced computed tomography (CT) images showing a hematoma of the colon (arrows) on March 23, 2018; C: CT image revealed that the colon hematoma had been absorbed (arrow) on March 27, 2018.

CASE PRESENTATION

Chief Complaints

A 76-year-old Chinese man complained of acutely worsening abdominal pain after treatment with 4,000 anti-Xa U of LMWH, q12h (low molecular weight heparin calcium injection, 0.4 ml/4000IU) as an anticoagulant for 3 days.

History of Present Illness

The patient was admitted to our hospital because of palpitation and shortness of breath for three days, and diagnosed with atrial fibrillation and heart failure, with cardiac function NYHA grade III at Northern Jiangsu People's Hospital on March 21, 2018. He had a CHA_2DS_2-VASc score of 4, which indicated a high risk of stroke. His body mass index was 21.66 kg/m^2, and renal function was normal. Therefore, he was given furosemide and spironolactone for diuretic therapy, valsartan capsules for antihypertensive treatment, and LMWH for anticoagulation therapy.

History of Past Illness

The patient had a prior history of hypertension well controlled by treatment with angiotensin-converting enzyme inhibitors.

Personal and Family History

The patient had no specific underlying disease. He had no family history of other significant diseases.

Physical Examination Upon Admission

Physical examination showed abdomen tenderness and no signs of peritoneal irritation.

Laboratory Examinations

On March 21, laboratory results showed that N-terminal pro–B-type natriuretic peptide was 1590 pg/ml, international normalized ratio was 1.14, activated partial thromboplastin time (APTT) was 38.20 s, fibrinogen was 1.67 g/L, hemoglobin was 113 g/L, red blood cell count was 3.34×10^{12}/L, creatinine was 83 μmol/L, alanine transferase was (ALT) 39.0 U/L, aspartate aminotransferase (AST) was 36.0 U/L, gamma-glutamyltransferase (GGT) was 115.0 U/L, and platelet cell count was 183×10^9/L. After anticoagulation therapy for 3 days, an emergency laboratory test showed that the red blood cell count was 2.56×10^{12}/L, and hemoglobin and platelet counts decreased to 82 g/L and 102×10^9/L, respectively. Furthermore, the coagulation function test demonstrated a prolonged APTT of 49.50 s. There was no bleeding per rectum, and his fecal occult blood test was negative. Considering the patient's symptoms of abdominal pain and the rapid drop in hemoglobin and red blood cell count, there was clinical suspicion for retroperitoneal or gastrointestinal hemorrhage.

Imaging Examinations

Abdominal computed tomography (CT) showed the thickening areas of the colon up to 110 mm × 78 mm in thickness, which was a symptom of hematoma of the colon (**Figures 1A,B**).

FINAL DIAGNOSIS

Hematoma of the colon took place after a subcutaneous LMWH injection. The patient had no medical history of hemorrhagic diseases, trauma, and any other anticoagulation therapy; we suspected that it was an adverse drug reaction (ADR) of LMWH. The assessment of ADR was evaluated *via* the Naranjo probability scale (Naranjo et al., 1981), which helps to identify the causal relation between an ADR and a drug based on the validated clinical questionnaire set by domain experts. The Naranjo scale consists of 10 questions which are administered for each patient's clinical record. The Naranjo scale assigns a causality score, which is the sum of the scores of all Naranjo questions, that classifies the case into one of four causality types: doubtful (≤0), possible (1–4), probable (5–8), and definite (≥9). This patient had a Naranjo probability score of 8, which indicated that LMWH was a probable cause of this bleeding event. All the above examinations revealed a final diagnosis of hematoma of the colon, a rare ADR caused by LMWH therapy.

TREATMENT

The patient accepted conservative management with bowel rest and intravenous fluids. His anticoagulation therapy of subcutaneous LMWH injection was discontinued immediately. Phloroglucinol injection (40 mg) as a musculotropic antispasmodic drug was prescribed to relieve abdominal pain. Tranexamic acid as a procoagulant was used to reduce the risk of

bleeding, and omeprazole was prescribed to prevent gastrointestinal mucosal injury.

OUTCOME AND FOLLOW-UP

On March 27th, the patient's abdominal pain was relieved, and a CT scan showed that intestinal hematoma was absorbed (**Figure 1C**). The patient was discharged from hospital 2 weeks later.

DISCUSSION

Spontaneous bowel intramural hematoma is a rare complication under anticoagulant therapy. Warfarin is the most common cause of spontaneous intramural small-bowel hematoma in adults. The incidence of bowel hematoma was reported to be 1/2500 per year in patients receiving warfarin, and the incidence is relatively higher in males (Bettler et al., 1983). Limmer and Clement (2017) reported a case of successful conservative treatment of bowel hematoma caused by overdose anticoagulation with warfarin in a 71-year-old man. Shaw et al. (2005) reported one case of small-bowel hematoma in a child who received therapeutic doses of LMWH because of deep venous thrombosis. Approximately 85% of spontaneous intestinal intramural hematomas in patients with anticoagulant therapy occur in the small bowel (Xiao et al., 2015); however, the incidence of spontaneous hematoma is extremely rare in the colon. Thus, we herein present a novel case of spontaneous intramural hematoma of the colon associated with subcutaneous LMWH therapy.

Clinical presentation of bowel hematoma can vary from mild abdominal pain to intestinal obstruction or an acute abdomen. Nausea and vomiting are found in half of the cases and are related to intestinal obstruction. The average time from the occurrence of symptoms until medical attendance is 2.5 days (Sorbello et al., 2007). The diagnosis of bowel hematoma requires imaging data. Abdominal CT is currently the preferred imaging method for intestinal hematoma. Some people suggested that non-contrast CT should be performed for oral and intravenous contrast medium application, as contrast-enhanced CT alone may mask the presence of intramural hemorrhage. Most bowel hematomas can be treated conservatively, including discontinuing or reversing the anticoagulation and alleviating abdominal pain caused by intestinal obstruction. Surgery is indicated for complications or persistence of bowel hematoma (Zammit et al., 2013). Our patient was 76 years old, with a body mass index of 21.66. He had normal coagulation, liver, and kidney function at admission, and had no medical history of hemorrhagic diseases. Abdominal pain occurred 3 days after subcutaneous injection of LMWH, and abdominal CT scan indicated an intramural hematoma of the colon. This colon hematoma ADR is not mentioned in the official product information of LMWH.

LMWH has become the preferred agent for the prophylaxis and treatment of thrombosis disease. Compared with heparin, it has been shown to be safe and effective, with reduced incidence of heparin-induced thrombocytopenia (HIT) complication. LMWH molecular weight around 5000 Da is considerably variable in the chemical structure and has anti-factor Xa and anti-factor IIa activities (Hao et al., 2019). LMWH has a lower anti-factor IIa activity and a relatively higher anti-factor Xa activity. Subcutaneous LMWH injection is absorbed completely, with a half-life period of 3–5 h. While routine monitoring of coagulation parameters is not usually necessary for LMWH, certain populations (including pregnant patients, children, obese patients, and patients with renal impairment) may benefit from the monitoring of anti-factor Xa activity to help guide drug therapy (Levine et al., 2004; Sunseri et al., 2018). The main risk of LMWH, as with any anticoagulation agent, is bleeding. Hemorrhagic events that are reported usually include subcutaneous hematoma, hematuria, hemorrhinia, and gastrointestinal and retroperitoneal hemorrhage, while bowel hematoma rarely occurs. One of the mechanisms leading to bowel intramural hematoma might be the rapid decompression of splanchnic circulation due to decreased abdominal pressure, causing the bowel to rupture and bleed while he was on therapeutic anticoagulation therapy. There were limitations in our case; it was unclear whether LMWH dosage was a factor in the hemorrhage as the anti-Xa level was not monitored, and some other features such as genetic factors were also not been measured.

