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Population data science in cardiovascular medicine

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Population data science in cardiovascular medicine

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SGLT2is vs. GLP1RAs Reduce Cardiovascular and All-Cause Mortality

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Lin et al. recently did a network meta-analysis based on cardiovascular (CV) outcome trials (CVOTs) of sodium-glucose cotransporter 2 inhibitors (SGLT2is) and those of glucagon-like peptide-1 receptor agonists (GLP1RAs). Due to the absence of CVOTs directly comparing SGLT2is with GLP1RAs, Lin et al.'s network meta-analysis identified the indirect evidence that SGLT2is vs. GLP1RAs reduced hospitalization for heart failure (HHF) but did not reduce CV death and all-cause mortality (ACM) in patients with type 2 diabetes (T2D). We did another meta-analysis incorporating those CV outcome cohort studies directly comparing SGLT2is with GLP1RAs, and identified that SGLT2is vs. GLP1RAs were significantly associated with the lower risks of not only HHF but also CV death and ACM. These findings may suggest that SGLT2is should be considered over GLP1RAs in terms of preventing CV and all-cause death and HHF in T2D patients.

Keywords: GLP1Ras, type 2 diabetes, death, cardiovascular, renal, SGLT2is

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INTRODUCTION

We read with great interest Lin et al.'s network meta-analysis (1) recently published in the journal *Diabetologia*. By performing network meta-analysis based on 21 placebo-controlled cardiovascular (CV) outcome trials (CVOTs), Lin et al. (1) yielded the estimators for the relative cardiorenal efficacy of three new classes of hypoglycemic drugs: sodium-glucose cotransporter 2 inhibitors (SGLT2is), glucagon-like peptide-1 receptor agonists (GLP1RAs), and dipeptidyl peptidase-4 inhibitors. They identified that SGLT2is vs. GLP1RAs reduced hospitalization for heart failure (HHF) and composite kidney outcome (CKO), but did not reduce CV death [risk ratio (RR) 0.97, 95% confidence interval (CI) 0.87–1.09] and all-cause mortality (ACM) (RR 0.97, 95% CI 0.88–1.08). Due to in Lin et al.' article (1) the effect estimators among active drugs deriving from indirect evidence, the relative efficacy of SGLT2is vs. GLP1RAs revealed by Lin et al. (1) requires to be confirmed by further studies directly comparing these two classes, as stated in the last paragraph of Lin et al.' article (1). Hence, we included CV outcome cohort studies directly comparing SGLT2is with GLP1RAs, due to the absence of CVOTs directly comparing them, to conduct another meta-analysis to determine the relative efficacy of SGLT2is vs. GLP1RAs on CV death and ACM as well as other cardiorenal outcomes.

METHODS

This meta-analysis was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (2). Its study protocol had been registered in PROSPERO (Registration number: CRD42021273721) before the study selection began. The studies eligible for inclusion were propensity score-matched (PSM) cohort studies which compared SGLT2is with GLP1RAs in terms of the effects of cardiorenal endpoints in patients with type 2 diabetes (T2D). Seven endpoints of interest were CV death, ACM, HHF, CKO, major adverse cardiovascular events (MACE), myocardial infarction (MI), and stroke. Composite kidney outcome and MACE were defined in detail in study protocol. PubMed and Embase were searched until August 16th 2021 to identify relevant cohort studies. The search terms mainly used in this meta-analysis were: "type 2 diabetes," "T2D," "sodium-glucose transporter 2 inhibitors," "SGLT*," "glucagon-like peptide-1 receptor agonists," "GLP1*," "death," "mortality," "cardiovascular," "CKD," "renal," and "PSM." Two authors independently assessed included studies for quality according to the Newcastle-Ottawa Scale (NOS) for cohort studies (3). Any agreements between them were addressed by discussion with a third author. We performed random-effects meta-analysis with the maximum likelihood method using hazard ratios (HRs) and 95% CIs derived from included articles. I^2 statistic was calculated to measure heterogeneity. All data analyses were done in Stata/MP (version 16.0).

RESULTS

In this meta-analysis we included 9 large PSM cohort studies (4–12). Each of included studies was assessed as high quality according to NOS. The detailed characteristics of included studies are shown in **Supplementary Table 1**, which also provides the outcome data extracted from included articles. Meta-analysis involving 93,710 SGLT2is users and 94,935 GLP1RAs users from seven trials showed that SGLT2is and GLP1RAs had similar risk of MACE (HR 0.97, 95% CI 0.93–1.02; P for drug effect =0.24; **Figure 1.1**). Meta-analysis involving 93,710 SGLT2is users and 94,935 GLP1RAs users from seven trials showed that SGLT2is and GLP1RAs had similar risk of MI (HR 0.95, 95% CI 0.88–1.03; P for drug effect = 0.22; **Figure 1.2**). Meta-analysis involving 93,710 SGLT2is users and 94,935 GLP1RAs users from seven trials showed that SGLT2is and GLP1RAs had similar risk of stroke (HR 1.02, 95% CI 0.94–1.11; P for drug effect = 0.65; **Figure 1.3**). Meta-analysis involving 62,419 SGLT2is users and 63,644 GLP1RAs users from three trials showed that SGLT2is vs. GLP1RAs were significantly associated with an 18% reduction in risk of CV death (HR 0.82, 95% CI 0.68–0.99; P for drug effect = 0.04; **Figure 1.4**). Meta-analysis involving 101,636 SGLT2is users and 97,703 GLP1RAs users from six trials showed that SGLT2is vs. GLP1RAs were significantly associated with an 8% reduction in risk of ACM (HR 0.92, 95% CI 0.85–0.99; P for drug effect = 0.03; **Figure 1.5**). Meta-analysis involving 107,858 SGLT2is users and 107,563 GLP1RAs users from 8 trials showed that SGLT2is vs. GLP1RAs were significantly associated with a 20% reduction in risk of HHF (HR 0.80, 95% CI 0.70–0.92; P for drug effect <0.01; **Figure 1.6**). Meta-analysis involving 30,641 SGLT2is users and 33,395 GLP1RAs users from two trials showed that SGLT2is and GLP1RAs had similar risk of CKO (HR 0.97, 95% CI 0.92–1.02; P for drug effect = 0.25; **Figure 1.7**).

DISCUSSION

This meta-analysis is the first one that provided the direct evidence regarding the relative efficacy of SGLT2is vs. GLP1RAs on death and cardiorenal endpoints in T2D patients by incorporating large PSM cohort studies directly comparing SGLT2is with GLP1RAs. Consistent with the indirect evidence from Lin et al.'s network meta-analysis (1), the direct evidence in our meta-analysis showed that SGLT2is vs. GLP1RAs significantly reduced HHF, but did not significantly affect MACE, MI, and stroke. On the contrary, the indirect evidence from Lin et al.'s network meta-analysis (1) showed that SGLT2is vs. GLP1RAs significantly reduced CKO, whereas the direct evidence in our meta-analysis showed that SGLT2is and GLP1RAs had the similar risk of CKO. The reason for this probably is that our meta-analysis was not powered to assess CKO since only two studies were included in the pooled analysis for this outcome. Most importantly, Lin et al.'s meta-analysis (1) failed to reveal the significantly reduced risks of CV death and ACM with SGLT2is vs. GLP1RAs in T2D patients, whereas our meta-analysis revealed those. Possible reasons are as follows. First, Lin et al.'s meta-analysis (1) gave the indirect evidence whereas ours gave the direct evidence. Second, for these two death outcomes our meta-analysis was with greater statistical power since cohort studies included in this meta-analysis had greater sample sizes than CVOTs. Third, our meta-analysis was based on HRs, whereas Lin et al.'s meta-analysis (1) was based on RRs. Compared to RRs, HRs additionally contain the information of the time when events happen apart from the information of whether events happen.

From 2015 to 2021, published are eight CVOTs (13–20) targeting the relative efficacy of GLP1RAs vs. placebo on cardiorenal outcomes in T2D patients. Although most of these CVOTs demonstrated the obvious benefits of GLP1RAs vs. placebo on CV composite and/or renal composite outcomes, none of them was powered enough to assess individual critical endpoints such as CV death and ACM. Therefore, several meta-analyses (21–23) based on the CVOTs of GLP1RAs were conducted to have confirmed the relative benefits of GLP1RAs compared to placebo on various cardiorenal outcomes including the above two death endpoints in T2D patients. Similar with

Abbreviations: SGLT2is, sodium-glucose cotransporter 2 inhibitors; GLP1RAs, glucagon-like peptide-1 receptor agonists; CVOTs, cardiovascular outcome trials; T2D, type 2 diabetes; PSM, propensity score-matched; RR, risk ratio; HR, hazard ratio; CI, confidence interval; MACE, major adverse cardiovascular events; HHF, hospitalization for heart failure; CV, cardiovascular; MI, myocardial infarction; ACM, all-cause mortality; CKO, composite kidney outcome; PRISMA, preferred reporting items for systematic reviews and meta-analyses; NOS, Newcastle-Ottawa Scale; ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes.

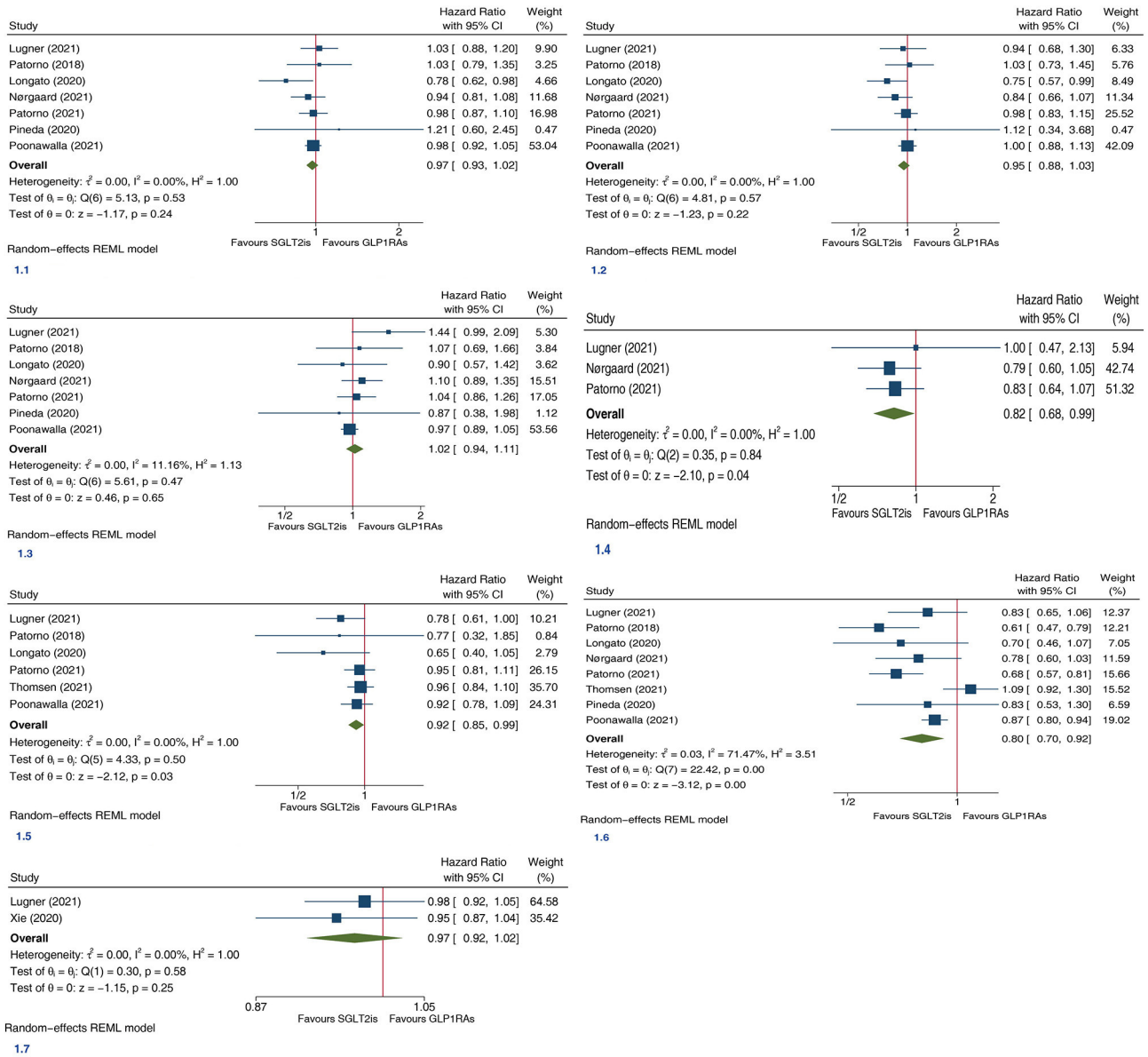

FIGURE 1 | Forest plots of the efficacy of SGLT2is vs. GLP1RAs on seven (**1.1**, Major adverse cardiovascular events; **1.2**, myocardial infarction; **1.3**, stroke; **1.4**, cardiovascular death; **1.5**, all-cause mortality; **1.6**, hospitalization for heart failure; **1.7**, composite kidney outcome) cardiorenal and death endpoints in patients with type 2 diabetes. SGLT2is, sodium-glucose cotransporter 2 inhibitors; GLP1RAs, glucagon-like peptide-1 receptor agonists; CI, confidence interval; REML, maximum likelihood method.

GLP1RAs, SGLT2is were confirmed, by relevant meta-analyses (24–26) based on their CVOTs, with the distinct benefits on multiple cardiorenal and mortality endpoints compared to placebo in T2D patients. Accordingly, the latest international consensus report (27) by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommends that both SGLT2is and GLP1RAs should be used in T2D patients with established CV or renal disease and in those at high cardiorenal risk to prevent cardiorenal events and deaths. It is worth mentioning that the cardiorenal benefits of SGLT2is have extended from T2D patients to renal failure patients and heart failure patients including those with heart failure and a reduced ejection fraction and those with heart failure and a preserved ejection fraction. On the contrary, the cardiorenal benefits of GLP1RAs are only limited to T2D patients, and their cardiorenal benefits have not been observed in patients with renal or heart failure without T2D until now.

Due to the absence of CVOTs comparing GLP1RAs and SGLT2is, the relative efficacy of these two drug classes on cardiorenal endpoints is not given in the ADA and EASD

consensus report (27). Thus, several network meta-analyses (1, 28, 29) including Lin et al.'s network meta-analysis (1) tried to derive the estimators of their relative cardiorenal efficacy by incorporating the indirect evidence from placebo-controlled CVOTs of GLP1RAs and those of SGLT2is. However, the different characteristics of those CVOTs included in the network meta-analyses (1, 28, 29) considerably weakened the credibility of the indirect evidence regarding the relative cardiorenal efficacy of GLP1RAs and SGLT2is. In contrast, more reliable is the direct evidence regarding their relative cardiorenal efficacy deriving from this present meta-analysis based on large PSM cohort studies directly comparing SGLT2is with GLP1RAs in terms of cardiorenal endpoints. Different from Lin et al.'s findings (1) that SGLT2is vs. GLP1RAs reduced HHF and CKO, but did not reduce CV death and ACM in T2D patients, our findings are that SGLT2is vs. GLP1RAs were significantly associated with the lower risks of not only HHF but also CV death and ACM. These findings may suggest that SGLT2is should be considered over GLP1RAs in terms of preventing CV and all-cause death and HHF in T2D patients.

SGLT2is and GLP1RAs exert their glycemic control effects via different mechanisms of actions: SGLT2is promote urinary glucose excretion (30), while GLP1RAs enhance insulin secretion and suppress glucagon secretion. Moreover, both of these two drug classes have favorable effects on some cardiometabolic risk factors such as blood pressure and body weight. More importantly, the long-term cardiorenal benefits exhibited by them are almost independent of their hypoglycemic effects. SGLT2is exert the long-term cardiorenal benefits mainly by improving mitochondrial function and myocardial efficiency, and reducing oxidative stress, inflammation, fibrosis, and sympathetic nervous system activation (31); while GLP1RAs exert these benefits mainly by improving endothelial function, reducing oxidative stress and vascular inflammation, and producing a natriuretic and vasodilator effect (32, 33). Besides, the benefits of these two drug classes on cardiometabolic risk factors also contribute to their benefits on long-term cardiorenal endpoints. Among the mechanisms of improving long-term cardiorenal prognosis, there are some similar mechanisms for these two drug classes, whereas there are more different mechanisms for them. Since those different mechanisms for SGLT2is and GLP1RAs might be complementary, the combination therapy of SGLT2is and GLP1RAs might yield more cardiorenal benefits than SGLT2is or GLP1RAs monotherapy. Future randomized CVOTs assessing this kind of combination therapy will be clinically meaningful.

Compared to previous network meta-analyses (1, 28, 29) based on those placebo-controlled CVOTs of SGLT2is and GLP1RAs, our meta-analysis is the first one that provided the direct evidence regarding the relative cardiorenal efficacy of SGLT2is vs. GLP1RAs. Compared to the eligible cohort studies included in our meta-analysis, this meta-analysis study has the following two strengths. First, included cohort studies produced many inconsistent findings. For example, some of the included cohort studies showed the significant association of SGLT2is with lower risks of HHF and MACE compared to GLP1RAs, whereas others showed that these two drug classes had similar risks of HHF and MACE. In contrast, this meta-analysis study addressed these controversies. Second, none of the included cohort studies revealed the significant association of SGLT2is with lower risks of CV death and ACM compared to GLP1RAs, which suggested the limited statistical power for these two death endpoints among included cohort studies. In contrast, this meta-analysis study, with the sufficient statistical power, revealed SGLT2is with significantly lower risks of CV death and ACM.