CONCLUSION

The most frequent minor bleeding events of LMWH anticoagulation are hemorrhage and subcutaneous hematoma. This case demonstrated that bowel hematoma despite its low incidence should be considered as an ADR of LMWH therapy, especially among patients who present with gastrointestinal symptoms.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

YZ was the patient's doctor, reviewed the literature, and contributed to revision of the manuscript; CW collected the clinical data; CX was responsible for English language revision; JL designed and wrote the article.

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Systematic Review and Meta-Analysis of Renin–Angiotensin–Aldosterone System Blocker Effects on the Development of Cardiovascular Disease in Patients With Chronic Kidney Disease

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Background: Cardiovascular events are one of the most serious complications that increase the risk of mortality and morbidity in pre-dialysis and on-dialysis chronic kidney disease (CKD) patients. Activation of the renin–angiotensin–aldosterone system (RAAS) is considered to contribute to the development of cardiovascular events in these populations. Therefore, several kinds of RAAS blockers have been frequently prescribed to prevent cardiovascular events in patients with CKD; however, their effectiveness remains controversial. This systematic review focuses on whether RAAS blockers prevent cardiovascular events in patients with CKD.

Method: PubMed were searched to retrieve reference lists of eligible trials and related reviews. Randomized prospective controlled trials that investigated the effects on cardiovascular events in CKD patients that were published in English from 2010 to 2020 were included.

Results: Among 167 identified studies, 11 eligible studies (n = 8,322 subjects) were included in the meta-analysis. The meta-analysis showed that RAAS blockers significantly reduced cardiovascular events in on-dialysis patients with CKD [three studies; odds ratio (OR), 0.52; 95% confidence interval (CI), 0.36 to 0.74; p = 0.0003], but there was no significant difference in pre-dialysis patients with CKD because of the heterogeneity in each study (eight studies). We also investigated the effects of each kind of RAAS blocker on cardiovascular events in CKD patients. Among the RAAS blockers, mineralocorticoid receptor antagonists significantly decreased cardiovascular events in pre-dialysis or on-dialysis patients with CKD (four studies; OR, 0.60; 95%CI, 0.50 to 0.73, p < 0.0001). However, angiotensin receptor blockers did not show significant effects (four studies; OR, 0.65; 95%CI, 0.42 to 1.01; p = 0.0529). The effects of angiotensin converting enzyme inhibitors and direct renin inhibitors on cardiovascular events in patients with CKD could not be analyzed because there were too few studies.

Conclusion: Mineralocorticoid receptor antagonists may decrease cardiovascular events in pre-dialysis or on-dialysis patients with CKD.

Keywords: renin-angiotensin-aldosterone system blocker, cardiovascular disease, chronic kidney disease, pre-dialysis, hemodialysis, peritoneal dialysis, systematic review, meta-analysis

INTRODUCTION

Cardiovascular events are one of the most serious complications that increase the risk of mortality and morbidity in chronic kidney disease (CKD) patients who are undergoing pre-dialysis, hemodialysis, or peritoneal dialysis (Kim-Mitsuyama et al., 2018; Tonelli et al., 2019). Activation of the renin–angiotensin–aldosterone system (RAAS) is considered to be an important factor that contributes to the development of cardiovascular disease in patents with CKD (Liu et al., 2014). Therefore, several types of RAAS blockers including angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and direct renin inhibitors (DRIs) have been frequently prescribed, and they are expected to prevent cardiovascular events and have reno-protective effects in patients with CKD. However, their protective effects in cardiovascular events in this population remain controversial (Xie et al., 2016). Additionally, different types of RAAS blockers may have different effects on reducing cardiovascular events in patients with CKD. To address these clinical questions, this systematic review focuses on whether each RAAS blocker prevents cardiovascular events in pre-dialysis or on-dialysis patients with CKD.

The Effects of Each Class of Renin–Angiotensin–Aldosterone System Blockers

Angiotensin Receptor Blockers

ARBs bind angiotensin receptor-1 and inhibit angiotensin II from binding to angiotensin receptor-1 (Pang et al., 2012). They then suppress vasoconstriction resulting in a decrease in blood pressure (Pang et al., 2012). ARBs act directly on vascular smooth muscle and suppress aldosterone secretion, thereby preventing sodium accumulation and lowering blood pressure, which leads to inhibition of fibrosis of heart and kidney (Hara et al., 2017; Isobe-Sasaki et al., 2017; Zhang et al., 2017).

Angiotensin Converting Enzyme Inhibitors

ACEIs activate angiotensin converting enzyme on the vascular endothelial cell membrane. They prevent the conversion of angiotensin I into angiotensin II by inhibiting angiotensin converting enzyme and then suppress vasoconstriction, which results in deceasing blood pressure (Ali et al., 2019; Park et al., 2019).

Mineralocorticoid Receptor Antagonists

MRAs show antihypertensive effects by competitively binding to mineralocorticoid receptors on the distal tubules and collecting ducts of the kidney and inhibiting the effects of mineralocorticoids (Farman and Rafestin-Oblin, 2001). MRAs excrete sodium and absorb potassium and hydrogen, resulting in a reduction in the volume of circulating and extracellular fluids and thereby a reduction in blood pressure (Sato et al., 2003) and an improvement in edema.

Direct Renin Inhibitors

DRIs act upon renin, which converts angiotensinogen into angiotensin-1. They inhibit plasma renin activity, which causes a decrease in blood pressure (Morishita and Kusano, 2013).

METHODS

Literature Search

We searched for clinical studies that were published in English in the PubMed database from 2010 to 2020. A literature search was conducted between November 9 and 16, 2020. For each term of "chronic kidney disease," "hemodialysis," and "peritoneal dialysis," we searched by connecting with terms including "cardiovascular disease," "heart failure," "heart attack," and "renin angiotensin aldosterone," "angiotensin receptor blocker," "ARB," "angiotensin converting enzyme inhibitor," "ACEI," "mineralocorticoid receptor antagonist," "direct renin inhibitor" as listed in **Supplementary Table S1**. We limited the article type to randomized controlled studies. The studies' eligibility was carefully checked for inclusion in accordance with Preferred Reporting Items for Systematic and Meta-Analyses (PRISMA) guidelines (**Figure 1**; Shamseer et al., 2015). The inclusion criteria for the studies were as follows: 1) the study reported the effects of RAAS blockers on cardiovascular events such as heart failure, stroke, myocardial infarction, and unstable angina in patients with CKD; and 2) the study was published as a full-text journal article in English. Exclusion criteria were as follows: 1) the effects of RAAS blockers on the cardiovascular events in patients with CKD were not mentioned; 2) there was no description of sample settings; 3) the study focused on side effects; 4) the study was ongoing; 5) the study was not published in English; 6) the study was not a placebo-controlled study; 7) there was no detailed description of outcome data; and 8) other cardioprotective drugs, such as diuretics and beta-blockers, were prescribed as an intervention (Bristow, 2011; Pugh et al., 2019). We also evaluated references that seems to be important from guidelines.

Statistical Methods

The main objective of this study was to access the incidence of cardiovascular diseases in CKD patients with RAAS blocker

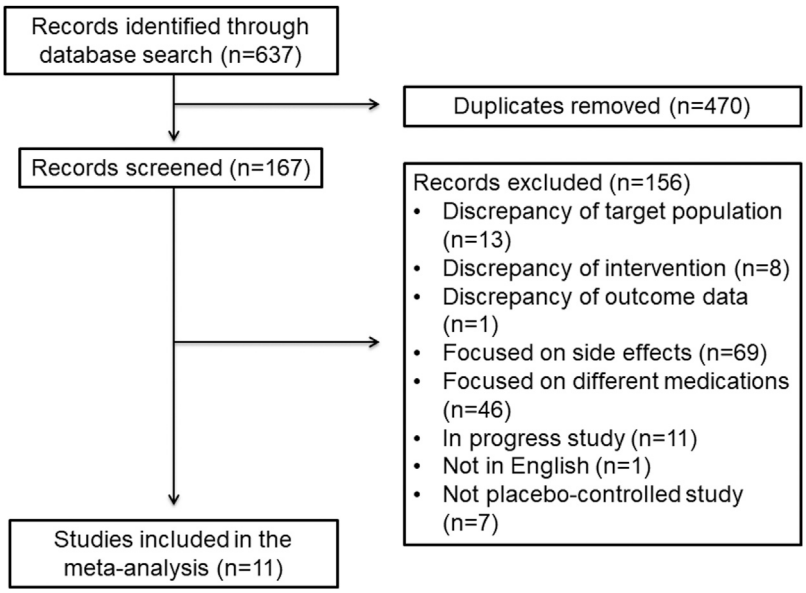


FIGURE 1 | Flow diagram of this systemic review and meta-analysis

treatment across different CKD types and to compare the relative risk of cardiovascular diseases between RAAS blockers and placebo. We calculated the incidence of cardiovascular diseases from the data that were available in each study. A meta-analysis was conducted with R software (version 4.0.3) (R Foundation for Statistical Computing, Vienna, Austria) using the Mantel–Haenszel and DerSimonian–Laird methods. A p value less than 0.05 was considered to represent statistical significance. Bonferroni adjustment for multiple testing in meta-analysis produced a rejection p-value of 0.05 divided by the total number of outcomes. Incidence rates for each study are displayed in forest plots with the estimated 95% confidence intervals (CIs). The relative risk and corresponding 95% CIs were also calculated for patients who were treated with a RAAS blocker compared with placebo. The statistical heterogeneity among the selected studies was verified using the Cochrane Q statistic and the I^2 statistic. If there was no statistically significant heterogeneity ($p > 0.05$ or $I^2 < 40\%$) among the results of the included trials, the pooled estimate was calculated based on the fixed-effects model. If significant heterogeneity ($p < 0.05$ or $I^2 > 40\%$) was observed in the analysis, a random-effects model was used for the meta-analysis. We determined beneficial effects of RAAS blockers for cardiovascular diseases if the results of the meta-analysis showed p-value was below 0.05, 95% CI was below 1.00 (did not cross 1.00), and no heterogeneity of each study was observed using the Cochrane Q statistic, the I^2 statistic and Bonferroni correction analysis (Grover and Kukreti, 2013). Funnel plots were generated to visually assess asymmetry and potential publication bias, along with the Egger's test.

RESULTS

Search Results

A flow diagram including the study inclusion and exclusion criteria is presented in **Figure 2**. Computer and manual searches identified 637 publications. After removing duplicates, 167 articles remained, and among them, 156 articles were excluded because they did not meet the study entry criteria. In patients with CKD, hemodialysis, and peritoneal dialysis, there were publications on the use of RAAS blockers, but they were excluded if they were not related to a direct cardiovascular event. After full-text screening, 11 studies ($n = 8{,}322$ subjects) were included in this systematic review and meta-analysis (ARBs, $n = 4$; ACEIs, $n = 1$; MRAs, $n = 4$; and combination of ARBs and ACEIs, $n = 2$) (**Figure 1**) (Cice et al., 2010; Imai et al., 2011; Tobe et al., 2011; Bowling et al., 2013; Eschalier et al., 2013; Fried et al., 2013; Torres et al., 2014; Walsh et al., 2015; Lin et al., 2016; Kim-Mitsuyama et al., 2018; Tsujimoto and Kajio, 2018). No studies that met the study inclusion criteria investigated the effects DRIs.

The Effects of Renin–Angiotensin–Aldosterone System Blockers for Prevention of Cardiovascular Events in Pre-dialysis and On-Dialysis Chronic Kidney Disease Patients

The meta-analysis showed that RAAS blockers (ARBs, ACEIs, MRAs, and combination of ARBs and ACEIs) significantly decreased cardiovascular events compared with the placebo group in pre-dialysis or on-dialysis patients with CKD [odds ratio (OR), 0.69; 95% CI, 0.57 to 0.83, $p < 0.0001$] (**Figure 2A**). However, heterogeneity among the cohorts was statistically