Although this meta-analysis provided the direct evidence regarding the relative cardiorenal efficacy of SGLT2is vs. GLP1RAs, the evidence derived from cohort studies, which involve more risks of biases than randomized trials do. Although the cohort studies included in this meta-analysis performed PSM analysis to adjusted lots of confounding factors, there were probably some omissive factors. Thus, there is a need for CVOTs comparing SGLT2is with GLP1RAs in T2D patients, to further confirm the direct evidence revealed in this meta-analysis. Although no substantial heterogeneity was observed in the meta-analyses on most of the endpoints assessed in this study, the substantial heterogeneity ($I^2 = 71.47\%$) was observed in the meta-analysis on HHF. Although we utilized the random-effects model to derive the conservative pooled results, it would be beneficial that future studies could perform relevant subgroup analyses for this outcome to explore the sources of heterogeneity.

CONCLUSION

Lin et al. (1) revealed that SGLT2is vs. GLP1RAs significantly reduced HHF and CKO, but did not reduce CV death and ACM in T2D patients, whereas we further revealed that SGLT2is vs. GLP1RAs were significantly associated with the lower risks of not only HHF but also CV death and ACM. These findings may suggest that SGLT2is should be considered over GLP1RAs in terms of preventing CV and all-cause death and HHF in T2D patients, although further validation by CVOTs directly comparing SGLT2is with GLP1RAs in T2D patients would be beneficial.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

MQ: design and writing manuscript. MQ, X-BW, and WW: conduct, data collection, and analysis. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.791311/full#supplementary-material

Supplementary Table 1 | Characteristics of included studies and extracted data.

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The CSP (Cardiogenic Shock Prognosis) Score: A Tool for Risk Stratification of Cardiogenic Shock

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Background: Cardiogenic shock (CS) is a critical condition and the leading cause of mortality after acute myocardial infarction (AMI). Scores that predict mortality have been established, but a patient's clinical course is often nonlinear. Thus, factors present during acute care management may be explored. This study intended to develop a risk-predictive model for patients with CS.

Methods: In this observational study, adult patients who received inotropic support at the Emergency Room (ER) from January 2017 to August 2020 and were admitted to the cardiac care unit (CCU) with a diagnosis of CS were enrolled in this study. Patients with out-of-hospital cardiac arrest, inotropic support for bradycardia, and survival <24 h after ER arrival were excluded. A total of 311 patients were enrolled and categorized into derivation ($n = 243$) and validation ($n = 68$) cohorts.

Results: A history of coronary artery disease, multiple inotrope use, ejection fraction <40%, lower hemoglobin concentration, longer cardiopulmonary resuscitation duration, albumin infusion, and renal replacement therapy were identified as independent prognostic factors for in-hospital mortality. The cardiogenic shock prognosis (CSP) score was established as a nomogram and three risk groups were identified: low-risk (score 115, 0% of mortality), medium-risk (score 116–209, 8.75% of mortality), and high-risk (score 210, 66.67% of mortality). The area-under-the-curve (AUC) of the CSP score was 0.941, and the discrimination value in the validation cohort was consistent (AUC = 0.813).

Conclusions: The CSP score represents a risk-predictive model for in-hospital mortality in patients with CS in acute care settings. Patients identified as the high-risk category may have a poor prognosis.

Keywords: cardiogenic shock, hospital mortality, nomogram, risk factors, prognosis, cardiogenic shock prognosis score

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INTRODUCTION

Cardiogenic shock (CS) is the most severe form of acute heart failure and as a state of ineffective cardiac output, it results in clinical and biochemical manifestations of inadequate tissue perfusion (1). CS complicates up to 10% of cases of acute myocardial infarction (AMI) and is a leading cause of mortality after AMI (2). Despite advances in treatment options, CS mortality remains high at

∼35–50% and is a challenging condition to manage in acute care settings (1, 2).

Several risk scores that help predict short-term mortality have been established (3–5). The SHOCK score and Intraaortic Balloon Pump in Cardiogenic Shock II trial (IABP-SHOCK II) trial were developed based on patients with MI and shock (3, 4). The CardShock study enrolled patients with all etiologies of CS, but more than half were acute CS (ACS) cases (5). The epidemiology of shock has evolved in recent years with AMI-related CS (AMICS) accounting for less than one-third of all CS cases, hence the role of hemodynamic stabilization using pharmacologic and nonpharmacologic therapies has been inconsistent (6, 7). All these risk scores revealed modest prognostic accuracy, with an internal validation area under the curve (AUC) of.74, 0.79, and.71, respectively (3–5).

The risk factors included in these models were mostly from the medical history and biochemistry results at admission; (3–5) however, CS is a critical condition that is ever-evolving from pre-shock to refractory shock states. Thus factors during a patient's acute care management may also affect the prognosis (2, 8). Besides, optimal management of CS requires timely interventions to prevent multiorgan system dysfunction (6). Early classification of CS may be needed to stratify illness severity to provide appropriate treatments and improve outcomes. Therefore, this study aimed to develop a risk-predictive model of in-hospital mortality for CS patients from varied etiologies, based on their medical history, examination results, and interventions during the early period of acute care to aid physicians in risk stratification and prognostication.

METHODS

Study Design

This retrospective study was conducted in a tertiary hospital with 110,000 annual emergency room (ER) visits. The Institutional Review Board of National Taiwan University Hospital (NTUH) approved this study (202001104RINC).

Study Population

This study enrolled 520 non-traumatic adult patients (≥20 years old) who received inotropic support at the ER and subsequent admission to the cardiac care unit (CCU) with a diagnosis code of cardiogenic shock from January 2017 to August 2020. A total of 140 patients who had an out-of-hospital cardiac arrest (OHCA), 66 who received inotropic support for bradycardia and conduction system disorders, and 3 with survival <24 h after ER arrival were excluded. Finally, 311 patients were included in this study and categorized into the derivation cohort ($n = 243$, January 2017 – December 2019) and the validation cohort ($n = 68$, January 2020–August 2020) based on the timing of ER visits to develop the predictive model (**Figure 1**).

Measurements

The following information was collected from the individual medical records: age, sex, preexisting comorbidities, clinical findings, laboratory and imaging exams nearest to the shock time at the ER, medications administered and clinical management at the acute care settings, discharge diagnosis, and length of hospital stay.

Vital signs were taken at the triage. Unconscious patients were defined if there was acute consciousness change on admission as documented on the medical record by the physician or the motor component of the Glasgow Coma Scale (GCS) has a score <6. Multiple inotrope use was the need for two or more of dopamine, norepinephrine, epinephrine, vasopressin, or dobutamine simultaneously to achieve hemodynamic stability. Patients who only required room air, nasal cannula, oxygen masks, or nonrebreathing masks were classified as having low respiratory support; whereas patients who required bilevel positive airway pressure (BiPAP), high flow oxygen therapy, or endotracheal intubation were classified as having high respiratory support.

The fluid challenge was considered when there was an infusion of more than 250 mL of a crystalloid before other interventions during shock. Coronary angiography (CAG) performed within 24 h of shock was considered emergent. Acute management for cardiogenic shock, when performed within 72 h of ER arrival, are as follows: cardiopulmonary resuscitation (CPR) attempt where CPR was performed at the ER or in the CCU; echocardiogram; renal replacement therapy (RRT) which encompassed patients who received dialysis, sustained low-efficiency dialysis (SLED), or continuous veno-venous hemofiltration (CVVH), after manifesting symptoms of fluid overload, respiratory distress, or severe electrolyte imbalance; transcutaneous pacing (TCP), referred as the noninvasive mode of temporary pacing by applying pads to the chest; pacemaker implantation, referred as the invasive method of inserting either temporary or permanent pacemakers (PPM); and the use of mechanical circulatory support (MCS) devices which included extracorporeal membrane oxygenation (ECMO) or intra-aortic balloon pump (IABP) insertion.

Discharge diagnoses were recorded based on the judgment of attending physicians, as documented in the medical discharge summary. Cases of STEMI, NSTEMI, and post-MI complications were classified as ACS; heart failure was classified as acute decompensated heart failure (ADHF); different types of cardiomyopathy (stress, restrictive, hypertrophic, dilated, ischemic) were classified as cardiomyopathy; tachyarrhythmia and bradyarrhythmia were classified as arrhythmia; CS with sepsis or pneumonia were classified as CS with septic complications; and valvular heart conditions, myocarditis, cardiac tamponade, aortic dissection, and pulmonary hypertension were considered as other causes.

Outcome Measures

The primary outcome of this study was to identify predictors of in-hospital mortality of patients with CS. The secondary outcome was a risk-stratified predictive model and the validation of its performance with existing scores. The SHOCK score, IABP-SHOCK II risk score, and CardShock risk score were validated using the closest equivalent variable available from this study's dataset (**Supplementary Table 1**). Under the SHOCK score, unconscious patients were substituted for patients with anoxic brain damage, shock on admission was documented if the

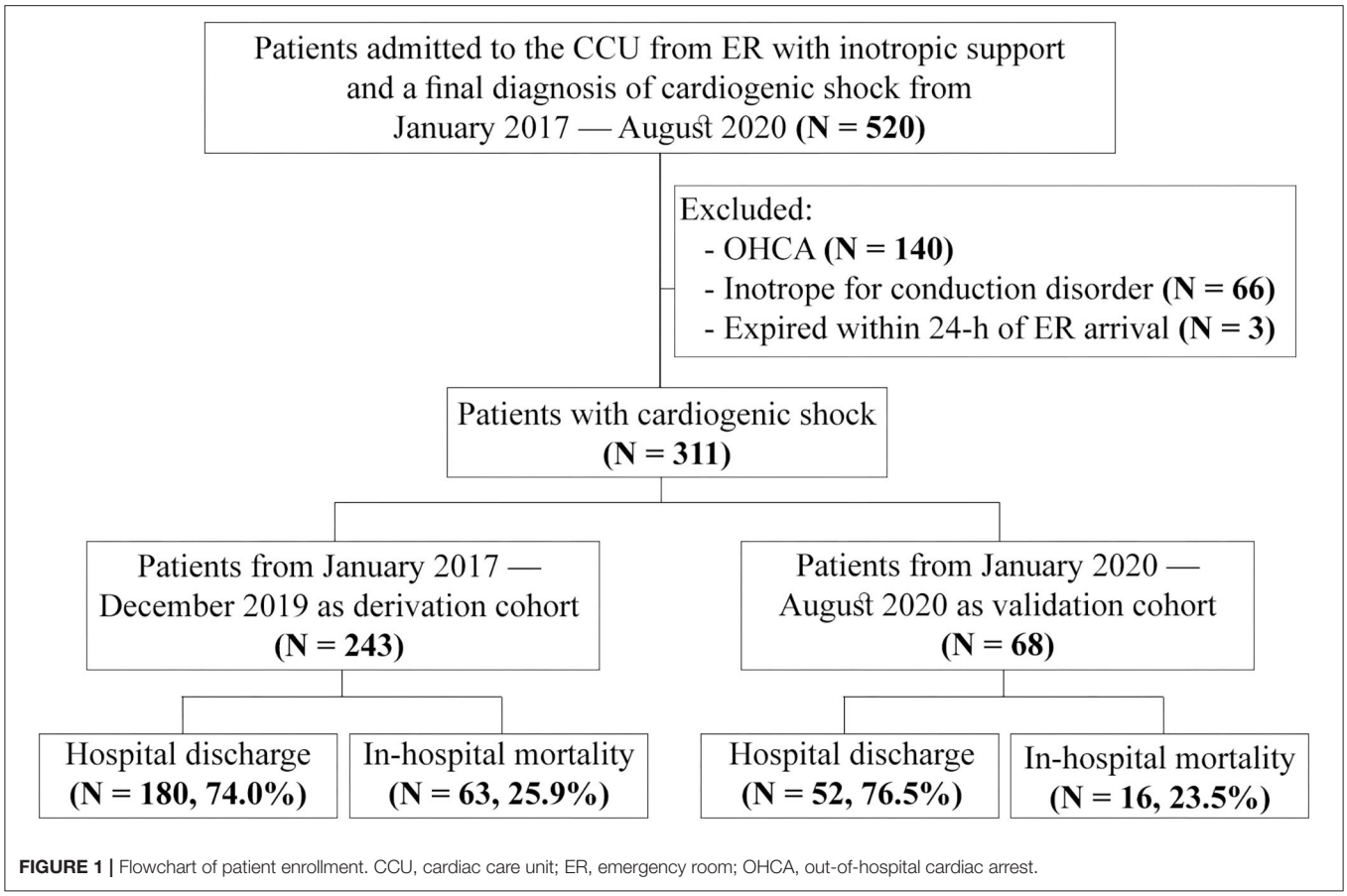

FIGURE 1 | Flowchart of patient enrollment. CCU, cardiac care unit; ER, emergency room; OHCA, out-of-hospital cardiac arrest.

patient's systolic blood pressure (SBP) was <90 mmHg upon ER arrival, non-inferior MI was not included due to the difference in the study population, and end-organ hypoperfusion was not included due to limited data from medical records. Besides, non-inferior MI would garner no point if left ventricular ejection fraction (LVEF) was added to the scoring system, which was the case when obtaining the SHOCK score for validation. Data on glucose level and TIMI (Thrombolysis in Myocardial Infarction) flow grade after percutaneous coronary intervention (PCI) were not available for computing the IABP-SHOCK II trial score. For the CardShock risk score, unconscious patients were substituted for confusion at presentation.

Statistical Data Analyses

Results are presented using frequencies for categorical variables and medians with quartiles for continuous variables. Fisher's exact or Pearson's chi-squared test for categorical variables and the Mann-Whitney U test for continuous variables were used for group comparisons. From the derivation cohort, 32 independent variables with significant associations ($p < 0.05$) and clinical importance in the univariate analysis were entered into the forward multiple logistic regression analysis (>0.1 for elimination) to identify the predictors of in-hospital mortality. The resulting variables from the multivariate analysis were then used to develop a risk-prediction nomogram. Discrimination was assessed with the AUC while calibration was evaluated with Hosmer-Lemeshow (HL) goodness-of-fit x^2 estimates. Three risk groups for in-hospital mortality (low-, medium-, and high-risk) were defined by splitting the scoring system into tertiles of patients, patterned after Maupain et al. (9).

All statistical analyses were performed using SPSS Statistics for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA), and R statistical software version 4.0.2 was used to construct the nomogram.

RESULTS

Characteristics of Study Subjects

The baseline characteristics, laboratory, and imaging examinations of patients in the derivation cohort are presented in **Table 1**. The median age is 70 years and the majority of patients are men (60.16%). The incidence of coronary artery disease (CAD), heart failure, cardiomyopathy, and renal disease was determined to be higher in the patients who did not survive to discharge, whereas dyslipidemia was more frequent in the patients who survived. Echocardiograms with LVEF lower than 40% and valvular lesions were also observed more frequently in patients who failed to survive.

Clinical management of patients who did not survive had received albumin infusion, multiple inotrope use, and heparin more frequently, as seen in **Table 2**. These patients also more frequently required high respiratory support, MCS devices,

TABLE 1 | Baseline characteristics and examination results between groups in the derivation cohort.

Variables	Survival to discharge			
	Total patients ***N* = 243**	**Survived** ***N* = 180 (74.07%)**	**Non-survived** ***N* = 63 (25.92%)**	***P-value***
Age (years)	70 (59–80)	71 (59–80.5)	70 (59–78)	0.566
Sex (male)	147 (60.5)	104 (57.8)	43 (68.3)	0.178
Clinical findings at triage				
SBP (mmHg)	100 (83–126)	102 (85–128)	94 (79–113)	0.021
Unconscious	39 (16.0)	23 (12.8)	16 (25.4)	0.027
Comorbidities				
Smoking	51 (21.0)	39 (21.7)	12 (19.0)	0.722
Alcoholism	9 (3.7)	5 (2.8)	4 (6.3)	0.243
Hypertension	126 (51.9)	96 (53.3)	30 (47.6)	0.466
Diabetes mellitus	88 (36.2)	62 (34.4)	26 (41.3)	0.362
Dyslipidemia	68 (28.0)	56 (31.1)	12 (19.0)	0.074
Old MI	10 (4.1)	8 (4.4)	2 (3.2)	0.739
CAD	77 (31.7)	49 (27.2)	28 (44.4)	0.013
Post CABG	12 (4.9)	10 (5.6)	2 (3.2)	0.529
Heart failure	65 (26.7)	38 (21.1)	27 (42.9)	0.001
Arrhythmia	67 (27.6)	47 (26.1)	20 (31.7)	0.415
Cardiomyopathy	25 (10.3)	14 (7.8)	11 (17.5)	0.034
Renal disease	37 (15.2)	22 (12.2)	15 (23.8)	0.040
ESRD	24 (9.9)	17 (9.4)	7 (11.1)	0.806
CVA	29 (11.9)	25 (13.9)	4 (6.3)	0.121
Malignancy	31 (12.8)	24 (13.3)	7 (11.1)	0.673
Laboratory exams				
pH value	7.35 (7.26–7.40)	7.35 (7.27–7.41)	7.31 (7.23–7.37)	0.062
Lactic acid (mmol/L)	3.38 (2.13–5.77)	3.05 (2.10–5.6)	5.26 (2.08–8.19)	0.000
Hemoglobin (g/dL)	12.70 (10.58–14.30)	13.10 (10.50–13.75)	11.80 (9.85–13.75)	0.021
Platelet (K/uL)	203 (156.50–266)	210 (153–253)	183 (140–266)	0.040
INR	1.08 (1.00–1.30)	1.06 (1.04–1.28)	1.27 (1.08–1.71)	0.000
Total bilirubin (mg/dL)	0.88 (0.65–1.99)	0.81 (0.62–1.54)	1.18 (0.69–3.87)	0.064
Creatinine (mg/dL)	1.65 (1.10–3.08)	1.50 (1.14–3.55)	2.20 (1.40–3.30)	0.001
eGFR	36 (18–59)	40 (21–65)	30 (14–43)	0.002
Sodium (mmol/L)	134 (130–137)	134.5 (130–137)	132 (127–134)	0.015
Potassium (mmol/L)	4.4 (3.7–5.1)	4.3 (3.6–5.4)	4.5 (3.7–5.1)	0.552
Troponin T (ng/L)	85.93 (28.91–370.20)	54.09 (28.18–283.15)	162.1 (85.82–399.40)	0.000
NT-proBNP (pg/mL)	4,932 (1,125–17,233)	3,470 (1,316–19,433)	13,415 (4,244–26,213)	0.000
ECG characteristics				
HR (bpm)	83 (54–108)	78 (64–116)	94 (76–111)	0.003
QRS duration (ms)	102 (88–138)	100 (92–149)	116 (97–146)	0.013
Chest X-ray				
Cardiomegaly	158 (65.0)	117 (65.0)	41 (65.1)	1.000
Lung edema	44 (18.1)	39 (21.7)	5 (7.9)	0.021
Pleural effusion	67 (27.6)	44 (24.4)	23 (36.5)	0.073
Echocardiogram				
LVEF < 40%	81 (36.8)	47 (28.8)	34 (59.6)	0.000
Valvular lesions	117 (48.1)	78 (43.3)	39 (61.9)	0.013

Data presented as no (%) or as median (IQR).

CABG, coronary artery bypass grafting; CAD, coronary artery disease; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; ER, emergency room; ESRD, end-stage renal disease; INR, international normalized ratio; LVEF, left ventricular ejection fraction; old MI, old myocardial infarction; NT-proBNP, N-terminal-pro B-type natriuretic peptide; SBP, systolic blood pressure.

TABLE 2 | Treatments and diagnosis classification between groups in the derivation cohort.

Variables	Survival to discharge			
	Total patients ***N* = 243**	**Survived** ***N* = 180 (74.0%)**	**Non-survived** ***N* = 63 (25.9%)**	***P-value***
Medications				
Bronchodilator	93 (38.3)	62 (34.4)	31 (49.2)	0.050
Albumin	116 (47.7)	64 (35.6)	52 (82.5)	0.000
Diuretic	154 (63.4)	112 (62.2)	42 (66.7)	0.548
Inotrope use				
Single inotrope	116 (47.7)	112 (62.2)	4 (6.3)	0.000
Multiple inotropes	127 (52.3)	68 (37.8)	59 (93.7)	—
NTG	70 (28.8)	55 (30.6)	15 (23.8)	0.337
Aspirin	124 (51.0)	97 (53.9)	27 (42.9)	0.145
P2Y12 inhibitors	117 (48.1)	90 (50.0)	27 (42.9)	0.380
Heparin	146 (60.1)	97 (53.9)	49 (77.8)	0.001
Clinical management				
Respiratory support				
Low	99 (40.7)	93 (51.7)	6 (9.5)	0.000
High	144 (59.3)	87 (48.3)	57 (90.5)	—
Fluid challenge	96 (39.5)	68 (37.8)	28 (44.4)	0.372
Emergent CAG	119 (49.0)	93 (51.7)	26 (41.3)	0.188
PCI	76 (63.9)	59 (63.4)	17 (65.4)	0.291
CPR attempt (min)				
None	203 (83.5)	162 (90.0)	41 (65.1)	0.000
<10	18 (7.4)	13 (7.2)	5 (7.9)	—
10-20	6 (2.5)	1 (0.6)	5 (7.9)	—
>20	16 (6.6)	4 (2.2)	12 (19.0)	—
RRT	71 (29.2)	29 (16.1)	42 (66.7)	0.000
TCP	42 (17.3)	35 (19.4)	7 (11.1)	0.175
Pacemaker implantation	72 (29.6)	62 (34.4)	10 (15.9)	0.006
MCS	58 (23.9)	26 (14.4)	32 (50.8)	0.000
Component transfusion	134 (55.1)	79 (43.9)	55 (87.3)	0.000
CABG	16 (6.6)	7 (3.9)	9 (14.3)	0.008
Discharge diagnosis classification				
ACS	79 (32.5)	61 (33.9)	18 (28.6)	0.532
ADHF	58 (23.9)	39 (21.7)	19 (30.2)	0.229
Arrhythmia	56 (23.0)	49 (27.2)	7 (11.1)	0.009
Cardiomyopathy	15 (6.2)	10 (5.6)	5 (7.9)	0.545
Septic complication	7 (2.9)	3 (1.7)	4 (6.3)	0.076
Others	25 (10.3)	15 (8.3)	10 (15.9)	0.097
CCU stay (days)	5 (3–13)	4 (3–9)	14 (5–33)	0.000
Hospital stay (days)	12 (6–27)	12 (6–24)	14 (6–33)	0.580

Data presented as no (%) or as median (IQR).

ACS, acute coronary syndrome; ADHF, acute decompensated heart failure; CABG, coronary artery bypass grafting; CAG, coronary angiography; CCU, cardiac care unit; CPR, cardiopulmonary resuscitation; MCS, mechanical circulatory support devices; NTG, nitroglycerin; PCI, percutaneous coronary intervention; RRT, renal replacement therapy; TCP, transcutaneous pacing.

CABG surgery, component transfusion, and RRT; whereas pacemaker implantation was seen more in patients who survived. Patients who did not develop cardiac arrest had a better prognosis and among the patients with cardiac arrest following CS, resuscitation efforts were longer for patients who did not survive than for those who did.

The discharge diagnosis classification indicated that ACS was perceived as the main etiology of CS, followed by ADHF and arrhythmia. Patients with CS complicated by arrhythmia and septic complications had higher rates of survival than those who did not. Patients who did not survive had significantly longer CCU stays (**Table 2**). In-hospital mortality for patients with CS

within 72 h from ER arrival was at 1.6% and upon discharge was at 25.9% (**Supplementary Table 2**).

The baseline characteristics, laboratory and imaging examinations, clinical management, and diagnosis classification of the validation cohort are presented in **Supplementary Tables 3, 4**. The median age is 72 years and the majority of such patients are men (61.76%). The ratios of patients per characteristic in the validation cohort were comparable to those in the derivation cohort. ACS remained the most common etiology of CS.

Model Development and Validation

In the derivation cohort, 32 variables (SBP, unconscious, dyslipidemia, CAD, heart failure, cardiomyopathy, renal disease, lactic acid, hemoglobin, platelet, international normalized ratio (INR), creatinine, sodium, troponin, N-terminal-pro B-type natriuretic peptide (NT-proBNP), heart rate, QRS duration, lung edema, pleural effusion, LVEF, valvular lesions, bronchodilator use, albumin infusion, inotrope use, heparin use, respiratory support, CPR attempt, RRT, pacemaker implantation, MCS, component transfusion, and CABG) were identified from the univariate analysis and entered into the stepwise multiple logistic regression (**Table 3**). A history of CAD (OR 3.68, 95% CI 1.30–10.45, p =0.014), multiple inotrope use (OR 24.99, 95% CI 5.34–116.81, $p < 0.001$), LVEF <40% (OR 0.20, 95% CI 0.07–0.55, $p = 0.002$), low hemoglobin (OR 0.83, 95% CI 0.69–1.00, $p = 0.053$), albumin infusion (OR 4.74, 95% CI 1.49–15.14, p =0.009), CPR attempt (OR 2.21, 95% CI 1.23–3.97, $p = 0.008$), and RRT (OR 3.00, 95% CI 1.11–8.12, $p = 0.031$) remain associated with an increased risk for in-hospital mortality and a risk-prediction nomogram, the CSP (Cardiogenic Shock Prognosis) score, was developed accordingly (**Figure 2**). The CSP score allocated the individual prediction for having in-hospital mortality. For every patient, a virtual vertical line to the horizontal axis determined how many points should be attributed for each variable. Then, the total points provided a probability of in-hospital mortality.

The CSP score of the derivation cohort yielded an AUC of 0.941 (95% CI 0.91–0.97), indicating a good ability to discriminate the outcome of mortality. The model had an adequate goodness of fit (HL $x^2 = 4.786$ with 8 df, $p = 0.780$). Internal validation resulted in a sensitivity of 75%, a specificity of 80.77%, and an AUC of 0.813 (95% CI 0.71–0.92). A comparison with other risk scores using the CS population (n=311) revealed the following AUCs: SHOCK score (0.615), IABP-SHOCK II trial score (0.638), and CardShock risk score (0.657). The results of the receiver operating characteristic (ROC) curves are illustrated in **Figure 3**.

Model Risk Stratification

The CSP score was further stratified into three risk categories for in-hospital mortality. A CSP score of <115 was considered low-risk with a sensitivity of 0 and 6.25% in the development and validation cohorts, respectively. On the other hand, a score of more than 210 was considered high-risk and was associated with a sensitivity and specificity of 88.89, 84.44, 68.75, and 80.77% in the development and validation cohorts, respectively (**Table 4**). This threshold identified around two-thirds of patients with a high-risk score for an unfavorable outcome (**Supplementary Table 5**).

TABLE 3 | Adjusted and unadjusted odds ratios of predictive factors.

Variables	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI) Stepwise method	*P*-value
SBP (mmHg)	0.99 (0.98–1.00)	—	
Unconscious	2.32 (1.13–4.76)	—	
Dyslipidemia	0.52 (0.26–1.05)	—	
CAD	2.14 (1.18–3.88)	3.68 (1.30–10.45)	0.014
Heart failure	2.80 (1.52–5.18)	—	
Cardiomyopathy	2.51 (1.07–5.86)	—	
Renal disease	2.24 (1.08–4.66)	—	
Lactic acid (mmol/L)	1.20 (1.09–1.32)	—	
Hemoglobin (g/dL)	0.89 (0.80–0.98)	0.83 (0.69–1.00)	0.053
Platelet (K/uL)	1.00 (0.99–1.00)	—	
INR	2.36 (1.35–4.15)	—	
Creatinine (mg/dL)	1.11 (1.00–1.23)	—	
Sodium (mmol/L)	0.97 (0.92–1.01)	—	
Troponin T (ng/L)	1.00 (1.00–1.00)	—	
NT-proBNP (pg/mL)	1.00 (1.00–1.00)	—	
HR (bpm)	1.01 (1.00–1.01)	—	
QRS duration (ms)	1.01 (1.00–1.02)	—	
Lung edema	0.31 (0.12-0.83)	—	
Pleural effusion	1.78 (0.96–3.28)	—	
LVEF < 40%	0.27 (0.146–0.51)	0.20 (0.07–0.55)	0.002
Valvular lesions	2.13 (1.18–3.83)	—	
Bronchodilator	1.84 (1.03–3.30)	—	
Albumin	8.57 (4.18–17.58)	4.74 (1.49–15.14)	0.009
Multiple inotrope use	24.29 (8.44–69.88)	24.99 (5.34–1,116.81)	0.000
Heparin	3.00 (1.54–5.81)	—	
Respiratory support	10.16 (4.17–24.74)	—	
CPR attempt	5.14 (2.56–10.35)	2.21 (1.23–3.97)	0.008
RRT	10.41 (5.40–20.10)	3.00 (1.11–8.12)	0.031
Pacemaker implantation	0.35 (0.17–0.75)	—	
MCS	6.11 (3.21–11.66)	—	
Component transfusion	8.79 (3.96-19.52)	—	
CABG	4.12 (1.47–11.58)	—	

CABG, coronary artery bypass grafting; CAD, coronary artery disease; CI, confidence interval; CPR, cardiopulmonary resuscitation; INR, international normalized ratio; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support devices; NT-proBNP, N-terminal-pro B-type natriuretic peptide; RRT, renal replacement therapy; SBP, systolic blood pressure.

DISCUSSION

In this retrospective observational study, factors including a history of CAD, multiple inotrope use, LVEF <40%, lower hemoglobin concentration, albumin infusion, longer CPR

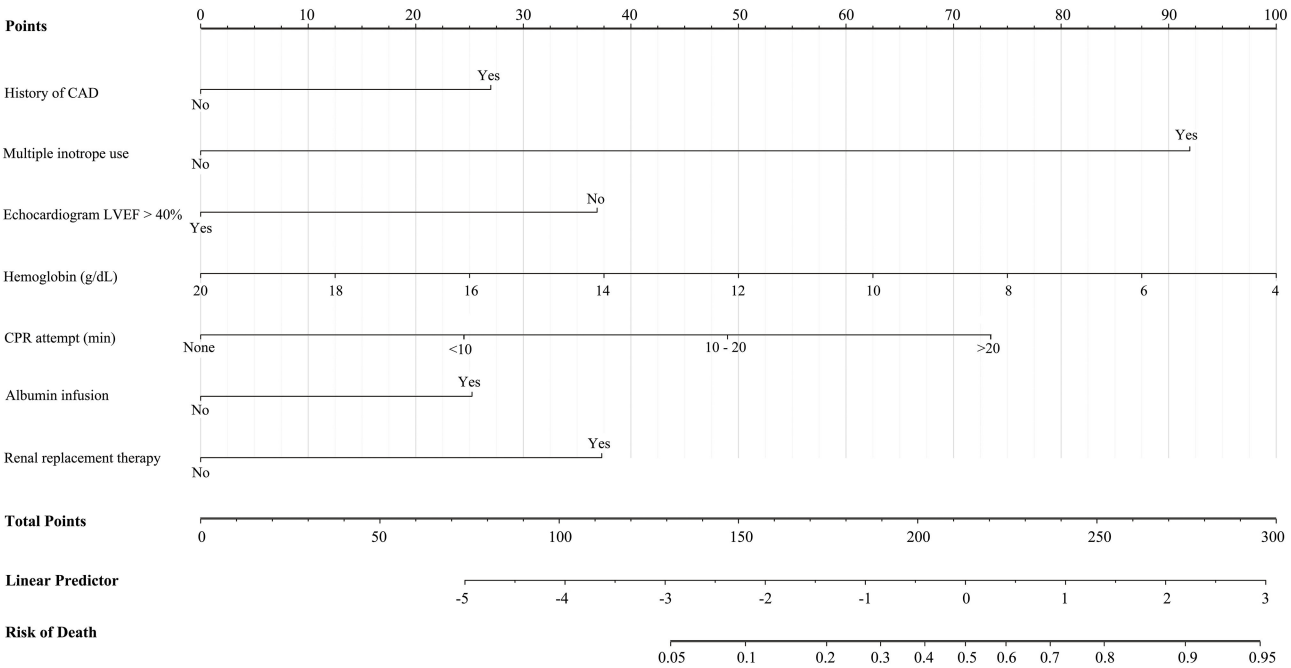

FIGURE 2 | The Cardiogenic Shock Prognosis score, a predictive nomogram of in-hospital mortality for patients with cardiogenic shock. CAD, coronary artery disease; CPR, cardiopulmonary resuscitation; LVEF, left ventricular ejection fraction.

attempt, and RRT were identified to be associated with increased in-hospital mortality among patients with cardiogenic shock. The CSP score, a risk-predictive nomogram, was developed with an intended predictive utility within 72 h of acute care or immediately after admission, and stratified patients into three risk groups with good performance.

Previous scoring systems mostly focused on cardiogenic shock secondary to ACS (3–5) but in recent years, a significant proportion of cases are due to other etiologies (7). As compared with patients with ACS etiology, non-ACS patients had a more favorable course (5). This study's focus to include cases with more heterogeneous causes of CS may be applicable for use in various populations. The evolving epidemiology of CS cases may mean approaches in managing patients with AMICS may not be as effective in treating patients with other CS etiologies (7). Hence, an important guide in clinical decision-making could be to first stratify patients according to mortality risk and adapt intervention strategies accordingly. This study developed the CSP score which classified CS patients into three risk groups: scores of <115 were determined to be low-risk (0% mortality), scores of 116–209 as medium-risk (8.75% mortality), and more than 210 as high-risk (66.67% mortality). The condition of patients with CS lies on a continuum, progressing from pre-shock states to severe shock states at different rates and requiring simultaneous interventions to maintain hemodynamic stability (2, 6). This study takes this into consideration and identified predictive factors for mortality risk within 72 h of acute care management or immediately after admission for more accurate prognostication.

Several mortality predictors have been identified in previous scoring systems. Among them, previous MI or CABG and reduced LVEF were risk factors based on the SHOCK (3) and CardShock risk scores (5), consistent with this study's history of CAD and reduced cardiac function. High creatinine levels or low eGFR were present in all three scores whereas the need for RRT during acute care was determined to be a risk factor in this study. Other predictors identified in this study but not reported in other scores include multiple inotrope use, albumin infusion, lower hemoglobin levels, and longer CPR duration.

These factors altogether contribute to the illness severity of patients with CS. Vasopressors and inotropes are the cornerstones of CS management but mortality was significantly higher with escalating use, and adrenaline being the most evident (10, 11). Albumin infusion for hypoalbuminemia is correlated with higher illness severity and can act as a frailty biomarker among patients with heart failure or ACS (12, 13). Among patients with ACS, studies have shown that lower hemoglobin levels on admission are an independent predictor of increased risk for short-term mortality, more so if complicated with comorbidities of hypertension or chronic renal disease (14, 15). When complicated with CS, a higher hemoglobin concentration is a protective factor for the development of in-hospital cardiac arrest (16). Lastly, cardiac arrest patients with a prolonged CPR duration were observed to be associated with a poorer prognosis (17, 18). Early stratification of these patients may guide clinician decision-making.