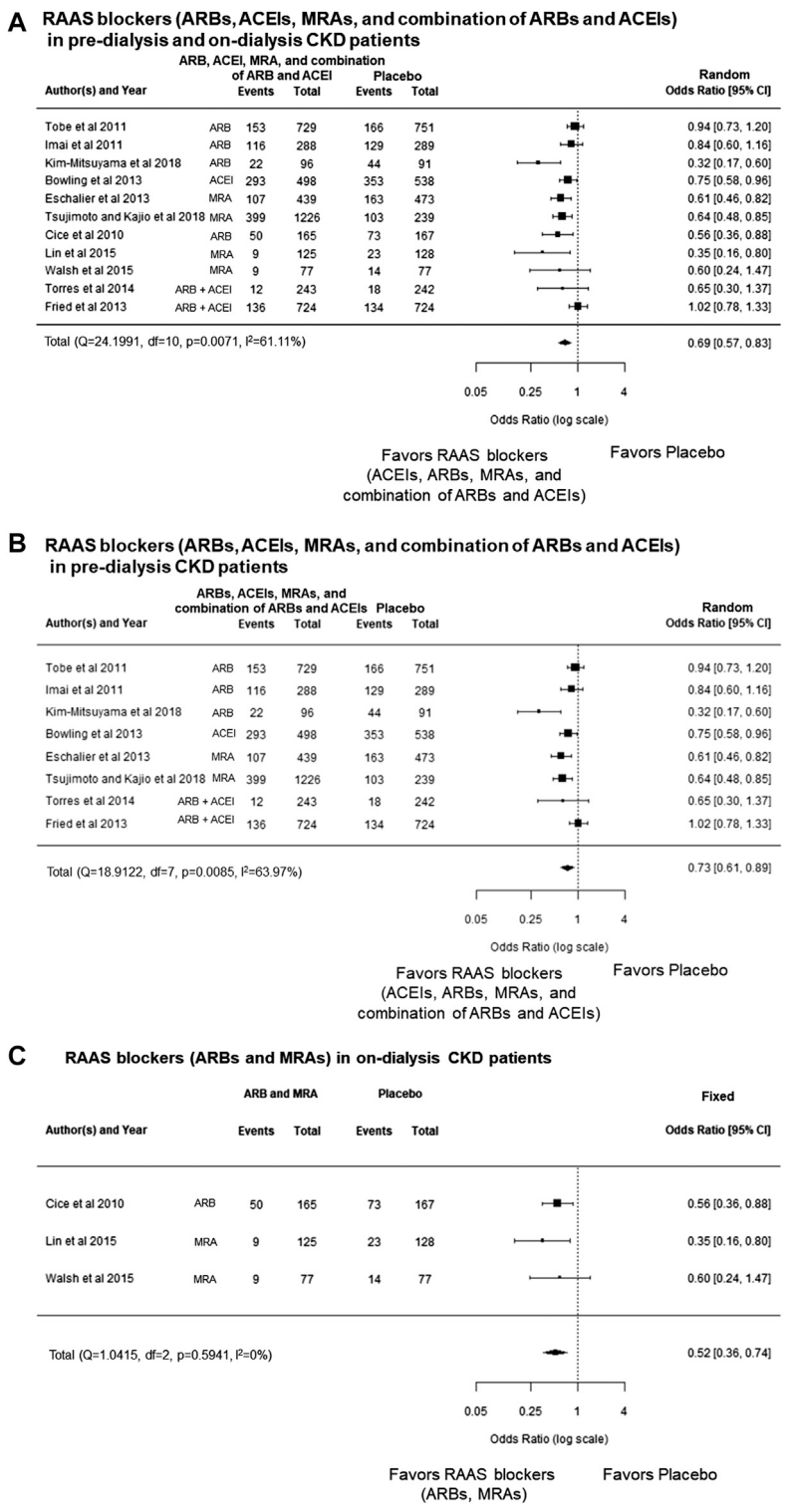


FIGURE 2 | (A) Forest plot describing a comparison of the incidence of cardiovascular events between RAAS blockers (ARBs, ACEIs, MRAs, and the combination of ARBs and ACEIs) and placebo in pre-dialysis and on-dialysis patients with CKD. **(B)** Forest plot describing a comparison of the incidence of cardiovascular events between RAAS blockers (ARBs, ACEIs, MRAs, and combination of ARBs and ACEIs) and placebo in pre-dialysis patients with CKD. **(C)** Forest plot describing a comparison of the incidence of cardiovascular events between RAAS blockers (ARBs and MRAs) and placebo in on-dialysis patients with CKD. ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CI, confidence intervals; CKD, chronic kidney disease; MRAs, mineralocorticoid receptor antagonists; RAAS, renin–angiotensin–aldosterone system

significant ($p = 0.0071$, $I^2 = 61.11\%$), which remained significant after Bonferroni correction.

In sub-group analysis, categorized pre-dialysis patients with CKD, and on-dialysis patients with CKD. The meta-analysis also showed that RAAS blockers significantly decreased cardiovascular events compared with placebo groups in pre-dialysis patients with CKD (OR, 0.73; 95% CI, 0.61 to 0.89, $p = 0.0017$) (**Figure 2B**); however, heterogeneity among cohorts was also statistically significant ($p = 0.0085$, $I^2 = 63.97\%$), which remained significant after Bonferroni correction. The meta-analysis also showed that RAAS blockers significantly decreased cardiovascular events compared with placebo groups on-dialysis patients with CKD (OR, 0.52; 95% CI, 0.36 to 0.74; $p = 0.0003$), and there was no heterogeneity ($p = 0.5941$, $I^2 = 0.0\%$) (**Figure 2C**). These results showed that RAAS blockers significantly decreased cardiovascular events in on-dialysis patients with CKD patients; however, these effects were not shown in pre-dialysis patients with CKD because there was heterogeneity among the cohorts.

The funnel plot appeared to be asymmetric (Egger's test, $p = 0.0091$), with some missingness at the lower right portion of the plot suggesting possible publication bias (**Figure 3**).

The Effects of Each Class of Renin–Angiotensin–Aldosterone System Blockers (Angiotensin Receptor Blockers, Angiotensin Converting Enzyme Inhibitors, Mineralocorticoid Receptor Antagonists, and Combination of Angiotensin Receptor Blockers and Angiotensin Converting Enzyme Inhibitors) for Prevention of Cardiovascular Events in Pre-dialysis and On-Dialysis Chronic Kidney Disease Patients

In the data base research in pre-dialysis patients with CKD or on-dialysis patients with CKD who took ARBs, three studies in pre-dialysis patients with CKD and on-dialysis patients with CKD, and one study on-dialysis patients with CKD were included in this systematic review and meta-analysis (Cice et al., 2010; Imai et al., 2011; Tobe et al., 2011; Kim-Mitsuyama et al., 2018; **Table 1**).

A study showed that add-on administration of 80 mg/day of telmisartan for 4–7 years did not significantly decrease cardiovascular outcomes in pre-dialysis patients with CKD (Tobe et al., 2011). Another study showed that add-on administration of 10–40 mg/day of olmesartan for 4 years did not significantly decrease cardiovascular outcomes in pre-dialysis patients with CKD (Imai et al., 2011). Contrarily, another study reported that add-on administration of 20–80 mg/day of olmesartan significantly improved cardiovascular outcomes in pre-dialysis patients with CKD during a 3-years observation period (Kim-Mitsuyama et al., 2018).

One study reported the cardioprotective effects of ARBs in on-dialysis patients with CKD (Cice et al., 2010). That study showed that add-on administration of 80 mg/day telmisartan for 3 years significantly decreased cardiovascular death and hospitalization for chronic heart failure over 3 years on-dialysis patients with CKD who had chronic heart failure (Cice et al., 2010).

In this study, meta-analysis revealed no significant decrease in cardiovascular events compared with the placebo group in pre-dialysis and on-dialysis CKD patients who took ARBs (OR, 0.65; 95% CI, 0.42 to 1.01; $p = 0.0529$) (**Figure 4A**). Additionally, meta-analysis showed no significant difference in reducing cardiovascular events in pre-dialysis patients with CKD compared with the placebo group (OR, 0.67; 95% CI, 0.36 to 1.23; $p = 0.1936$) (**Figure 4B**).

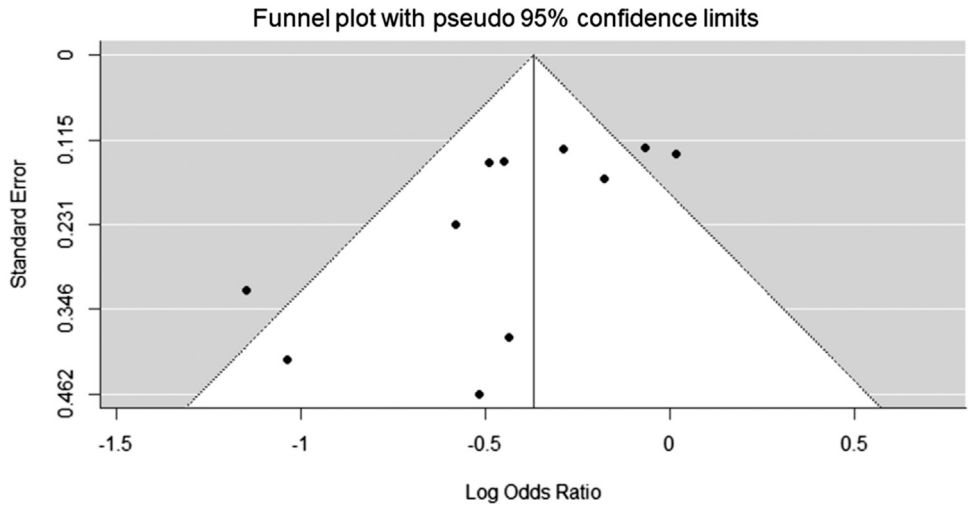


FIGURE 3 | Funnel plot of meta-analysis.