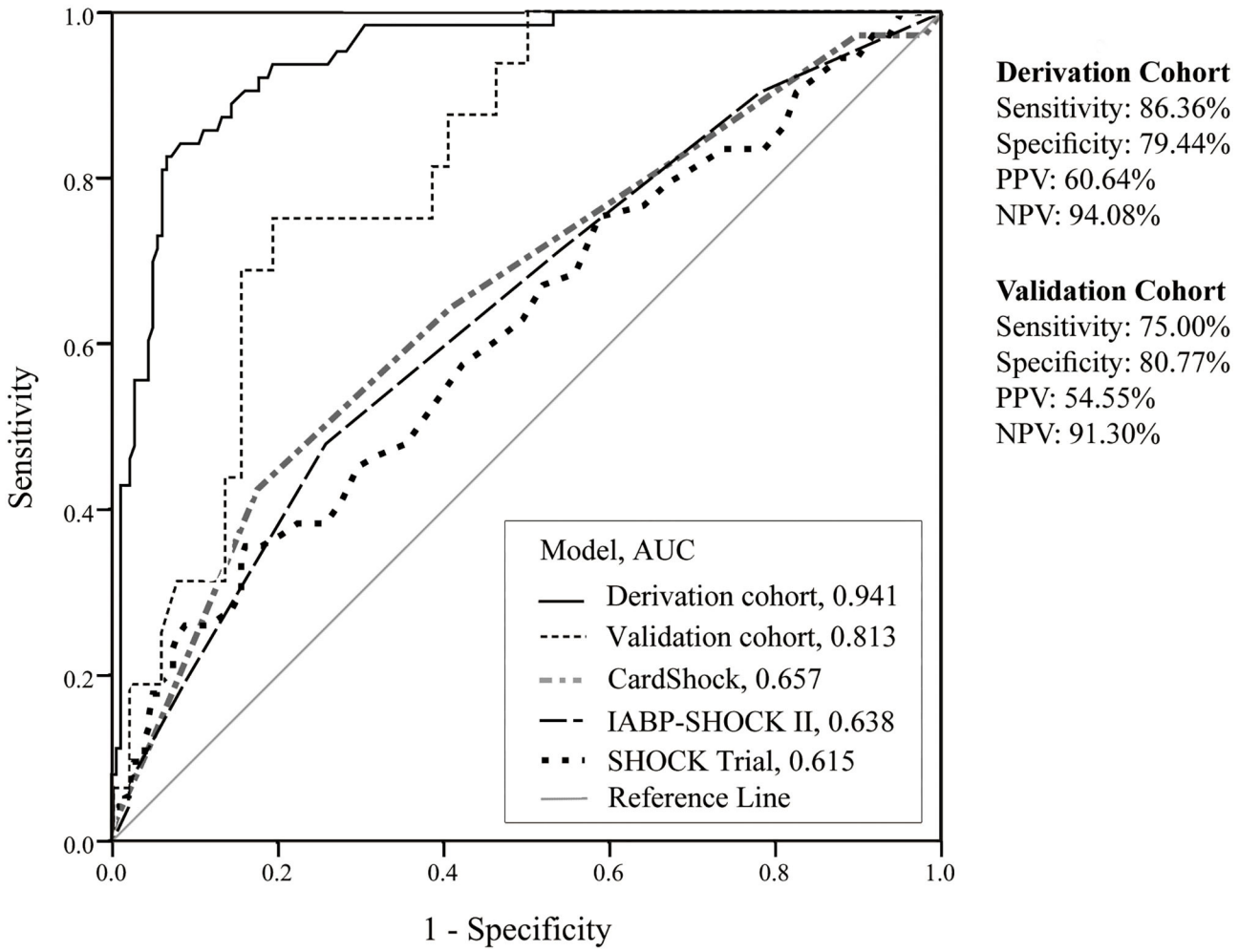

FIGURE 3 | Discrimination performances of derivation cohort, validation cohort, and other scores. AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value.

Limitations

Several limitations of this study should be considered. First, the retrospective nature of the study caused unavoidable selection bias. Unrecognized confounding factors may be present. Second, the small sample size from a single center may have resulted in nonsignificant differences between groups in some variables. Besides, patients resuscitated from OHCA and without the survival of more than 24 h were excluded from the current study, therefore, patients with the most severe CS may not be evaluated. Third, this study is largely based on an Asian demographic and thus may be more applicable for similar populations. Certain hospitalization procedures may vary per country such as the availability of IABP and ECMO support may differ from the Western practices. Another difference in procedure is the preference for albumin infusion as a volume expander in shock patients after fluid challenge in Taiwan, which is covered by the National Health Insurance. Furthermore, the limited availability of variable substitutes from this study's dataset for validation of the SHOCK trial score, IABP-SHOCK II trial score, and CardShock risk score may have contributed to a better predictive performance in the CSP score and a lower mortality rate in this study. Thus, a larger sample size and external validation for the model are necessary before extrapolating it to other populations. Finally, this study focused on developing a risk-stratification tool for in-hospital mortality, therefore recommending effective interventions depending on risk severity or predicting long-term prognosis after discharge will require future investigation through well-designed studies.

CONCLUSIONS

The CSP score which included a history of CAD, multiple inotrope use, ejection fraction <40%, lower hemoglobin

TABLE 4 | Discrimination performance of Cardiogenic Shock Prognosis score with mortality.

Study sample	CSP score	
	Low-risk ≤ 115	High-risk ≥ 210
Derivation cohort ($n = 243$)		
Sensitivity (95% CI)	0 (0–7.16)	88.89% (77.84–95.04)
Specificity (95% CI)	56.11% (48.53–63.43)	84.44% (78.13–89.25)
Positive predictive value (95% CI)	0 (0–5.78)	66.67% (55.44–76.35)
Negative predictive value (95% CI)	61.59% (53.65–68.97)	95.60% (90.79–98.06)
Accuracy (95% CI)	41.56% (38.52–45.43)	85.60% (78.07–91.10)
Validation cohort ($n = 68$)		
Sensitivity (95% CI)	6.25% (0.33–32.39)	68.75% (41.48–87.87)
Specificity (95% CI)	48.08% (34.22–62.22)	80.77% (67.03–89.92)
Positive predictive value (95% CI)	3.57% (0.19–20.24)	52.38% (30.34–73.61)
Negative predictive value (95% CI)	62.50% (45.81–76.83)	89.36% (76.11–96.02)
Accuracy (95% CI)	38.24% (29.33–51.55)	77.94% (63.33–89.19)

CSP, Cardiogenic Shock Prognosis.

concentration, longer CPR attempt, albumin infusion, and RRT was generated with high performances in predicting in-hospital mortality among CS patients in the acute care setting. The high-risk group (CSP score ≥ 210) showed a high sensitivity for poor prognosis.

DATA AVAILABILITY STATEMENT

The de-identified datasets used and analyzed during the study will be shared upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of National Taiwan University Hospital (202001104RINC). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MST, CHH, WJC, and CHW contributed to the study concept and design. YTT, MST, CCH, CHW, CSH, WTChe, WTCha, and JJL contributed to the acquisition of the data. YTT and MST analyzed and interpreted the data and drafted the manuscript. CHH and WJC provided critical revision of the manuscript for important intellectual content and supervised the study. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.842056/full#supplementary-material

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Angiotensin Receptor-Neprilysin Inhibitors in Patients With Heart Failure With Reduced Ejection Fraction and Advanced Chronic Kidney Disease: A Retrospective Multi-Institutional Study

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Background: Data regarding using angiotensin receptor-neprilysin inhibitor (ARNI) in patients with both heart failure with reduced ejection fraction (HFrEF) and advanced chronic kidney disease (CKD) are limited.

Methods and Results: Between January 2016 and December 2018, patients with HFrEF and advanced CKD (estimated glomerular filtration rate [eGFR] ≤30 mL/min/1.73 m^2) were identified from a multi-institutional database in Taiwan. Patients who had never been prescribed with an ARNI, angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB) were excluded. We used inverse probability of treatment weighting (IPTW) to balance baseline covariates, and compared outcomes between ARNI and ACEI/ARB users. There were 206 patients in the ARNI group and 833 patients in the ACEI/ARB group. After IPTW adjustment, the mean ages (65.1 vs. 66.6 years), male patients (68.3 vs. 67.9%), left ventricular ejection fraction (30.5 vs.31.2%), eGFR (20.9 vs. 20.3 mL/min/1.73 m^2) were comparable in the ARNI and ACEI/ARB groups. Over 85% of the patients had beta-blockers prescriptions in both groups (86.2 vs. 85.5%). After IPTW adjustment, the mean follow-up durations were 7.3 months and 6.6 months in the ARNI and ACEI/ARB groups, respectively. ARNI and ACEI/ARB users had a comparable risk of the composite clinical event (all-cause mortality or heart failure hospitalization) (hazard ratio [HR], 1.31; 95% confidence interval (CI) 0.91–1.88) and progression to dialysis (HR 1.04; 95% CI 0.54–2.03). In subgroup analysis, dialysis patients who used ARNIs were associated with higher incidence of heart failure hospitalization (subdistribution HR, 1.97; 95% CI 1.36–2.85).

Conclusions: Compared with ACEIs or ARBs, ARNIs were associated with comparable clinical and renal outcomes in patients with HFrEF and advanced CKD (eGFR ≤ 30 mL/min/1.73 m^2). In short-term, HF hospitalization may occur more frequently among ARNI users, especially in patients on dialysis.

Keywords: heart failure with reduced ejection fraction, chronic kidney disease, end-stage renal disease, angiotensin receptor-neprilysin inhibitor, sacubitril/valsartan

INTRODUCTION

Chronic kidney disease (CKD) is not uncommon in patients with heart failure with reduced ejection fraction (HFrEF), as they have similar upstream risk factors and interact to increase adverse events. Reduced estimated glomerular filtration rate (eGFR) has been reported to be an independent predictor of mortality and hospitalization in patients with heart failure (HF) (1). In addition, HF patients have been shown to have a 2-fold faster decline in eGFR than the general population (2). Although the number of patients with both advanced CKD (eGFR $\leq$ 30 mL/min/1.73 m^2) and HFrEF is increasing globally with high morbidity and mortality, (3, 4) they have been systemically excluded from randomized trials of pharmacological therapies for HFrEF. Thus, evidence-based therapies for this special population are still lacking.

Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), was added to guidelines for the treatment of HFrEF after the publication of the Prospective comparison of Angiotensin Receptor-neprilysin inhibitor (ARNI) with Angiotensin converting enzyme inhibitor (ACEI) to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial (5) In subgroup analysis, sacubitril/valsartan were found to be superior to enalapril in reducing cardiovascular mortality or HF hospitalization, irrespective of the presence or absence of CKD. However, patients with eGFR below 30 mL/min/1.73 m^2 were again not enrolled in this trial. The instructions for users of sacubitril/valsartan in Taiwan do not list advanced CKD as a contraindication. Thus, despite a lack of evidence, some cardiologists in Taiwan prescribed sacubitril/valsartan for patients with HFrEF and advanced CKD in an attempt to either improve symptoms, reduce HF hospitalization, or prolong survival.

Using a multi-institutional claims database, the purpose of the present study was to report the baseline characteristics and pharmacological therapies of patients with both HFrEF and advanced CKD from real-world experience. In addition, the clinical, renal, and echocardiographic outcomes of patients receiving ARNIs were compared to those receiving angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs).

METHODS

Database

Data for the present study were obtained from the Chang Gung Research Database (CGRD). The CGRD contains the standardized electronic medical records from seven institutes of Chang Gung Memorial Hospital (CGMH), which is the largest hospital system in Taiwan with 10,070 beds and admits more than 280,000 patients each year. The outpatient department visits and emergency department visits to CGMH were over 8,500,000 and 500,000, respectively in 2015. CGRD has collected and standardized the electronic medical records of all patients since 2000 without selection criteria. One strength of the CGRD is that it includes each patient's medical diagnosis, laboratory results, image findings, medications, and procedure reports. Diagnoses were registered using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes before 2016, and ICD-10 codes thereafter. More details about the CGRD have been reported elsewhere (5, 6).

The personal information of each patient was de-identified using a consistent encryption procedure; therefore, the need for informed consent was waived for this study. This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of CGMH, Linkou (IRB number: 202000410B0).

Study Design

Figure 1 shows the process of patient inclusion and exclusion. Between January 2016 and December 2018, patients with both HFrEF and advanced CKD were identified from the CGRD. Patients with HFrEF had to fulfill the following two criteria: (1) a principal or secondary diagnosis of HF in inpatient or outpatient claims data; (2) a baseline left ventricular ejection fraction (LVEF) less than 40% by echocardiography within 3 months before the first diagnosis of HF. The identification of patients with HFrEF in the CGRD has been reported previously (7, 8). Advanced CKD was defined as two consecutive records of eGFR $\leq$ 30 mL/min/1.73 m^2 in the previous year before the cohort entry date (defined later).

HFrEF patients who had been prescribed an ARNI, ACEI, or ARB (candesartan, valsartan, losartan, or a fixed-dose combinations including these three ARBs) for at least 30 days were further identified. The date of the first prescription of an ARNI was defined as the cohort entry date for the ARNI group. The cohort entry date for the ACEI/ARB group was assigned from the ARNI group to avoid immortal time bias (9). In the meanwhile, the two groups were frequency matched based on age, sex, and baseline LVEF. The baseline period was defined as the 12 months before the cohort entry date. We excluded those who had no serum creatinine data and those with an eGFR $>$ 30 mL/min/1.73 m^2. Patients without follow-up data were also excluded.

Covariates

Data on covariates including baseline characteristics (age, sex, height, and weight), vital signs, previous cardiac treatments, comorbidities, medications, laboratory, and echocardiographic findings were extracted from the CGRD. Body height, body weight, blood pressure, and heart rate were obtained from a vital sign sub-database within 3 months before the cohort entry date. Comorbidities were defined if any inpatient or two outpatient diagnoses were recorded with ICD-9 or ICD-10 codes during the baseline period. Data on prior cardiac treatments, including valve surgery, cardiac resynchronization therapy and coronary artery bypass graft were extracted from inpatient data. Medications, laboratory, and echocardiographic results were obtained within 3 months before the cohort entry date.

Outcomes

The clinical outcomes of interest were all-cause mortality, HF hospitalization, the composite of both, and admission due to any cause. After excluding patients on dialysis at baseline, the renal outcomes observed were progression to end-stage renal disease (ESRD) and severe hyperkalemia (serum potassium $\geq$ 6 mEq/L).

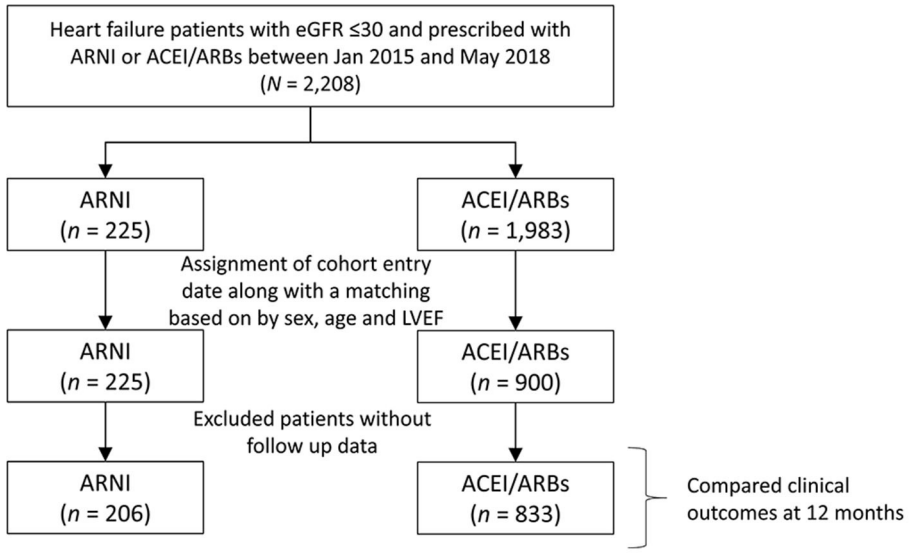

FIGURE 1 | Flowchart of the inclusion and exclusion criteria of the study patients.

HF hospitalization was defined as having a principal discharge diagnosis of HF and at least one treatment during hospitalization, including diuretics, nitrites, or inotropic agents. Progression to ESRD was defined as maintenance dialysis for $\geq$ 28 days. The follow-up period was defined as the period from the cohort entry date until the first occurrence of an outcome, day of mortality, the last outpatient visits or discharge date in the CGRD, the end of the study period (December 31, 2018), or at 12th month, whichever occurred first.

Finally, changes in echocardiographic parameters (mean LVEF, left ventricular end diastolic and end systolic diameters, left atrial diameter) from baseline in each group will be compared, using persons with available follow-up echocardiography after the index date.

Statistical Analysis

To achieve comparability in clinical outcomes between the study groups, we conducted inverse-probability-of-treatment weighting (IPTW) based on propensity score. Compared to propensity score matching (PSM), the results based on IPTW have greater statistical power without losing sample size. The propensity score was calculated using multivariable logistic regression where the study group was regressed on all of the covariates (listed in **Table 1**, except the follow-up month) and possible interactions among the covariates were not considered. To reduce the impact of extreme propensity scores, we used a stabilized weight (10). We used the total cohort and compared the risk of all-cause mortality, HF hospitalization, and admission due to any cause after IPTW adjustment. To compare the risk of progression to ESRD and severe hyperkalemia, we performed another IPTW adjustment after excluding persons on dialysis at baseline. The balance of covariate distribution between groups was checked using the absolute value of the standardized difference (STD) before and after weighting, where a value of <0.2 was considered to be a small difference. In addition, due to the existence of missing laboratory data, the missing values were first imputed using the single expectation–maximization imputation method, and IPTW was conducted using the imputed data.

The risks of fatal outcomes (i.e., composite of all-cause death and HF hospitalization, all-cause death, MAKEs) between groups were compared using a Cox proportional hazard model. The incidence of other non-fatal time-to-event outcomes (i.e., HF hospitalization, progression to ESRD) between groups was compared using a Fine and Gray sub-distribution hazard model which considered all-cause death during follow-up as a competing risk. We further conducted subgroup analysis stratified by renal function status (non-dialysis vs. dialysis) on clinical events including the composite of all-cause death or HF hospitalization, HF hospitalization, and all-cause death. Finally, changes in echocardiography data from baseline to the 12th month within either group were compared using the paired sample *t*-test for continuous variables and the McNemar test for dichotomized variables (severe mitral regurgitation). Differences in changes between the ARNI and ACEI/ARB groups were compared using generalized estimating equations in which the interaction of 'group by time point' was included in the model.

A two-sided *P*-value of < 0.05 was considered to be statistically significant. All statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Baseline Characteristics

Between January 2016 and December 2018, a total of 1,039 HFrEF patients with two consecutive records of eGFR $\leq$ 30 mL/min/1.73 m^2 at baseline, who received an ARNI, ACEI, or ARB, and had available follow-up information were eligible for analysis.

TABLE 1 | Baseline characteristics between the ARNI and ACEI/ARB groups before and after IPTW adjustment.

Variable	Valid N	Before EM imputation and IPTW* Total (n = 1,039)	ARNI (n = 206)	ACEI/ARB (n = 833)	STD	After EM imputation and IPTW† ARNI (n = 974.8)	ACEI/ARB (n = 1,044.1)	STD
Demographics								
Age, years	1,039	66.4 ± 13.3	65.1 ± 14.4	66.8 ± 13.0	−0.12	65.1 ± 16.0	66.6 ± 12.9	−0.11
Male	1,039	701 (67.5)	142 (68.9)	559 (67.1)	0.04	68.3%	67.9%	0.01
Height cm	875	161.1 ± 11.0	162.5 ± 9.4	160.8 ± 11.3	0.17	162.4 ± 9.8	161.1 ± 10.9	0.13
Body weight kg	971	62.4 ± 13.0	65.0 ± 14.4	61.8 ± 12.6	0.24	64.4 ± 14.9	62.2 ± 12.7	0.16
CKD group	1,039							
Stage 4 (eGFR: 15–30)		325 (31.3)	80 (38.8)	245 (29.4)	0.20	39.5%	32.0%	0.16
Stage 5 (eGFR <15)		96 (9.2)	16 (7.8)	80 (9.6)	−0.07	6.0%	8.9%	−0.11
ESRD on dialysis		618 (59.5)	110 (53.4)	508 (61.0)	−0.15	54.5%	59.1%	−0.09
Vital signs								
SBP mmHg	1,037	129.6 ± 24.0	129.3 ± 23.6	129.7 ± 24.1	−0.02	128.0 ± 23.7	129.3 ± 23.8	−0.06
DBP mmHg	1,037	72.0 ± 16.8	73.0 ± 17.2	71.8 ± 16.7	0.07	70.9 ± 16.8	71.9 ± 16.4	−0.06
Heart rate	1,029	79.9 ± 16.3	79.3 ± 16.1	80.1 ± 16.4	−0.05	80.1 ± 14.9	79.9 ± 16.2	0.01
History of cardiac treatment								
Valve surgery	1,039	39 (3.8)	8 (3.9)	31 (3.7)	0.01	5.0%	3.6%	0.07
CRT	1,039	17 (1.6)	5 (2.4)	12 (1.4)	0.07	2.6%	1.5%	0.07
CABG	1,039	95 (9.1)	28 (13.6)	67 (8.0)	0.18	8.5%	8.8%	−0.01
Comorbidities								
Coronary artery disease	1,039	653 (62.8)	140 (68.0)	513 (61.6)	0.13	61.7%	63.0%	−0.03
Myocardial infarction	1,039	319 (30.7)	66 (32.0)	253 (30.4)	0.04	28.1%	30.3%	−0.05
Hypertension	1,039	855 (82.3)	173 (84.0)	682 (81.9)	0.06	84.5%	81.7%	0.07
Dyslipidemia	1,039	584 (56.2)	121 (58.7)	463 (55.6)	0.06	49.8%	55.9%	−0.12
Diabetes mellitus	1,039	625 (60.2)	127 (61.7)	498 (59.8)	0.04	58.9%	59.7%	−0.02
Stroke	1,039	117 (11.3)	17 (8.3)	100 (12.0)	−0.12	11.3%	11.2%	0.00
Atrial fibrillation	1,039	177 (17.0)	38 (18.4)	139 (16.7)	0.05	18.5%	17.1%	0.04
Chronic obstructive pulmonary disease	1,039	107 (10.3)	24 (11.7)	83 (10.0)	0.05	11.3%	10.6%	0.02
Peripheral arterial disease	1,039	126 (12.1)	22 (10.7)	104 (12.5)	−0.06	11.2%	12.5%	−0.04
Medications								
Beta–blockers	1,039	892 (85.9)	183 (88.8)	709 (85.1)	0.11	86.2%	85.5%	0.02
MRAs	1,039	228 (21.9)	63 (30.6)	165 (19.8)	0.25	31.3%	22.8%	0.19
Ivabradine	1,039	139 (13.4)	55 (26.7)	84 (10.1)	0.44	13.7%	13.8%	0.00
Loop diuretics	1,039	669 (64.4)	155 (75.2)	514 (61.7)	0.29	70.9%	64.6%	0.14
Digoxin	1,039	147 (14.1)	34 (16.5)	113 (13.6)	0.08	16.0%	14.5%	0.04
Amiodarone	1,039	132 (12.7)	37 (18.0)	95 (11.4)	0.19	17.1%	13.1%	0.11
Laboratory data								
Creatinine mg/dL‡	421	3.3 ± 1.8	3.2 ± 1.8	3.4 ± 1.8	−0.13	3.2 ± 1.7	3.3 ± 1.7	−0.02
eGFR mL/min/1.73 m^{2}‡	421	20.1 ± 6.8	21.5 ± 6.7	19.7 ± 6.8	0.27	20.9 ± 6.3	20.3 ± 6.7	0.08
BNP pg/mL	720	2,160 [838, 4442]	2,130 [669, 4700]	2,209 [888, 4320]	NA	2,130 [974, 4675]	2,216 [888, 4426]	NA
BUN mg/dL	1,006	57.6 ± 27.8	56.8 ± 27.4	57.8 ± 28.0	−0.04	55.7 ± 26.5	57.0 ± 27.6	−0.05
Sodium (Na) mEq/L	1,017	137.2 ± 4.7	137.8 ± 5.1	137.1 ± 4.5	0.15	137.3 ± 5.0	137.2 ± 4.5	0.03
Potassium (K) mEq/L	1,028	4.3 ± 0.7	4.3 ± 0.8	4.4 ± 0.7	−0.08	4.4 ± 0.8	4.3 ± 0.7	0.02
Uric acid mg/dL	862	7.2 ± 2.6	7.3 ± 2.8	7.1 ± 2.5	0.08	7.5 ± 2.8	7.2 ± 2.6	0.14
Calcium mg/dL	901	8.9 ± 0.9	8.9 ± 0.8	8.9 ± 0.9	0.01	8.9 ± 0.8	8.9 ± 0.9	0.01
Phosphates mg/dL	841	4.8 ± 1.7	4.7 ± 1.7	4.8 ± 1.7	−0.05	4.6 ± 1.8	4.8 ± 1.7	−0.09
Hemoglobin g/dL	1,023	10.6 ± 2.0	11.0 ± 2.1	10.5 ± 1.9	0.28	10.7 ± 1.7	10.6 ± 2.0	0.05
Hematocrit g/dL	1,022	32.2 ± 5.9	33.7 ± 6.2	31.9 ± 5.7	0.31	32.7 ± 5.2	32.3 ± 5.9	0.07
Serum albumin mg/dL	881	3.5 ± 0.5	3.6 ± 0.5	3.5 ± 0.5	0.11	3.6 ± 0.5	3.5 ± 0.5	0.17

(Continued)

TABLE 1 | Continued

Variable	Valid N	Before EM imputation and IPTW* Total (n = 1,039)	ARNI (n = 206)	ACEI/ARB (n = 833)	STD	After EM imputation and IPTW† ARNI (n = 974.8)	ACEI/ARB (n = 1,044.1)	STD
Proteinuria (U/A dipstick) mg/dL	625							
Negative (0–4)		78 (7.5)	23 (11.2)	55 (6.6)	0.16	10.3%	8.1%	0.07
Trace (5–29)		42 (4.0)	10 (4.9)	32 (3.8)	0.05	4.8%	4.2%	0.03
≥1+ (≥30)		505 (48.6)	86 (41.7)	419 (50.3)	−0.17	50.9%	48.6%	0.05
Unknown		414 (39.8)	87 (42.2)	327 (39.3)	0.06	34.0%	39.1%	−0.11
Echocardiography								
LVEF%	1,039	31.3 ± 6.7	28.7 ± 6.9	32.0 ± 6.5	−0.49	30.5 ± 6.9	31.2 ± 6.9	−0.10
LVEDD mm	1,036	57.4 ± 8.5	60.0 ± 8.7	56.8 ± 8.3	0.38	58.6 ± 8.5	57.5 ± 8.4	0.13
LVESD mm	1,036	46.4 ± 9.4	50.7 ± 8.6	45.4 ± 9.3	0.60	47.6 ± 8.6	46.5 ± 9.5	0.12
LA mm	1,034	44.1 ± 7.7	45.4 ± 7.6	43.8 ± 7.7	0.22	45.2 ± 7.4	44.1 ± 7.6	0.14
MR severity	1,002							
Severe		88 (8.8)	25 (12.6)	63 (7.8)	0.16	11.1%	9.6%	0.05
Moderate		258 (25.7)	50 (25.1)	208 (25.9)	−0.02	27.1%	25.6%	0.03
Mild		537 (53.6)	97 (48.7)	440 (54.8)	−0.12	51.2%	53.3%	−0.04
Trivial/None		119 (11.9)	27 (13.6)	92 (11.5)	0.06	10.5%	11.5%	−0.03
Follow up month	1,039	6.9 ± 4.2	7.4 ± 4.1	6.7 ± 4.2	0.17	7.3 ± 4.2	6.6 ± 4.2	0.17

*EM, expectation maximization; IPTW, inverse probability of treatment weighting; ARNI, angiotensin receptor–neprilysin inhibitor; ACEI, angiotensin–converting enzyme inhibitor; ARB, angiotensin receptor blocker; STD, standardized difference; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end–stage renal disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRT, cardiac resynchronization therapy; CABG, coronary artery bypass graft; MRA, mineralocorticoid receptor antagonist; BUN, blood urea nitrogen; BNP, B–type natriuretic peptide; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end–diastolic dimension; LVESD, left ventricular end–systolic diameter; LA, left atrium; MR, mitral regurgitation; NA, not available. *Data are presented as number (%), mean ± standard deviation or median [25th, 75th percentile]; †Data are presented as %, mean ± standard deviation or median [25th, 75th percentile]; ‡Patients with dialysis at baseline were excluded.*

Of these patients, 206 received ARNI and 833 patients received ACEIs or ARBs. After excluding those with ESRD at baseline, there were 96 patients in the ARNI group and 325 patients in the ACEI/ARB group.

Baseline characteristics, laboratory and echocardiographic data, and medical therapies for HFrEF before and after imputation and weighting are presented in **Table 1**. After IPTW, the mean ages were 65.1 ± 16.0 and 66.6 ± 12.9 years (STD = −0.11) and male patients accounted for 68.3 and 67.9% (STD = 0.05) in the ARNI and ACEI/ARB group, respectively. The prevalence of comorbidities was not substantially different between the two groups before and after weighting. Ischemic cardiomyopathy was assumed to be the most prevalent etiology for HFrEF since more than 60% of the patients had coronary artery disease and around 30% had a history of myocardial infarction in both groups after weighting. The proportion of patients with diabetes mellitus (DM) was exceptionally high (nearly 60%) in both groups after weighting.

After IPTW adjustment, LVEF (30.5 vs. 31.2%) and eGFR (20.9 vs. 20.3 mL/min/1.73 m2) were comparable in the ARNI and ACEI/ARB group, respectively. Other laboratory and echocardiographic data were not substantially different (absolute STD values <0.2). Baseline B-type natriuretic peptide were available in about 70% of the patients in both groups, and the level was high (over 2,000 pg/mL) and comparable before and after adjustment.

Beta-blockers were prescribed in more than 80% of the patients in both groups. Before weighting, the ARNI users were more likely to have a concomitant prescription of mineralocorticoid receptor blockers, ivabradine, or loop diuretics. After weighting, only mineralocorticoid receptor blockers (31.3 vs. 22.8%, STD = 0.19) were more frequently prescribed in the ARNI users.

The mean follow-up durations were 7.3 ± 4.2 months and 6.6 ± 4.2 months in the ARNI and ACEI/ARB groups, respectively (**Table 1**).

Clinical Outcomes

Table 2 summarizes the clinical outcomes after weighting adjustments. The composite clinical outcomes (all-cause death or HF hospitalization) occurred in 47.1% of the ARNI group and 37.4% of the ACEI/ARB group (hazard ratio [HR], 1.26; 95% confidence interval (CI) 0.88–1.81) (**Figure 2A**). All-cause death was high and comparable between the ARNI (15.0%) and ACEI/ARB (12.9%) groups (HR, 1.03; 95% CI 0.57–1.86). There was a trend of increased HF hospitalization in the ARNI group (43.5%) compared to the ACEI/ARB group (32.2%) (subdistribution HR [SHR], 1.36; 95% CI, 0.94–1.96), although this was not significant (**Figure 2B**). More than half of the patients were admitted for any cause during follow up in both groups, which was comparable (SHR, 1.16; 95% CI, 0.82–1.66). **Supplementary Table 1** shows the results based on matching which were consistent to that of the primary

TABLE 2 | Follow–up outcomes between the ARNI and ACEI/ARBs groups at 12 months of follow–up after IPTW adjustment.

	Data before IPTW		Data after IPTW			
	ARNI (n = 206)	ACEI/ARB (n = 833)	ARNI (n = 974.8)	ACEI/ARB (n = 1,044.1)	ARNI *vs.* ACEI/ARB	
Outcome variable					HR/SHR (95% CI)	*P*-value
Primary outcome: composite of heart failure hospitalization and all–cause death	94 (45.6)	308 (37.0)	47.1%	37.4%	1.26 (0.88, 1.81)	0.202
Secondary outcome						
All–cause death	20 (9.7)	106 (12.7)	15.0%	12.9%	1.03 (0.57, 1.86)	0.935
Heart failure hospitalization	88 (42.7)	263 (31.6)	43.5%	32.2%	1.36 (0.94, 1.96)	0.109
Admission due to any cause	120 (58.3)	425 (51.0)	60.0%	50.6%	1.16 (0.82, 1.66)	0.400
Progression to ESRD (n = 421)*	17 (17.7)	45 (13.8)	14.7%	12.2%	1.04 (0.54, 2.03)	0.901
K ≥ 6 mg/dL (n = 421)*	17 (17.7)	41 (12.6)	20.3%	11.4%	1.50 (0.73, 3.05)	0.268

*IPTW, inverse probability of treatment weighting; ARNI, angiotensin receptor–neprilysin inhibitor; ACEI, angiotensin–converting enzyme inhibitor; ARB, angiotensin receptor blocker; HR, hazard ratio; SHR, subdistribution hazard ratio; CI, confidence interval; ESRD, end–stage renal disease. *After excluding patients with dialysis at baseline and the IPTW was re-performed.*

analysis. **Supplementary Table 2** shows the clinical outcomes after excluding patients on dialysis at baseline and adjusting by IPTW. The results in this subgroup were similar to those of the whole cohort.

Progression to ESRD and Severe Hyperkalemia

As shown in **Table 2**, after excluding persons on dialysis at baseline the adjusted by IPTW, 14.7% of the patients in the ARNI group and 12.2% in the ACEI/ARB group had progressed to ESRD (SHR, 1.04; 95% CI, 0.54–2.03) (**Figure 2C**). Severe hyperkalemia tended to occur more frequently in the ARNI users, however the difference was not significant. **Supplementary Table 1** shows the results based on matching which were consistent to that of the primary analysis.

Clinical Outcomes Stratified by Renal Function at Baseline

Figure 3 illustrates the subgroup analysis of clinical outcomes stratified by renal function at baseline. The results suggested that renal function at baseline significantly modified the association between the use of ARNIs and the risk of clinical outcomes, especially on the composite outcome (P for interaction = 0.0498) and HF hospitalization (P for interaction = 0.026). In the patients not receiving hemodialysis, the clinical outcomes were comparable between the ARNI and ACEI/ARB groups. However, in the patients on dialysis at baseline, the ARNI users tended to have a higher risk of the composite clinical outcome, which was driven by an elevated risk of HF hospitalization.

Clinical Outcomes Stratified by Diabetes Mellitus at Baseline

Figure 4 showed the subgroup analysis of clinical outcomes stratified by DM status at baseline. All clinical outcomes were comparable between ARNI users and ACEI/ARB users, irrespective of the presence or absence of DM.

Echocardiographic Outcomes

Follow-up echocardiography data were available for half of the patients in both groups. **Table 3** shows the changes in echocardiographic data from baseline in these patients. Reverse remodeling was observed in both groups, as evidenced by a significant increase in LVEF (change in value: 8.3 ± 14.6 vs. 10.8 ± 15.2%, P for interaction = 0.228) and decreases in left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD). Compared to the ACEI/ARB users, the ARNI users had a significantly more pronounced reduction in both LVEDD (change in value: −3.1 ± 7.8 mm vs. −1.0 ± 6.1 mm, P for interaction = 0.013) and LVESD (change in value: >4.7 ± 9.7 mm vs. −2.1 ± 8.1 mm, P for interaction = 0.017). The percentage of severe mitral regurgitation remained the same from baseline to the 12th month in the ACEI/ARB group. In the ARNI group, 13.7% of the patients had severe mitral regurgitation at baseline, which reduced to 7.4% at the 12th month (P = 0.058). Compared to ACEI/ARB, there was a trend for improving severe mitral regurgitation by ARNI (P= 0.079).

DISCUSSION

Data regarding real-world use of ARNI in HFrEF patients with advanced CKD (eGFR ≤ 30 mL/min/1.73 m^2) is limited; a population that was not included in the PARADIGM-HF trial. In the present study, we found that: (1) the burden of comorbidities was noticeably high (especially DM) in this specific population; (2) the incidence rates of mortality, HF hospitalization, and progression to ESRD were high within 1 year; (3) ARNI and ACEi/ARB users had comparable clinical and renal outcomes; (4) in short-term, ARNIs may be associated with a higher risk of HF hospitalization, especially in patients on dialysis; (5) reverse remodeling was observed in both groups.