TABLE 1 | Effects of angiotensin receptor blockers on the development of cardiovascular disease in pre-dialysis or on-dialysis patients with CKD.

Class of RAAS blocker	Authors, Year; Reference number	Patients	Study design	Study protocol	Results
ARB	Tobe et al., 2011; 24	N = 1480; eGFR <60 (mL/min/1.73 m^2) Serum creatinine concentration <3.0 mg/dL	RCT; Multicenter double-blind placebo-controlled clinical trial	Telmisartan 80 mg or placebo once daily; 4–7 years	No improvement in cardiovascular outcomes, including cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure was found with telmisartan therapy compared with placebo in patients with CKD (p value was not shown).
	Imai et al., 2011; 10	N = 577; Serum creatinine concentration was 1.2–2.5 mg/dL in men and 1.0–2.5 mg/dL in women	RCT; Double-blind placebo-controlled clinical trial; Secondary outcomes	Olmesartan 10–40 mg once daily or placebo; 4 years	No improvement in cardiovascular outcomes, including cardiovascular death, non-fatal stroke except for transient ischemic attack, nonfatal myocardial infarction, hospitalization for unstable angina, hospitalization for heart failure, revascularization of coronary was found with olmesartan therapy compared with placebo in patients with CKD (HR, 0.73; 95% CI, 0.48 to 1.09; p = 0.126).
	Kim-Mitsuyama et al., 2018; 13	N = 187; eGFR <45 (mL/min/1.73 m^2)	RCT; Multicenter open-label placebo-controlled clinical trial; Secondary outcomes	Olmesartan 20–80 mg once daily or placebo; 3 years	In patients with advanced CKD, olmesartan-based therapy may confer greater benefit in prevention of cardiovascular events than placebo therapy (HR, 0.465; 95% CI, 0.224 to 0.965; p = 0.040).
	Cice et al., 2010; 4	N = 332; Hemodialysis; Chronic heart failure with reduced ejection fraction <40% within 6 months	RCT; Multicenter double-blind placebo-controlled clinical trial	Telmisartan 80 mg or placebo per day; 3 years	Telmisartan significantly reduced cardiovascular death (HR,0.42; 95% CI, 0.38 to 0.61; p < 0.0001), and hospital admission of chronic heart failure (HR, 0.38; 95% CI, 0.19 to 0.51; p < 0.0001) in 3 years in patients on maintenance hemodialysis compared with placebo.

ARB, angiotensin receptor blocker; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; RAAS, renin–angiotensin–aldosterone system; RCT, randomized controlled trial

Mineralocorticoid Receptor Antagonists

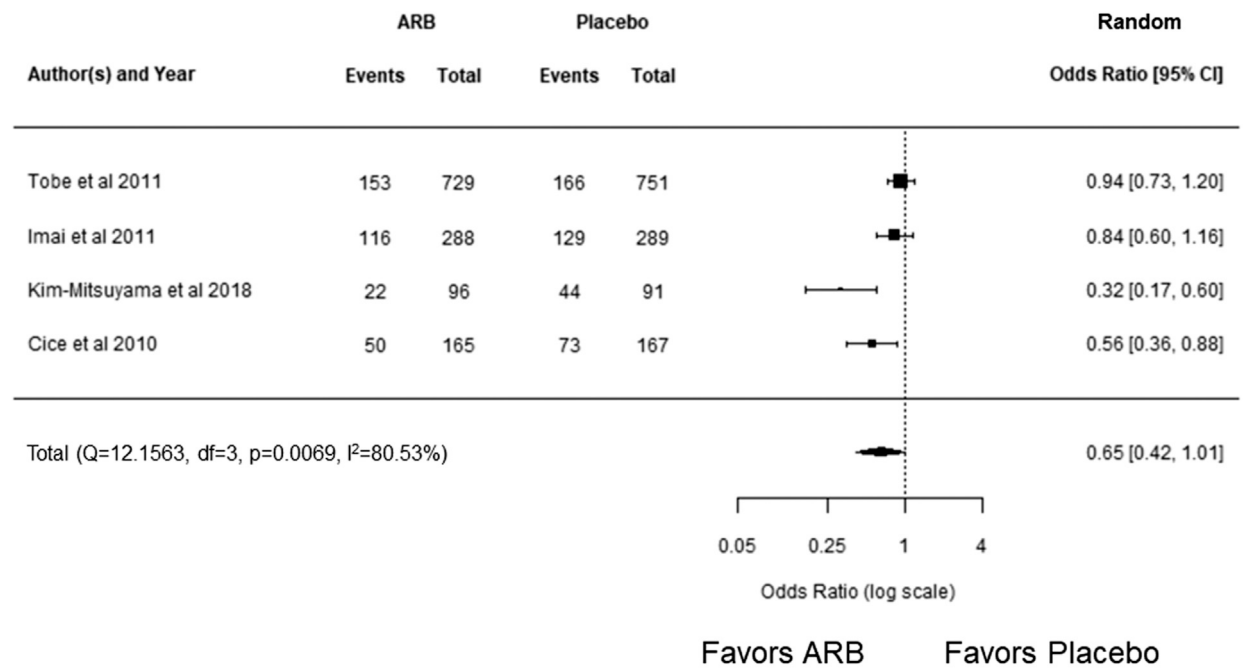
In the data base research in pre-dialysis patients with CKD and on-dialysis patients with CKD who took MRAs, two studies in pre-dialysis patients with CKD patients and two studies in on-dialysis patients with CKD were included in this systematic review and meta-analysis (Tsujimoto and Kajio, 2018; Lin et al., 2016; Walsh et al., 2015; **Table 2**). A study reported that once-daily 25 mg or 50 mg administration of eplerenone for 3 years was shown to significantly reduce the risk of cardiovascular events in pre-dialysis patients with CKD who had chronic heart failure (Eschalier et al., 2013).

Another study showed that administration of spironolactone for 6 years significantly reduced cardiovascular events in pre-dialysis patients with CKD who had chronic heart failure (Tsujimoto and Kajio, 2018). The other study reported the cardioprotective effects of spironolactone in on-dialysis (hemodialysis) patients with CKD (Lin et al., 2016). That study reported that administration of 25 mg/day of spironolactone significantly reduced the risk of death from cardiocerebrovascular events in on-dialysis (hemodialysis) patients with CKD compared with the control group who were administrated placebo for the 2-years observation period (Lin et al., 2016). Contrarily, another study reported that add on administration of 50 mg/day eplerenone did not significantly decrease cardiovascular events in on-dialysis (hemodialysis and peritoneal dialysis) patients with CKD during a 13-weeks observation period (Walsh et al., 2015).