In a previous study by our group which also investigated HFrEF patients using the CGRD (regardless of renal function), (7) all-cause mortality occurred in 3.3% and HF hospitalization occurred in 20.8% of the patients within 12 months. In the

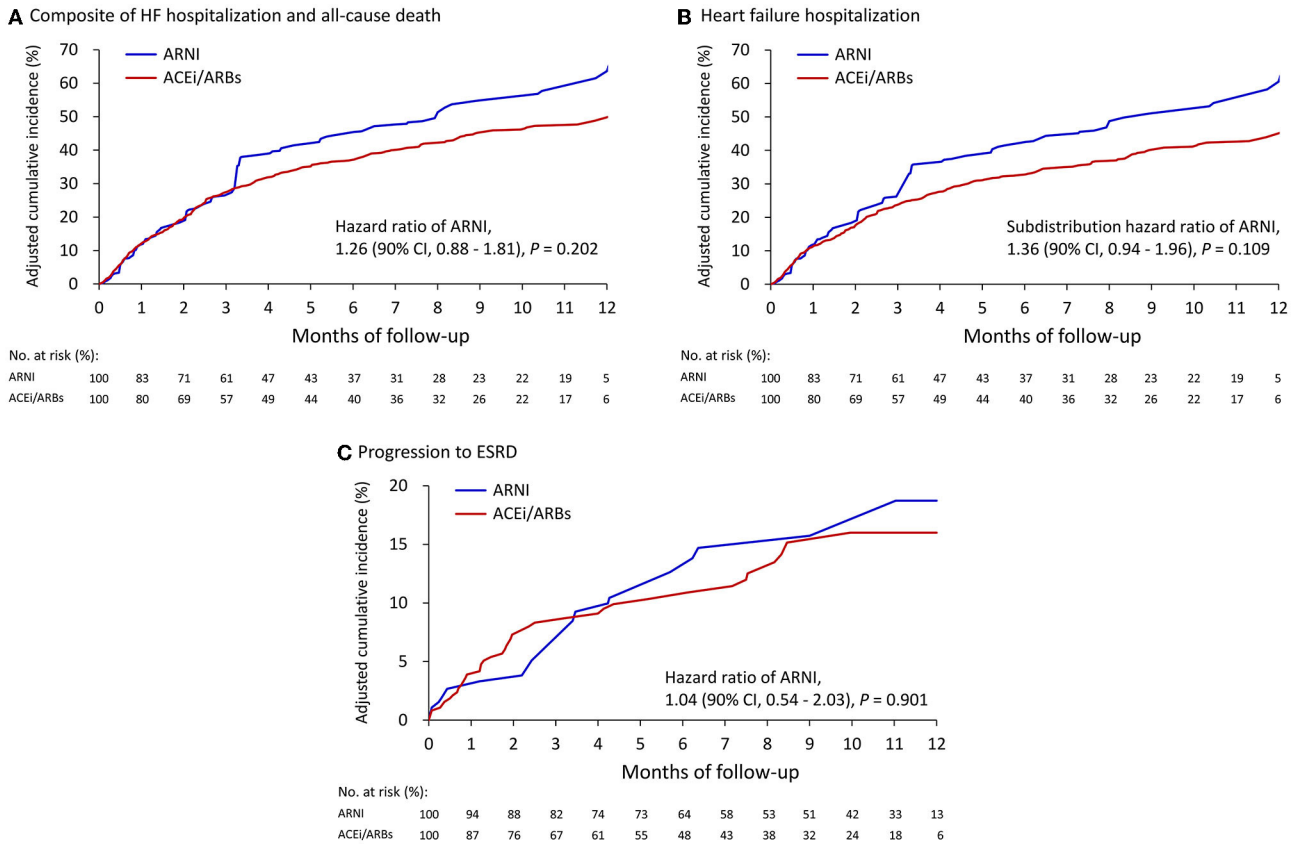

FIGURE 2 | Cumulative event rate of the composite of HF hospitalization and all-cause death **(A)**, HF hospitalization **(B)**, and progression to ESRD **(C)** between the ARNI and ACEI/ARB users. **(A)** and **(B)** compared with the IPTW cohort from all patients; **(C)** after excluding persons on dialysis at baseline then creating another IPTW cohort.

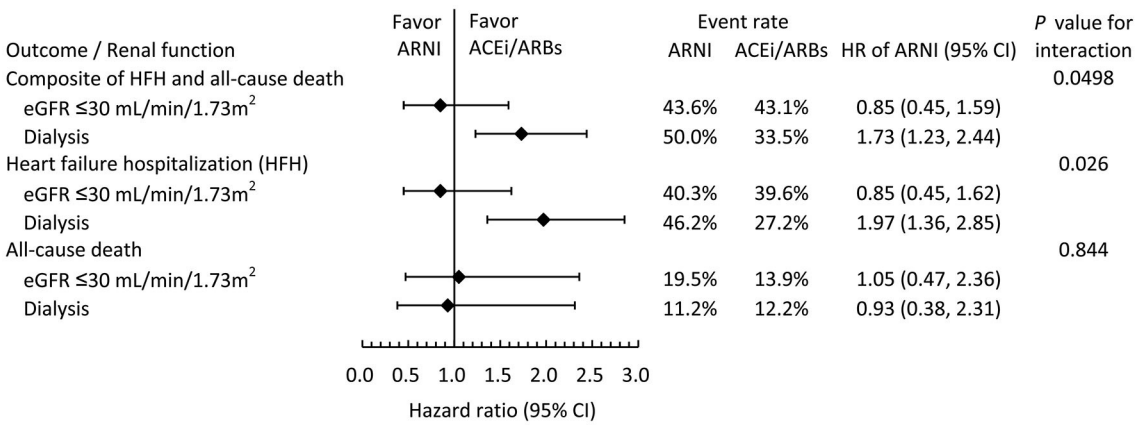

FIGURE 3 | Subgroup analysis comparing the risk of clinical outcomes between the ARNI and ACEI/ARB users in the IPTW-adjusted cohort stratified by baseline renal function.

present study, rates of both all-cause mortality (12.1%) and HF hospitalization (33.8%) within 12 months were much higher. This finding is in concordance with existing evidence, showing that CKD has a negative prognostic impact on patients with HFrEF (1). Moreover, one cohort study reported that 15.3% of patients with stage 4 CKD (46.9% had CV disease, including HF) started renal replacement therapy during an average 23.4 months of follow-up (11). In our study, a similar proportion (14.7%) of the patients progressed to ESRD requiring hemodialysis within only 1 year. These findings highlight the difficulty in

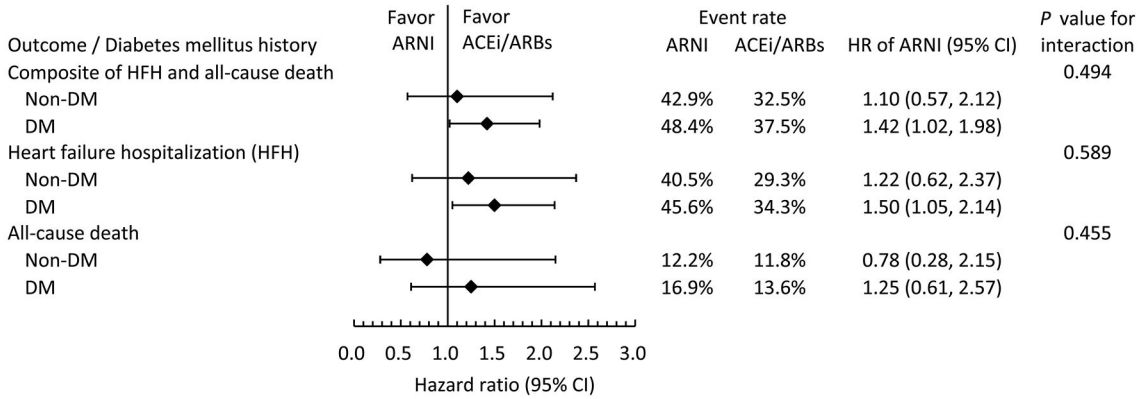

FIGURE 4 | Subgroup analysis comparing the risk of clinical outcomes between the ARNI and ACEI/ARB users in the IPTW-adjusted cohort stratified by baseline DM status.

TABLE 3 | Follow–up changes in echocardiography in the original cohort.

	ARNI group				ACEi/ARB group				
Parameter	**Valid *N***	**Baseline**	**Follow–up**	**Variation (%)**	**Valid *N***	**Baseline**	**Follow–up**	**Variation (%)**	***P*-value†**
LVEF%	105	29.1 ± 6.6	37.4 ± 14.7*	8.3 ± 14.6	467	31.7 ± 7.1	42.5 ± 15.7*	10.8 ± 15.2	0.228
LVEDD mm	106	60.5 ± 9.2	57.3 ± 8.6*	−3.1 ± 7.8	467	56.7 ± 9.0	55.7 ± 8.9*	−1.0 ± 6.1	0.013
LVESD mm	106	51.0 ± 8.7	46.3 ± 10.3*	−4.7 ± 9.7	467	45.3 ± 10.2	43.2 ± 10.7*	−2.1 ± 8.1	0.017
LA mm	107	45.3 ± 8.2	44.5 ± 7.8	−0.8 ± 7.8	469	43.8 ± 7.2	43.5 ± 8.1	−0.2 ± 6.2	0.456
	Valid *N*	**Baseline**	**12 months**	***P*-value**	**Valid *N***	**Baseline**	**12 months**	***P*-value**	
Severe MR	111	13 (13.7%)	7 (7.4%)	0.058	492	25 (7.3%)	25 (7.3%)	1.000	0.079

*ARNI, angiotensin receptor–neprilysin inhibitor; ACEi, angiotensin–converting enzyme inhibitor; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end–diastolic dimension; LVESD, left ventricular end–systolic diameter; LA, left atrium; MR, mitral regurgitation. *P < 0.05 vs. the baseline value; † The difference in the change between the ARNI and ACEi/ARB groups.*

caring for patients with both HFrEF and advanced CKD, and that collaborative efforts of both cardiologists and nephrologists are important.

Randomized trials comparing the clinical outcomes of ARNIs with ACEIs/ARBs in patients with HFrEF and advanced CKD are still lacking. One single center observational study showed that patients with stage 4 or 5 CKD treated with ARNI had 28% fewer cardiovascular deaths or HF hospitalizations than those treated with standard HF treatment after a mean follow-up of 15 months, including 102 patients with eGFR of <30 mL/min/1.73 m^{2}·. However, the authors did not adjust for confounding factors and there were only 36 patients in the ARNI group and 66 patients in the ACEI/ARB group (12). In a single arm observational study including 23 participants with ESRD on dialysis, ARNI reduced cardiac biomarkers and improved LVEF (13). Hypotension is a well-known adverse effect of ARNI. In the PARADIGM-HF trial,[5] symptomatic hypotension during randomized treatment occurred more frequently in the sacubitril/valsartan group than in the enalapril group. In the United Kingdom Heart and Renal Protection-III (UK HARP-III) trial which enrolled patients with CKD (eGFR 20 to 60 mL/min/1.73 m^2), (14) both systolic and diastolic blood pressures were lower in the sacubitril/valsartan group than in the irbesartan group. In persons with advanced CKD, hypotension may lead to renal hypoperfusion, reduced glomerular filtration, and subsequent congestion, which could be a plausible explanation for the higher risk of HF hospitalization in the ARNI group. The risk of HF hospitalization increased shortly (3 months) after the initiation of ARNI and more hyperkalemia in the ARNI group in our study maybe indirect support for this assumption. In dialysis-dependent patients, low blood pressure may result in inadequate fluid removal or even fluid supplement during dialysis. Fluid overload and subsequent acute decompensation can occur as a consequence of inadequate fluid removal during consecutive hemodialysis sessions. Unfortunately, follow-up blood pressure measurements, hypotension episodes, or information regarding net volume removed during dialysis were not available. In summary, the interaction between reverse remodeling, cardiac output, renal perfusion, and medication dosage are complex in this special population. Thus, the appropriate BP thresholds remained to be defined to preserve kidney function while optimizing medical therapies for HFrEF. Also, Future prospectively study with longer follow-up period is needed to illustrate if ARNI is beneficial in persons with HFrEF and severe CKD if blood pressure is periodically monitored, so the dose could be meticulously adjusted.

In our study, reverse remodeling was numerically more pronounced in the ARNI group. In a meta-analysis, (15) ARNI

improved left ventricular size and hypertrophy compared with ACEI/ARB in patients with HFrEF, even after short-term follow-up. In a small randomized trial, (16) ARNI reduced mitral regurgitation to a greater extent than did valsartan among patients with functional mitral regurgitation. Reverse remodeling was also observed in persons with HFrEF and ESRD on dialysis in the study by Lee et al. (13). Although the etiology of mitral regurgitation (degenerative or functional) was unavailable in the present study and only half of the patients had follow-up echo, our findings regarding ARNI in reverse remodeling was generally comparable to previous studies.

Since evidence-based pharmacological therapies for persons with both HFrEF and advanced CKD are limited, preventing the development of either disease is the most important task for clinicians. DM is one of the most important upstream risk factors for both HFrEF and CKD. The prevalence of DM has often been reported to be around 35–40% in previous randomized trials or registries of patients with HFrEF (17–19). However, up to 60.2% of the patients had DM in our study. The cardiovascular outcome trials of sodium-glucose cotransporter 2 inhibitors (SGLT2Is) have demonstrated that SGLT2Is can reduce future HF in persons with diabetes (20–22). SGLT2is were also showed to reduce renal events and to slow renal function deterioration in participants with or without diabetes in randomized trials (23, 24) In patients with HFrEF, SLGT2Is slowed the rate of decline in eGFR (25–27). Moreover, in patients with CKD, SGLT2Is reduced the risk of incident HF hospitalization (23, 24) In summary, SGLT2Is should be the first-line treatment for patients with DM, HFrEF, or CKD.

There are several limitations to the present study, First, number of the patients in the ARNI group was small and the follow-up period was short. Second, this was a retrospective observational study. Although we used IPTW to adjust for important outcome-related baseline characteristics, unmeasured confounders may still have been present (including functional class, duration of heart failure, etiology of CKD and HFrEF). Third, missing laboratory data at baseline (such as B-type natriuretic peptide) and the need to input missing values is not uncommon in real-world data and should be acknowledged as another limitation. Clinical events that occurred outside CGMHs were not recorded in the CGRD, which may have led to underestimation of the actual event rates. Forth, this study was conducted using an on-treatment design and did not adjust for temporal changes in medical condition during the follow-up period. Finally, the present study only enrolled Asian patients, and whether our results can be extrapolated to patients of other ethnicities remains unclear.

CONCLUSION

Compared to ACEIs or ARBs, ARNIs were associated with comparable clinical and renal outcomes in patients with HFrEF and advanced CKD (eGFR $\leq$30 mL/min/1.73 m^2). In short-term, HF hospitalization may occur more frequently among ARNI users, especially in patients with ESRD on dialysis.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the datasets used in this study are available only in the Chang Gung Medical Data Center of Taiwan. Requests to access the datasets should be directed to P-HC, taipei.chu@gmail.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Chang Gung Memorial Hospital, Link. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

F-CH is the guarantor of this work. F-CH, P-HC, and C-CY conceptualized and designed the study. C-PL, C-CY, and Y-CT acquired, analyzed, and interpreted the data. F-CH and C-PL wrote the first draft of the manuscript. C-CY and P-HC drafted the revision. All authors are fully responsible for all content and editorial decisions. All authors have approved the final 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/fcvm.2022.794707/full#supplementary-material

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Association Between Cholinesterase Inhibitors and New-Onset Heart Failure in Patients With Alzheimer's Disease: A Nationwide Propensity Score Matching Study

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Background: Autonomic nervous dysfunction is a shared clinical feature in Alzheimer's disease (AD) and heart failure (HF). Cholinesterase inhibitors (ChEIs) are widely used autonomic modulators in patients with AD, but their primary preventive benefit on new-onset HF is still uncertain.

Objective: This study examined whether ChEIs have a primary preventive effect on new-onset HF in patients with AD.

Methods: This propensity score matching (PSM) study was conducted using data from the National Health Insurance Research Database of Taiwan for 1995 to 2017. Certificated patients with AD and without a history of HF were divided into ChEI (donepezil, rivastigmine, or galantamine) users or nonusers. The primary endpoint was new-onset HF, and the secondary endpoints were myocardial infarction and cardiovascular death after 10-year follow-up.

Results: After screening 16,042 patients, 7,411 patients were enrolled, of whom 668 were ChEI users and 1,336 were nonusers after 1:2 PSM. Compared with nonusers, ChEI users exhibited a significantly lower incidence of new-onset HF (HR 0.48; 95% CI 0.34–0.68, $p < 0.001$) and cardiovascular death (HR 0.55; 95% CI 0.37–0.82, $p = 0.003$) but not of myocardial infarction (HR 1.09; 95% CI 0.52–1.62, $p = 0.821$) after 10-year follow-up. The preventive benefit of ChEI use compared with Non-use (controls) was consistent across all exploratory subgroups without statistically significant treatment-by-subgroup interactions.

Conclusions: Prescription of ChEIs may provide a preventive benefit associated with lower incidence of new-onset HF in patients with AD after 10-year follow-up.

Keywords: Alzheimer's disease, cholinesterase inhibitors, new-onset heart failure, primary prevention, propensity score matching

INTRODUCTION

With longer human life spans, the incidences of age-related diseases such as Alzheimer's disease (AD) and heart failure (HF) are increasing (1). Autonomic nervous dysfunction with sympathetic activation and cholinergic neurotransmission deficiency are the shared features of AD and HF (2–4). In healthy people, the parasympathetic system is more dominant than sympathetic tone under resting conditions. However, under stressful conditions, the sympathetic system is activated, and the parasympathetic system is suppressed to help the body respond to the emergency; additional energy expenditure is involved in this. During aging and the development of AD, parasympathetic vagal tone diminishes, and sympathetic tone becomes more predominant; therefore, the incidences of cardiovascular disorders such as hypertension and HF increase in AD (5, 6). Inhibition of sympathetic activity by beta-blockers has been the standard therapy for HF, but the primary preventive effect on the development of HF in the early stages is controversial (7). How parasympathetic activation is involved in HF prevention and treatment is still uncertain and under investigation (8–10).

Cholinesterase catalyzes acetylcholine into choline and acetic acid, and choline is then recycled to make acetylcholine in a continuous process during neuronal synaptic transmission. Cholinesterase inhibitors (ChEIs), such as donepezil, rivastigmine, and galantamine, increase the concentration of acetylcholine through acetylcholine catalysation reduction and have been shown to improve cognitive function significantly; they are widely used in patients with AD (11–13). The effect of ChEIs on cholinergic activation, however, is not limited to the central neurons; the intrinsic cardiac neurons, which regulate the chronotropic and dromotropic functions of the heart, are also affected by ChEIs (14). Therefore, when patients with AD are prescribed ChEIs, clinical manifestations such as bradycardia or sinoatrial or atrioventricular blocks should be monitored (15). In addition to these clinical warning signs, anti-inflammatory and negative chronotropic effects mean that ChEIs may offer potential cardioprotective effects that mainly result in reduced incidence of myocardial infarction (MI) and mortality (16, 17). Regarding effect of ChEIs on caridac muscle, reduction of cardial remodeling and ischemic reperfusion injury have been reported in animal studies, but whether a clinical benefit of ChEIs on the prevention of HF exists remains unclear (18, 19). The aim of this study was to investigate the primary preventive effect of ChEIs on new-onset HF development in patients with AD.

MATERIALS AND METHODS

The Institutional Review Board of Chang Gung Memorial Hospital approved the protocol for this cohort study and waived the need for informed consent because all patient data were deidentified before analysis (IRB No. 202100758B1). This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Data Source

We conducted this national database cohort study of patients with dementia or AD aged ≥40 years by using data from the Taiwan National Health Insurance program, which has been implemented since 1995 and covers nearly 99.9% of Taiwan's population of 23 million. We used claims data to collect demographic information, diagnoses based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), treatment procedures, and prescription records. The claims data are characterized by continual longitudinal recording and comprehensive coverage; updated data are released annually by the NHRI. The database information is anonymously collected and protected by a unique identification number for each individual.

Study Population

Patients aged 40 years or older and newly diagnosed as having dementia or AD (ICD-9-CM codes 290.0–290.9 and 331.0) were identified from the catastrophic illness file of the National Health Insurance Research Database (NHIRD) between 1 May 1995 and 30 September 2017. To reduce the confounding bias of underlying diseases, patients who had a concomitant diagnosis of vascular dementia (ICD-9-CM code 290.4), Parkinson's disease (ICD-9-CM code 332), or occurrence of HF (ICD-9-CM codes 428, 425.4, 425.5, 425.6, 425.7, 425.8, 425.9, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 785.51) before dementia diagnosis or treatment were excluded. After exclusion, the remaining patients with AD were divided into either the exposure group (ChEI users) or the control group (ChEI nonusers). The exposure of interest—the use of ChEIs or not—was identified through prescription records. ChEIs included donepezil (Anatomical Therapeutic Chemical Classification System [ATC] code: N06DA02), rivastigmine (ATC code: N06DA03), and galantamine (ATC code: N06DA04). Comorbidities at baseline were identified using ICD-9-CM diagnostic codes at the index date and 1 year before the index date. The ICD-9-CM codes used to identify the study covariates and outcomes are summarized in the supplement. In addition, cardiovascular medications, including antiplatelet and anticoagulation medications, statins, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin receptor blockers (ARBs) were also documented. The propensity score matching (PSM) method was employed to balance these baseline comorbidities and use of cardiovascular medications. A flowchart of the study cohort enrolment process is shown in **Figure 1**.

The index date of initial follow-up was the date of first administration of ChEIs in the exposure group. In the control group, the index date was the date of receiving a diagnosis of AD. The primary outcome was new onset of HF. The definition of new-onset HF in this present study was newly diagnosis of HF at outpatient and/or discharge from hospital (ICD-9-CM codes 428, 425.4, 425.5, 425.6, 425.7, 425.8, 425.9, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 785.51). The secondary endpoints were the occurrence of either MI or cardiovascular death. Cardiovascular death was defined as mortality due to cardiovascular etiology (ICD-9-CM codes 390–459). All study participants were followed up from the index date

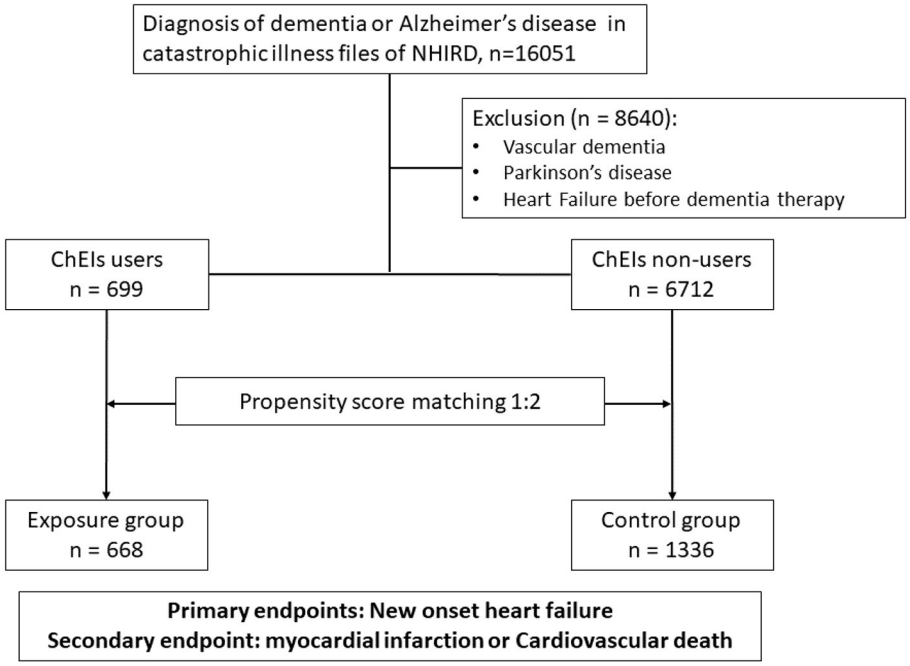

FIGURE 1 | Flow chart of patient enrolment in this study.

until the occurrence of a relevant event, withdrawal from the insurance program, follow-up at 10 years, or follow-up until 31 December 2018, whichever occurred first.

Statistical Analysis of Cohort Study

We assessed the differences in baseline characteristics, comorbidities, and medications between the treatment and control groups. Covariates introduced to construct the propensity score included age, sex, comorbidities, and medications. The Cox proportional hazards model and competing risk regression analysis were used to estimate the treatment effects on clinical outcomes. A two-sided p-value of <0.05 indicated statistical significance. All data analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

A subgroup analysis was conducted to determine whether the hazard ratios (HRs) of outcomes for the ChEIs and controls were similar in the prespecified subgroups. The subgrouping factors included age (75 years old); sex; presence of diabetes mellitus, hypertension, or hyperlipidaemia; prior stroke; presence of chronic kidney disease, chronic lung disease, or peripheral vascular disease.

RESULTS

Clinical Characteristics of Patients Before and After PSM

From 1 May 1995 to 30 September 2017, a total of 16,051 patients were diagnosed as having AD in the catastrophic illness file of the NHIRD. After excluding 8,640 patients with vascular dementia, Parkinson's disease, or a diagnosis of HF before using ChEIs, a total of 7,411 patients were enrolled in the study. Of the total, 699 participants comprised the exposure group and were treated with ChEIs, and 6,712 comprised the control group and were patients undergoing conventional therapy. The comparison of baseline characteristics and medication use between ChEI users and nonusers is listed in **Table 1**. Generally, when comparing ChEI users with nonusers, unmatched patients were substantially younger, more often women, and more likely to be patients with diabetes mellitus, hypertension, hyperlipidemia, chronic liver disease, or peripheral vascular disease; ChEI users were also more likely to use antiplatelet or anticoagulation medications, statins, beta-blockers, ACEIs, or ARBs but less likely to be diagnosed as having chronic kidney disease than nonusers were. No substantial differences between ChEI users and nonusers were observed for prior MI, prior stroke, chronic lung disease, atrial fibrillation, or venous thromboembolism before PSM. In the ChEI group, most patients used donepezil (72.5%), 16.2 and 11.3% of them used rivastigmine and galantamine, respectively.

After 1:2 PSM, 668 patients (ChEI users) were included in the exposure group and 1,336 patients (ChEI nonusers) in the control group. All matched characteristics and medications listed on the left side of **Table 1** were similar for the exposure and control groups. The types of ChEIs in the matched exposure group included donepezil 74.0%, rivastigmine 15.1%, and galantamine 10.9%.

Clinical Outcomes

The Kaplan–Meier survival curves for new-onset HF between ChEI users and controls (log-rank $p < 0.001$) are displayed in **Figure 2**. **Table 2** lists the clinical outcomes and relative

TABLE 1 | Baseline characteristics before and after propensity score matching.

	Unmatched patients			Matched patients		
	Control	**ChEIs**	***P*-value**	**Control**	**ChEIs**	***P*-value**
Patient number, *n*	6,712	699		1,336	668	
Female gender, *n* (%)	4,125 (61.5)	466 (66.7)	0.008	860 (64.4)	440 (65.9)	0.540
Age, years	77.8 ± 9.2	76.2 ± 8.5	<0.001	76.2 ± 9.1	76.3 ± 8.5	0.885
Diabetes mellitus, *n* (%)	1,925 (28.7)	245 (35.0)	0.001	431 (32.3)	231 (34.6)	0.322
Hypertension, *n* (%)	3,749 (55.9)	475 (68.0)	<0.001	903 (67.6)	445 (66.6)	0.699
Hyperlipidemia, *n* (%)	1,452 (21.6)	281 (40.2)	<0.001	493 (36.9)	251 (37.6)	0.806
Prior MI, *n* (%)	122 (1.8)	14 (2.0)	0.842	22 (1.6)	14 (2.1)	0.593
Prior stroke, *n* (%)	2,423 (36.1)	267 (38.2)	0.291	511 (38.2)	253 (37.9)	0.909
Chronic lung disease, *n* (%)	2,142 (31.9)	248 (35.5)	0.061	484 (36.2)	235 (35.2)	0.681
Chronic liver disease, *n* (%)	1,012 (15.1)	152 (21.7)	<0.001	270 (20.2)	141 (21.1)	0.681
Chronic kidney disease, *n* (%)	279 (4.2)	10 (1.4)	0.001	15 (1.1)	10 (1.5)	0.618
Atrial fibrillation, *n* (%)	185 (2.8)	16 (2.3)	0.548	24 (1.8)	15 (2.2)	0.607
Peripheral vascular disease, *n* (%)	610 (9.1)	100 (14.3)	<0.001	158 (11.8)	94 (14.1)	0.175
Venous thrombosis or embolism, *n* (%)	66 (1.0)	9 (1.3)	0.571	18 (1.3)	6 (0.9)	0.514
Antiplatelet, *n* (%)	811 (12.1)	165 (23.6)	<0.001	281 (21.0)	150 (22.5)	0.501
Anticoagulation, *n* (%)	19 (0.3)	7 (1.0)	0.009	8 (0.6)	3 (0.4)	0.761
Statin, *n* (%)	395 (5.9)	157 (22.5)	<0.001	240 (18.0)	127 (19.0)	0.610
Beta-blocker, *n* (%)	889 (13.2)	171 (24.5)	<0.001	160 (24.0)	304 (22.8)	0.550
ACEi/ARB, *n* (%)	911 (13.6)	234 (33.5)	<0.001	416 (31.4)	204 (30.5)	0.824
Type of ChEIs						
Donepezil, *n* (%)	0 (0.0)	507 (72.5)		0 (0.0)	494 (74.0)	
Rivastigmine, *n* (%)	0 (0.0)	113 (16.2)		0 (0.0)	101 (15.1)	
Galantamine, *n* (%)	0 (0.0)	79 (11.3)		0 (0.0)	73 (10.9)	

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ChEIs, Cholinesterase inhibitors; MI, myocardial infarction.

risks between ChEI users and controls after 10-year follow-up. New onset HF at 10-year follow-up was 6.1% for ChEI users and 13.0% for nonusers. The incidence of new-onset HF among donepezil, rivastigmine, and galantamine were 34/494 (6.88%), 1/101 (1%), 5/73 (6.85%), respectively and there were no statistical significance differences (p-value = 0.071). The incidence rate for new-onset HF per 1,000 patient-years was 9.5 for ChEI users and 18.1 for controls. Compared with nonusers, ChEI users had a lower risk of new onset HF both in the Cox proportional hazards model (HR 0.51; 95% CI: 0.36–0.72, $p < 0.001$) and in the competing risk regression analysis (HR 0.48; 95% CI: 0.34–0.68, $p < 0.001$).

After 10-year follow-up, cardiovascular death had occurred in 4.6% of patients in the ChEI user group and in 8.9% of patients in the nonuser group. The incidence rate of cardiovascular death per 1,000 patient-years was 7.1 for ChEI users and 11.9 for nonusers. Compared with controls, the use of ChEIs reduced the risk of cardiovascular death by 41% in the Cox proportional hazards model (HR 0.59; 95% CI: 0.40–0.88, $p = 0.009$) and by 45% in the competing risk regression analysis (HR 0.55; 95% CI: 0.37–0.82, $p = 0.003$).

MIs occurred in 1.8% of the patients in the ChEI group and in 1.6% of the patients in the nonuser group after 10-year follow-up. The incidence rates of MI per 1,000 patient-years were 2.7 for ChEI users and 2.1 for nonusers. The risk of MI in ChEI users was not significantly different from that in the control group in the Cox proportional hazards model (HR 1.20; 95% CI: 0.58–2.50, $p = 0.620$) or in the competing risk regression analysis (HR 1.09; 95% CI: 0.52–2.28, $p = 0.821$).

Subgroups Analysis for Primary Preventive Effect ChEIs on New-Onset HF

Figure 3 displays the results of subgroup analysis for the occurrence of HF according to baseline characteristics in the matched study populations. In comparisons with the control group, the preventive benefit of ChEIs was consistent across all exploratory subgroups without statistically significant treatment-by-subgroup interactions.

DISCUSSION

The cardioprotective effect of ChEIs has been noted during the past decade in animal and clinical studies. However, due to the inhibition of platelets activation, microphage production of cytokines, and reductions in oxidative stress, most of these studies have focused on the benefit of ChEIs in reducing the occurrence of atherosclerotic events (17, 20, 21). The main findings of the present study demonstrate that chronic use of ChEIs is associated with a lower incidence of new-onset HF and

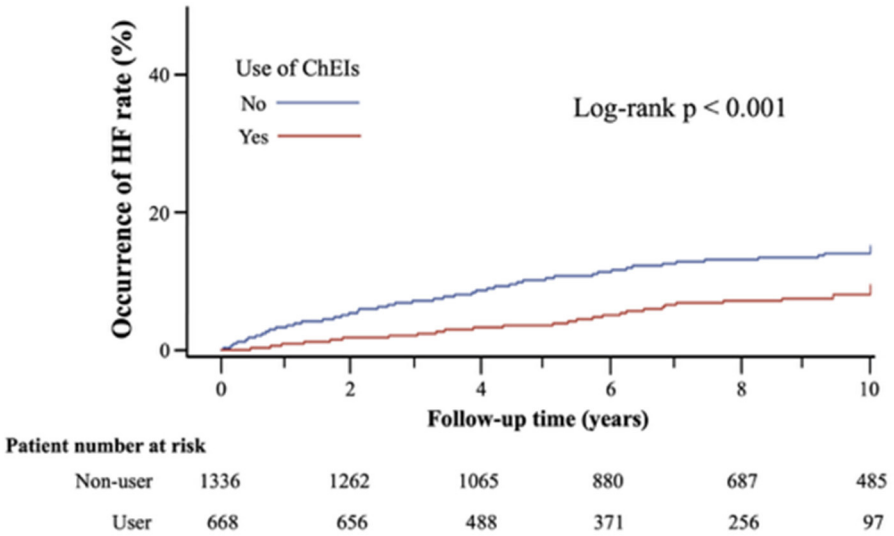

FIGURE 2 | Kaplan-Meier survival curves of new onset of HF after 10-years follow-up in matched cohort.

TABLE 2 | Clinical outcomes and relative risks between ChEI users and controls after 10-year follow-up.

Clinical events in groups	Events, n (%)	Person-years	Incidence per 1,000 person-years	Cox proportional model		Competing risk regression	
				HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
HF							
Control	174 (13.0)	9,630	18.1	1.00 [Reference]	–	1.00 [Reference]	–
ChEIs	41 (6.1)	4,332	9.5	0.51 (0.36–0.72)	< 0.001	0.48 (0.34–0.68)	< 0.001
MI							
Control	22 (1.6)	10,483	2.1	1.00 [Reference]	–	1.00 [Reference]	–
ChEIs	12 (1.8)	4,424	2.7	1.20 (0.58–2.50)	0.620	1.09 (0.52–2.28)	0.821
Cardiovascular death							
Control	119 (8.9)	10,011	11.9	1.00 [Reference]	–	1.00 [Reference]	–
ChEIs	31 (4.6)	4,377	7.1	0.59 (0.40–0.88)	0.009	0.55 (0.37–0.82)	0.003

ChEI, Cholinesterase inhibitor; CI, confidence interval; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

cardiovascular death, and this potential preventive effect is not related to the occurrence of MIs in patients with AD.

The incidences of HF and AD increase with age (1), but the incidence of new-onset HF in patients with AD has never been examined. In the general population, the incidence for HF (per 1,000 person-years) increases from <5 in patients 50–59 years of age to more than 25 in patients 80–89 years of age and more than 40 in those 90 years of age or older (22, 23). The incidence rate for AD (per 1,000 person-years) increases from 2.8 in patients 65–69 years age to 56 in patients 90 years of age or older (24). A long-term observational study reported that most elderly patients with HF had dementia and usually the onset of dementia had occurred before patients were diagnosed as having HF (25). Studies indicate that HF, with a prevalence rate of ∼10%, is one of the most common comorbidities in patients with AD (26). The results of the present study are consistent with these findings in that the prevalence of HF in the total study cohort was 10.6% (6.1% in ChEI users vs. 13.0% in nonusers). In addition, this study is the first to report a significant reduction in new-onset HF in ChEI users compared with control; the incidence of new-onset HF was 18.1 per 1,000 person-years in control patients with AD at a mean age of 76 years; after using ChEIs for 10 years, the incidence of new-onset HF significantly decreased to 9.5 per 1,000 person-years.