In this study, a meta-analysis showed that MRAs decreased cardiovascular events compared with the placebo group in both pre-dialysis and on-dialysis patients with CKD (OR, 0.60; 95% CI, 0.50 to 0.73; $p < 0.0001$), and there was no heterogeneity ($p = 0.6157$, $I^2 = 0.0\%$) (**Figure 5A**). Additionally, MRAs decreased cardiovascular events compared with the placebo group in pre-dialysis patients with CKD (OR, 0.63; 95% CI, 0.51 to 0.77; $p < 0.0001$), which showed no heterogeneity ($p = 0.8516$, $I^2 = 0.0\%$) (**Figure 5B**), and in the on-dialysis patients with CKD (OR, 0.45; 95% CI, 0.24 to 0.82; $p = 0.0091$), which also showed no heterogeneity ($p = 0.4028$, $I^2 = 0.0\%$) (**Figure 5C**). Taken together, the results of this meta-analysis showed that MRAs showed protection effects of cardiovascular disease both in pre-dialysis patients and on-dialysis patients with CKD.

Angiotensin Converting Enzyme Inhibitors

Only one clinical study reported the effects of ACEIs on the development of cardiovascular events in pre-dialysis patients with CKD, and the results are summarized in **Table 3** (Bowling



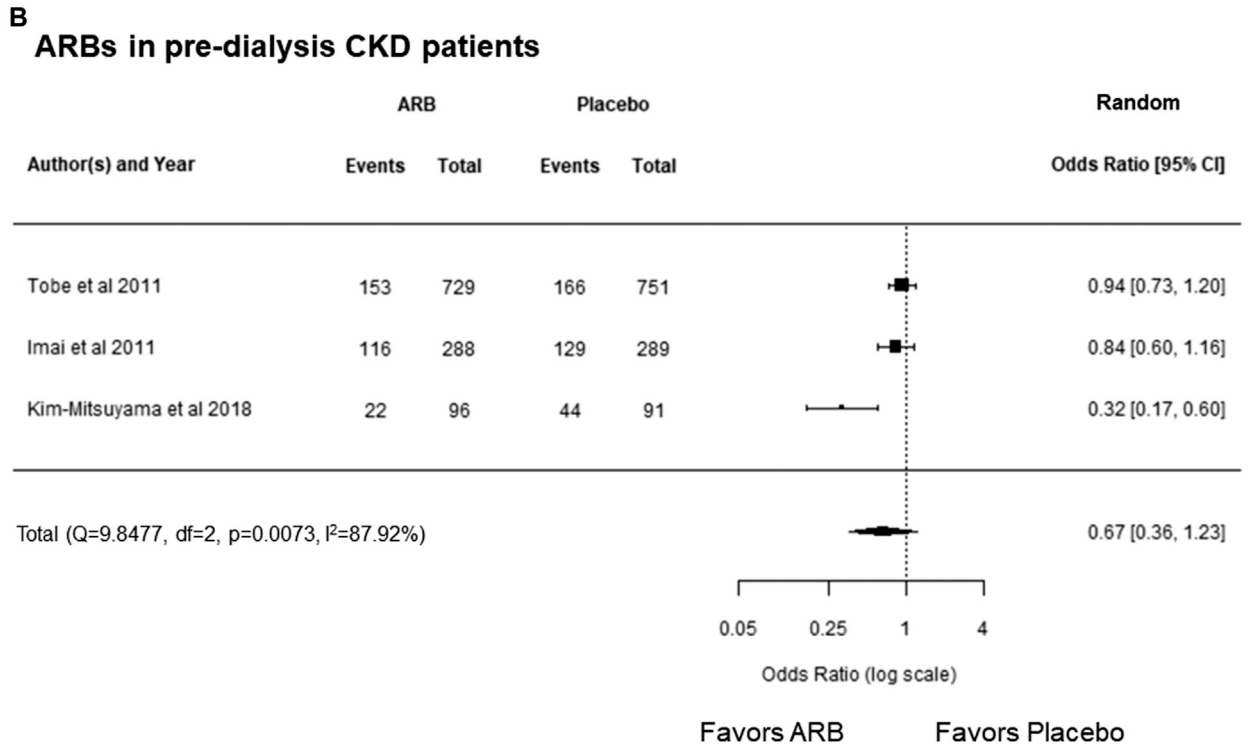


FIGURE 4 | (A) Forest plot describing a comparison of the incidence of cardiovascular events between ARBs and placebo in pre-dialysis and on-dialysis patients with CKD. **(B)** Forest plot describing a comparison of the incidence of cardiovascular events between ARBs and placebo in pre-dialysis patients with CKD. ARB, angiotensin receptor blocker; CI, confidence intervals; CKD, chronic kidney disease.

TABLE 2 | Effects of mineralocorticoid receptor antagonists for the development of cardiovascular disease in pre-dialysis or on-dialysis patients with CKD.

RAAS blocker class	Authors, Year; Reference number	Patients	Study design	Study protocol	Results
Mineralocorticoid receptor antagonists	Eschalier et al., 2013; 5	N = 912 eGFR 30 < 60 (mL/min/1.73 m^2) Chronic heart failure with reduced ejection fraction <35 %	RCT; Multicenter double-blind placebo-controlled clinical trial	Eplerenone 25–50 mg once daily or placebo; 3 years	Compared with placebo, eplerenone reduced the risk of cardiovascular events, including hospitalization for heart failure or cardiovascular mortality, compared with placebo in patients with CKD (HR, 0.62; 95% CI, 0.49 to 0.79; p = 0.0001).
	Tsujimoto and Kajio et al., 2018; 27	N = 1465; eGFR 30 < 60 (mL/min/1.73 m^2) or urine albumin-to-creatinine ratio >30 mg/gCre; Left ventricular ejection fraction >45%	RCT; Multicenter double-blind placebo-controlled clinical trial	Spironolactone or placebo (Dose was not shown); 6 years	Compared with placebo, spironolactone reduced cardiovascular events, including non-fatal myocardial infarction, non-fatal stroke or hospitalization for heart failure, in patients associated with CKD (HR, 0.75; 95% CI, 0.60 to 0.95; p = 0.01).
	Lin et al., 2016; 14	N = 253; Hemodialysis	RCT; Multicenter double-blind placebo-controlled clinical trial	Spironolactone 25 mg or placebo per day after hemodialysis or in the morning; 2 years	Compared with placebo, spironolactone reduced the risk of a composite death from cardiocerebrovascular events, including new occurrence or exacerbation of heart failure that was not improved by water removal through dialysis, ventricular fibrillation, or sustained ventricular tachycardia, new or recurrent acute myocardial infarction, new occurrence or exacerbation of angina pectoris, dissecting aneurysm of the aorta, stroke, and new or recurrent transient ischemic attack in patients on maintenance hemodialysis (HR, 0.42; 95% CI, 0.26 to 0.78; p = 0.017).
	Walsh et al., 2015; 28	N = 146; Dialysis, including hemodialysis and peritoneal dialysis	RCT; Multicenter double-blind placebo-controlled clinical trial; Secondary outcomes	Eplerenone 50 mg or placebo per day; 13 weeks	Compared with placebo, eplerenone did not reduce the risk of cardiovascular events in patients on maintenance hemodialysis (relative risk, 0.7; 95% CI, 0.2 to 2.3; p value was not shown.).

CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; RAAS, renin–angiotensin–aldosterone system; RCT, randomized controlled trial

et al., 2013). Add-on administration of 2.5–20 mg/day of enalapril for 3 years significantly reduced cardiovascular hospitalization in pre-dialysis patients with CKD (Stage 1–5) who had chronic heart failure (Bowling et al., 2013). We could not perform a meta-analysis to investigate the effects of ACEIs on cardiovascular events in patients with CKD because there was only one cohort and the statistical power would have been low. Further cohorts to investigate the effects of ACEIs on cardiovascular events in patients with CKD are required to confirm the utility of ACEIs for reducing cardiovascular events in patients with CKD.

Direct Renin Inhibitors

Several studies reported that DRIs may be effective for treating hypertension in patients with CKD (Morishita et al., 2011; Sakai et al., 2012; Ito et al., 2014). However, there are no studies on the cardioprotective effects DRIs in pre-dialysis or on-dialysis patients with CKD. Therefore, we could not perform a meta-analysis on the effects of DRIs on cardiovascular events in patients with CKD.

Combination Therapy

Two studies reported that combination therapy using ARBs and ACEIs was not effective in reducing cardiovascular events in pre-dialysis patients with CKD (Fried et al., 2013; Torres et al., 2014; **Table 4**). A study reported that administration of lisinopril on telmisartanl for 5–8 years did not significantly reduce cardiovascular hospitalization in pre-dialysis patients with CKD (Torres et al., 2014). Additionally, another study reported that administration of 50–100 mg of losartan on 50–100 mg of losartan and 10–40 mg of lisinopril for 4 years did not significantly reduce cardiovascular events in pre-dialysis patients with CKD (Stage 2–3) (Fried et al., 2013).

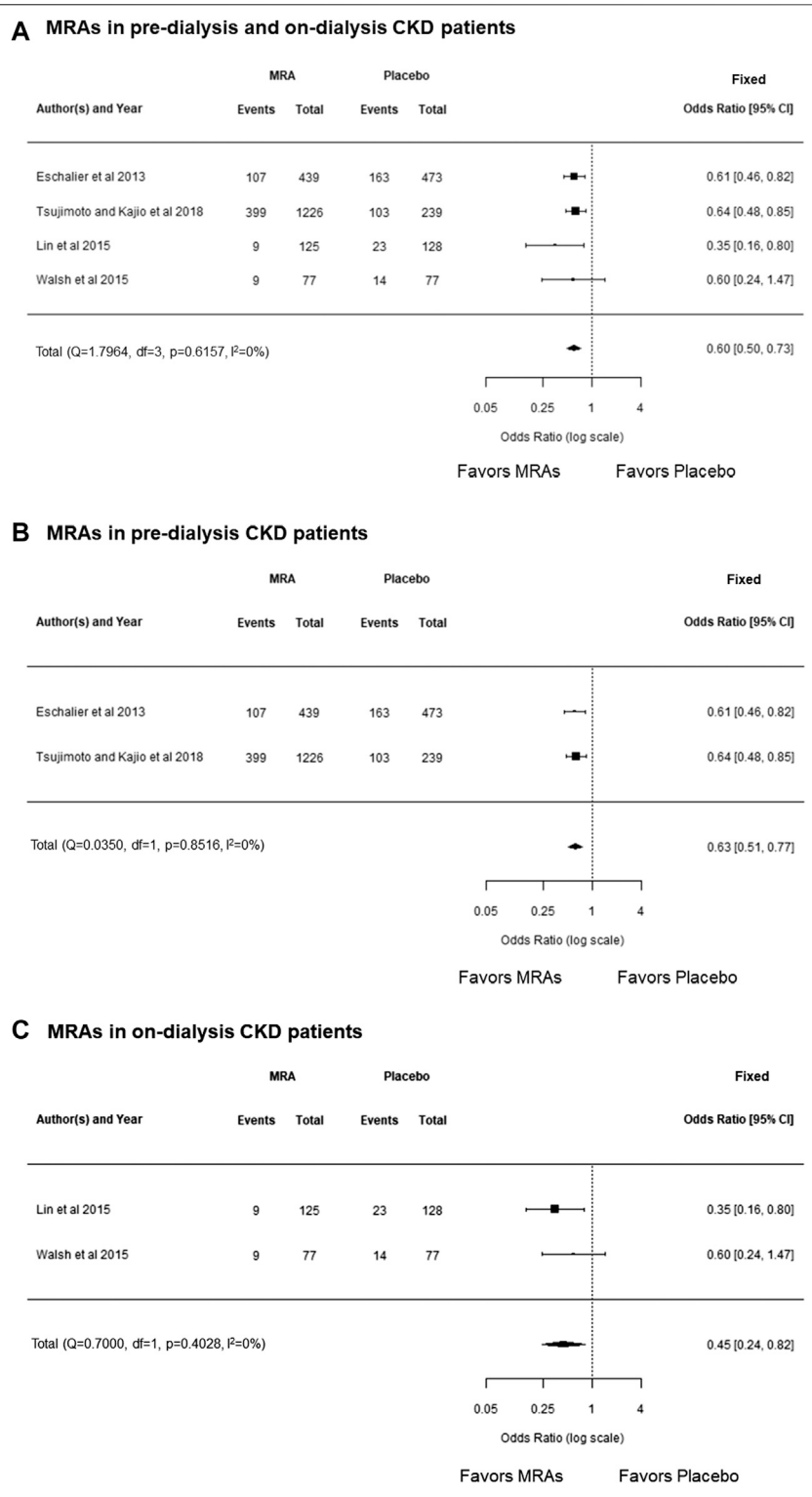


FIGURE 5 | (A) Forest plot describing a comparison of the incidence of cardiovascular events between MRAs and placebo in pre-dialysis and on-dialysis patients with CKD. **(B)** Forest plot describing a comparison of the incidence of cardiovascular events between MRAs and placebo in pre-dialysis patients with CKD. **(C)** Forest plot describing a comparison of the incidence of cardiovascular events between MRAs and placebo in on-dialysis patients with CKD. CI, confidence intervals; CKD, chronic kidney disease; MRAs, mineralocorticoid receptor antagonists.

TABLE 3 | Effects of angiotensin converting enzyme inhibitors on the development of cardiovascular disease in pre-dialysis patients with CKD.

Class of RAAS blocker	Authors, Year; Reference number	Patients	Study design	Study protocol	Results
ACEI	Bowling et al., 2013; 2	N = 1036; Stage 1–5 Chronic heart failure with ejection fraction <35% and serum creatinine <2.5 mg/dL	RCT; Multicenter double-blind placebo-controlled clinical trial	enalapril 2.5–20 mg daily or placebo; 3 years	Enalapril reduced cardiovascular hospitalization in patients with CKD compared with placebo (HR, 0.77; 95% CI, 0.66 to 0.90; p < 0.001).

ACEI, angiotensin converting enzyme inhibitor; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; RAAS, renin–angiotensin–aldosterone system; RCT, randomized controlled trial

In this study, the meta-analysis showed that combination therapy with ARBs and ACEIs was not significantly different in reducing cardiovascular events compared with the placebo group in pre-dialysis or on-dialysis CKD patients (OR, 0.94; 95% CI, 0.66 to 1.32; $p = 0.7069$) and there was no heterogeneity ($p = 0.2645$, $I^2 = 19.67\%$) (**Figure 6**). These results suggests that combination therapy using ARBs and ACEIs may not be effective at decreasing cardiovascular events in pre-dialysis patients with CKD. There are no studies on the cardioprotective effects of RAAS blockers used in combination in on-dialysis patients with CKD.

DISCUSSION

In this study, the meta-analysis showed that RAAS blockers (ARBs, ACEIs, MRAs, and combination of ARBs and ACEIs) significantly decreased cardiovascular events compared with the placebo group in on-dialysis patients with CKD. However, those effects could not be shown in pre-dialysis patients with CKD owing to heterogeneity among the cohorts (**Figures 2A–C**). Additionally, we found significant publication bias that the studies showing beneficial effects of RAAS blockers for protection of cardiovascular disease in patients with CKD (**Figure 3**). That results also may support careful estimations of the beneficial effects of RAAS blocker for prevention of cardiovascular disease in patient with CKD.

In each class of RAAS blockers, meta-analysis revealed MRAs decreased cardiovascular events compared with the placebo group in pre-dialysis and on-dialysis patients with CKD (**Figures 5A–C**); however, ARBs and the combination of ARBs and ACEIs were failed to show decrease cardiovascular events in those populations determined by range of 95% CI and heterogeneity among the cohorts (**Figures 4A,B**; **Figure 6**). These results may suggest MRA may have beneficial effects for decreasing cardiovascular events in pre-dialysis and on-dialysis patients with CKD. In this study, the effects of ACEIs and DRIs for cardiovascular diseases in patients with CKD could not be analyzed owing to lack of study number. Additionally, it should be note that heterogeneity among cohorts and possible publication bias (**Figure 3**) affected the results of this study. Therefore, further randomized controlled studies will need to investigate the effects of RAAS blockers for cardiovascular disease in patients with CKD.

TABLE 4 | The effects of angiotensin receptor blockers and angiotensin converting enzyme inhibitor combination therapy on the development of cardiovascular disease in pre-dialysis patients with CKD.

Class of RAAS blocker	Authors, Year; Reference number	Patients	Study design	Study protocol	Results
Combination therapy of ACEI and ARB	Torres et al., 2014; 26	N = 486; eGFR 25 < 60 (mL/min/1.73 m^2); autosomal dominant polycystic kidney disease	RCT; Multicenter double-blind placebo-controlled clinical trial; Secondary outcomes	Combination of lisinopril and telmisartan compared with lisinopril and placebo (Dose was not shown); 5–8 years	There were no significant differences between the lisinopril–placebo group and the lisinopril–telmisartan group in the rate of hospitalization for cardiovascular disorders (2.30 events per 100 person-years and 1.28 events per 100 person-years, respectively) in patients with CKD.
	Fried et al., 2013; 7	N = 1448; Stage 2–3	RCT; Multicenter double-blind placebo-controlled clinical trial	Losartan 50–100 mg plus lisinopril 10–40 mg a day or losartan 50–100 mg plus placebo; 4 years	There was no significant difference in the rate of cardiovascular events, including myocardial infarction, stroke, and hospitalization for congestive heart failure, between the two groups in patients with CKD (HR, 0.97; 95% CI, 0.76 to 1.23; p = 0.79).

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; RAAS, renin–angiotensin–aldosterone system; RCT, randomized controlled trial

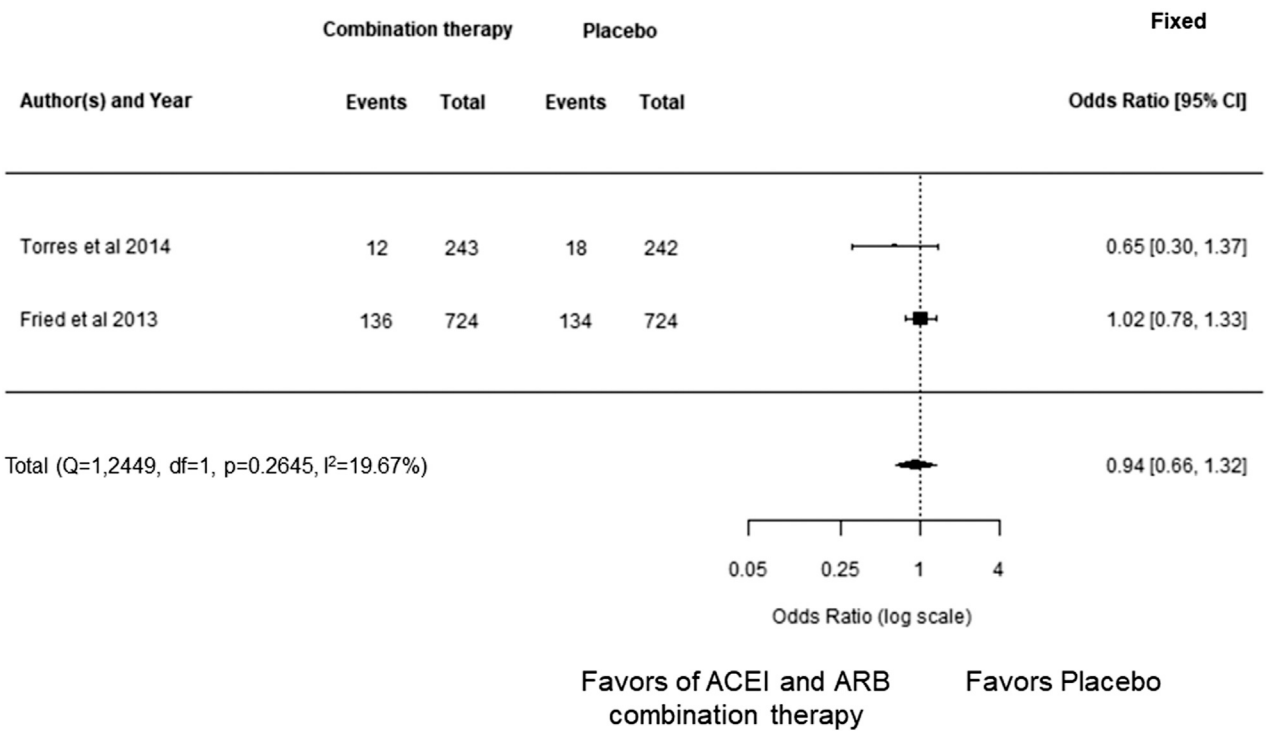


FIGURE 6 | Forest plot describing a comparison of the incidence of cardiovascular events between combination therapy with ARBs and ACEIs and placebo in pre-dialysis patients with CKD. ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CI, confidence intervals; CKD, chronic kidney disease.

Our systematic review and meta-analysis have several limitations. First, we only searched for studies that were published in English. Second, we only used the PubMed database to identify publications. Third, cardiovascular outcomes were different among studies. For example, one study included stroke as a cardiovascular event (Tsujimoto and Kajio, 2018), while another study did not include stroke as a cardiovascular event (Cice et al., 2010). Fourth, the random-effects model was used in the outcome analyses because of the high heterogeneity, which may be related to different doses and intervention duration of the RAAS blockers. Therefore, studies that are designed as high-quality, large-scale randomized controlled trials are required to evaluate the effectiveness of RAAS blockers to protect against the development of cardiovascular disease in patients with CKD.

In conclusion, RAAS blockers significantly reduced cardiovascular events in on-dialysis patients with CKD, but there were no significant results in pre-dialysis patients with CKD because of the heterogeneity in each study. Among the RAAS blockers, MRAs may decrease cardiovascular events in pre-dialysis and on-dialysis patients with CKD. However, other RAAS blockers, such as ARBs, ACEIs, and DRIs, did not show these cardioprotective effects in these populations. This was at least partially because of the small number of cohorts. Therefore, additional large-scale cohorts are required to investigate the effects of RAAS blockers on cardiovascular disease in patients with CKD.

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

KY conducted database search, performed meta-analysis and wrote manuscript. KI and YM revised the manuscript critically for important intellectual content.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.662544/full#supplementary-material

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