The interplay between HF and AD is complex and has long been noted. HF and AD share similar common risk factors such as age, hypertension, diabetes mellitus, and obesity (27, 28). In addition, AD and HF share some genetic variants (29, 30). Low cardiac output in patients with HF leads to chronically inadequate cerebral blood flow and increased oxidative stress, which are followed by a series of pathological consequences such as protein and enzyme dysfunctions, amyloid beta protein deposition, and eventual neuronal cell death (31, 32). Therefore, HF is recognized as a risk factor in the development of AD (33). Conversely, AD patients are also a high-risk population for the development of cardiovascular diseases. Troncone et al. found

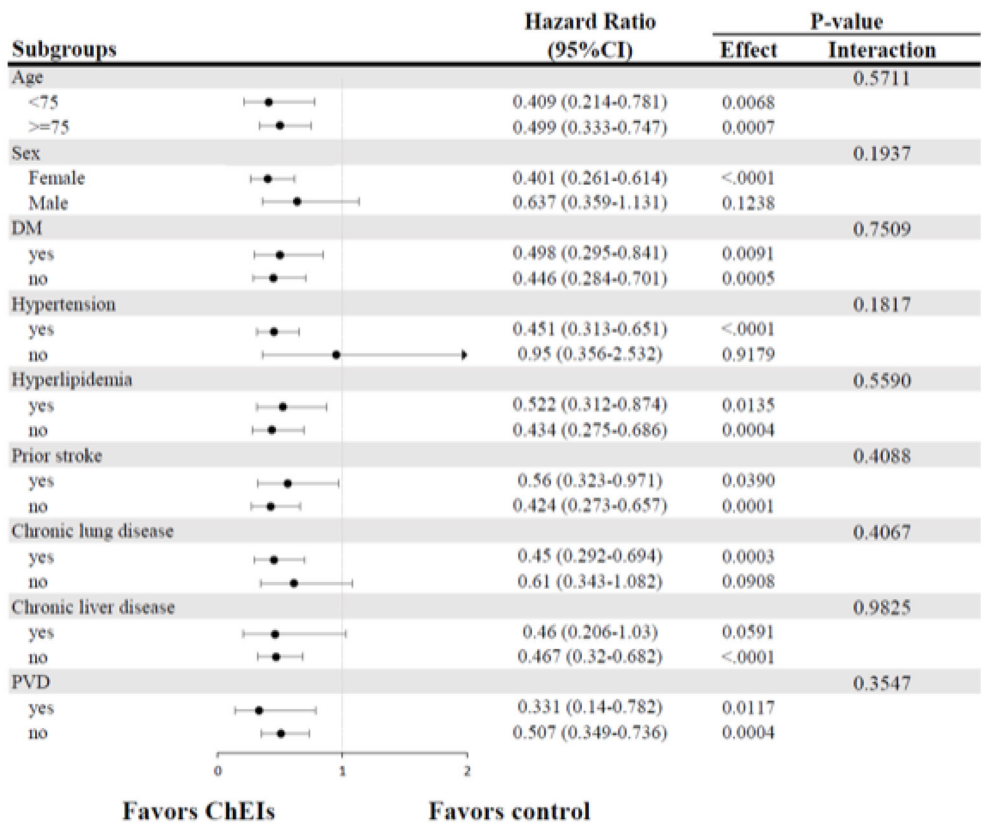

FIGURE 3 | Forest plots of subgroup analysis for new-onset HF. CI, confidence intervals; DM, diabetes mellitus; HF, heart failure; PVD, peripheral vascular disease.

that patients with AD had a thicker left ventricle than those without AD. The hallmark feature of AD, the accumulation of beta-amyloid proteins in the extracellular space of the brain, can also be found in the left ventricle (34). This amyloid deposition mechanism places patients with AD at a higher risk for the occurrence of atherosclerosis and HF (35). Because of involvement of cholinesterase in amyloid fibril formation process, using of ChEIs not only can reduce beta-amyloid deposition in the brain, but also can delay the development of HF through the same mechanism (36).

Autonomic imbalance, including sympathetic nervous activation and parasympathetic withdrawal, is another pathogenetic mechanism in the development and progression of HF (3, 4). Whether parasympathetic stimulation therapy is a treatment for HF is still under investigation. A small clinical trial demonstrated the benefit of cholinergic agents on exercise hemodynamic profile improvement in patients with HF (37). In addition, baroreflex activation appeared to be safe and effective for patients with HF (10). Despite sparseness of cholinergic innervation of ventricular myocardium, Non-neuronal cardiac cholinergic system plays an important role in cardiac homeostasis regulation (38, 39). Acetylcholine or muscarinic receptor agonist, through upregulation of choline acetyltransferase and choline transporter in cardiomyocytes, can synthesized acetylcholine themselves. This autocrine or paracrine effects can circumvent mitochondrial overshoot to protect cardiomyocytes from energy depletion when suffering from stress or energy demand (40, 41). Application of cholinergic agents to prevent HF development in large scale study has never been reported. Though there are theoretically cardiovascular benefits, intolerable side effects or toxicity limit the long-term application of these cholinergic agents (42, 43). The safety of the chronic use of ChEIs, which is well known in patients with AD, indicates that this class of medications has greater potential than other cholinergic agents do in the primary prevention of HF (44). *In vivo* and *vitro* studies proved donepezil, the most common used ChEIs, was different from other cholinergic agents in increasing expression of choline acetyltransferase promoter and activating intrinsic cardiac acetylcholine synthesis to positively regulate cardiomyocytes in terms of its energy metabolism, ischemic response, angiogenesis, and oxidative stress (40). This may be another reason to explain why ChEI is effective to prevent development of HF in this present study.

The strength of this study was the exclusion of patients with a diagnosis of HF to elucidate the possible primary preventive effect of using ChEIs. In addition, this study cohort also excluded patients with vascular dementia or Parkinson's disease and included a few numbers of patients with prior MI, with chronic kidney disease, and with atrial fibrillation, thus reducing the presence of comorbidity-related confounders in the evaluation of ChEI efficacy. Though animal studies have proved the effect of chronic parasympathetic nervous activation on the prevention of cardiac chamber remodeling and the development of HF (45), the present study is the first human

study to report the potential primary preventive benefit of using a chronic parasympathetic modification agent–ChEI in association with a lower incidence of new-onset HF. Additional studies should examine whether this preventive benefit of ChEIs can extend to other populations without AD or whether ChEIs may be an effective treatment for patients with already established HF.

However, this study has several limitations. First, because of the retrospective nature of the study, the study groups may have had inherent differences. Although we used PSM to balance differences associated with major characteristics at baseline, hidden bias may still have occurred. Second, the participants in this study were all elderly patients with dementia. Patients with severe dementia may lose their sense of illness related to cardiovascular diseases. However, patients' cognitive condition, functional ability, and the effects of ChEIs will remain in this database. Third, this is a retrospectively database-based study, so the serum levels of acetylcholine and cholinesterase before and after ChEIs are not available to identify the response of ChEIs. Finally, an underestimation resulting from noncompliance is likely because information available about prescribed medications may not reflect their actual use.

In conclusion, this real-world observational study demonstrated that the use of ChEIs in patients with AD is associated with lower incidence of new-onset HF, which may translate to a lower risk of cardiovascular death, and this possible preventive effect is not related to MI.

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.

ETHICS STATEMENT

The Institutional Review Board of Chang Gung Memorial Hospital approved the protocol for this cohort study and waived the need for informed consent because all patient data were deidentified before analysis (IRB No. 202100758B1).

AUTHOR CONTRIBUTIONS

M-JH: conceptualization. M-JH, D-YC, and C-HL: methodology. C-LW, Y-JC, Y-TH, and S-HC: formal analysis and investigation. M-JH, S-HC, and Y-TH: writing review and editing. S-HC and Y-TH: funding acquisition and supervision. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.831730/full#supplementary-material

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Association of Gonadotropin-Releasing Hormone Therapies With Venous Thromboembolic Events in Patients With Prostate Cancer: A National Cohort Study

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Although androgen deprivation therapy (ADT) has been proposed to be associated with a higher risk of venous thromboembolisms (VTEs), whether gonadotropin-releasing hormones (GnRHs), such as both agonists and antagonists, are also associated with VTEs remain unclear. Using the Taiwan Cancer Registry (TCR) linked with the National Health Insurance Research Database, we identified patients diagnosed with prostate cancer from 2008 to 2015. Patients who received GnRH were 1:1 propensity score matched with non-GnRH users by age and cancer stage at diagnosis and clinical stage. Cox regression analysis was applied to estimate the incidences of VTEs with death as a competing event at the 5-year follow-up. The VTE incidence among GnRH users was 1.13% compared with 0.98% among non-users. After adjusting with potential confounding factors, the risk of VTEs showed borderline statistical significance among GnRH users and non-users. Notably, in the subgroup analysis among patients receiving GnRH therapy, those younger than 70 years old or at an earlier stage (stage I/II) were at a higher risk of VTEs. Different from previous studies, our findings highlighted critical concerns regarding the cardiac safety of GnRH therapies in prostate cancer patients at a relatively younger age or at an earlier stage.

Keywords: prostate cancer, GnRH therapies, androgen deprivation therapies, venous thromboembolic events, age, cancer stage

BACKGROUND

As the second most prevalent cancer in the male gender, prostate cancer frequently affects the aged population (1). To date, androgen deprivation therapy (ADT) has significantly improved the outcome and prevented the most extensive surgeries (2, 3). Nevertheless, numerous observational studies have indicated an increased risk of thrombosis events in association with ADT use (4–7). Cancer *per se* is a risk factor for thrombosis, and treatments for cancer also increase the risk (4–7). For prostate cancer, venous thromboembolism (VTE), such as deep-venous thrombosis (DVT) and pulmonary embolism (PE), are frequently observed complications after prostatectomy, ranging from 0.5 to 40% (7–10). Likewise, several studies have reported a positive correlation between the use of ADT and an increased risk of thromboembolism (4, 5, 7). With the advancement of ADT, agonists and antagonists targeting gonadotropin-releasing hormone (GnRH) continuously suppress testosterone to a castration level through negative feedback on GnRH receptors (2, 3, 11, 12) GnRH therapies improve the outcomes of patients with prostate cancer, but evidence regarding the association between prostate cancer and VTEs is scarce (11, 13, 14). Given that the risk of VTEs increases exponentially with age, whether the effects of ADT on VTEs differentially depend on age and cancer stage remains unknown. Using a nationwide database, we aimed to study whether GnRHs, such as both agonists and antagonists, are associated with VTEs in prostate cancer patients.

METHODS

Data Source

In this population-based cohort, integrated by the Health and Welfare Data Science Center (HWDC), data derived from Taiwan's National Health Insurance Research Database (NHIRD) from 2005 to 2017 and the Taiwan Cancer Registry (TCR) from 2008 to 2015 were obtained. The NHIRD is based on the whole Taiwanese population from Taiwan's National Health Insurance Program and has been validated in many studies (15). The diagnosis codes in the NHIRD were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) for cases before 2015 and the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) for cases since 2016. The TCR included approximately 97% of cancer patients, and the data quality was confirmed after comparison with other cancer registry databases (16). This study was approved by the local institutional review committee of Clinical Research Center in Chi-Mei Medical Center, Tainan, Taiwan (IRB no.: 11005-E03), and they granted a waiver of informed consent.

Study Population

The patients newly diagnosed with cancer were identified following a diagnosis of malignant neoplasm of the prostate (ICD-9-CM: 185) from the TCR between 2008 and 2015. After linking with the NHIRD, detailed information, such as age, clinical stage, comorbidities, treatment types, drug usage, and subsequent outcomes, was presented in this study. Study subjects with incomplete medical records of cancer stage and those aged under 18 years were excluded. Because the aim of this study was to estimate the risk of venous thromboembolic events (VTEs; ICD-9-CM codes 453.8, 415.1, and ICD-10-CM codes I82, I26.9, I27.82), patients with a history of VTEs were excluded. Considering the potential immortal time bias of patients who had a too short period of survival to receive GnRH therapies after the diagnosis of prostate cancer, the landmark analysis method was used to set the beginning date of follow-up, the date after 6 months of a prostate cancer diagnosis (17, 18). Thus, patients who were died within 6 months or censored of non-following more than 6 months were all excluded. The survival analysis with the landmark approach was frequently used in previous studies (17, 18). Ultimately, prostate cancer patients who received GnRH agonist/antagonist therapies within 2 years after the date as prostate cancer were initially diagnosed were set as the case cohort. To minimize the impact of confounding effects on age and clinical stages, those who received GnRH were 1:1 propensity score matched with non-GnRH patients (comparison cohort) by age and clinical stages at the time of their cancer diagnosis. The longest follow-up time among the study population was set as 5 years for reducing the potential intervention to affect the outcomes. The flowchart of the study design is shown in **Figure 1**.

Outcomes and Measurements

The interesting outcomes of this study were VTEs, such as PE and DVT. All study subjects were right-censored of death, loss of follow-up, or the end of dataset date (December 31, 2017). Furthermore, potential confounding factors were assessed in this study, such as age, clinical stage, comorbidities, treatment type, and drug usage. The comorbidities included diabetes mellitus (DM), hyperlipidemia, valvular heart diseases, asthma, chronic kidney disease, coronary heart disease (CAD), hypertension (HTN), and chronic obstructive pulmonary disease (COPD). Radiation and chemotherapy were the major treatment types, and the usage of drugs consisted of angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARBs), and beta blockers. The ICD coding is listed in **Supplementary Table 1**.

Statistical Analysis

Pearson's chi-square tests or Fisher's exact tests were used to estimate the distribution difference between prostate patients who received GnRH and those did not. The study subjects' following times are presented as medians with quintiles with Wilcoxon rank-sum tests for comparing the differences. The trend of the primary outcome, VTE, was plotted by the Kaplan-Meier approach, and the log-rank test was used to compare the differences between the two groups. To calculate the risk of VTEs between prostate patients who received GnRH and those without, the Cox proportional hazards model was applied to report the hazard ratio (HR) and 95% CI. Furthermore, Schoenfeld residual tests were used in Cox regression to assess violations of the proportional hazards assumption. Subgroup analysis was also presented to interpret the VTE risk among different subjects. Considering the follow-up period and events in this study, the detectable HR of 1.33 between GnRH and Non-GnRH groups was estimated at 90% statistical power and the probability of type I error at 0.05. SAS 9.4 for Windows (SAS Institute Inc., Cary,

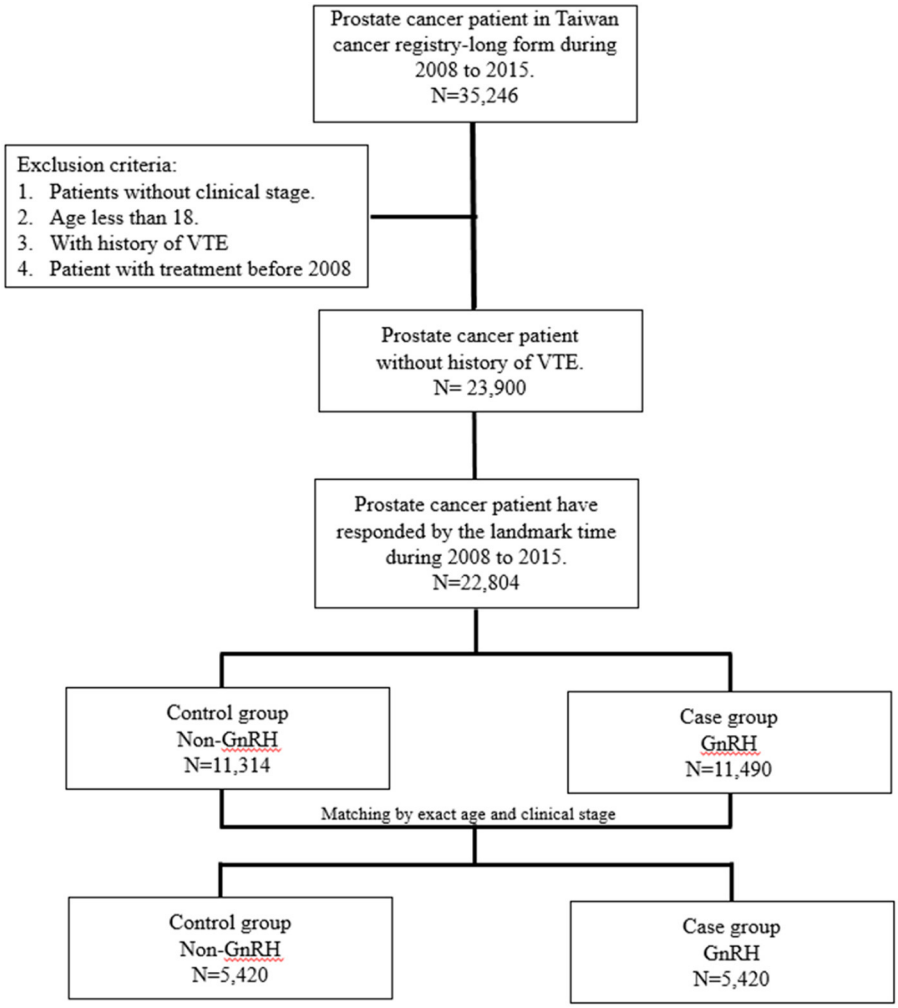

FIGURE 1 | Study flow chart.

NC, USA) and STATA 14.0 (Stata Corp LLP, College Station, TX, USA) were used in this study.

RESULTS

Demographic Information of the Prostate Cancer Patients

The demographic information of the prostate cancer patients with and without GnRH use before matching is presented in **Supplementary Table 2**. There was a higher prevalence of cardiovascular risk factors, such as DM and chronic kidney disease (CKD), in patients receiving GnRH therapies. More patients who received GnRH were also under radiation and chemotherapy instead of surgery. After 1:1 propensity scoring matched by age and clinical stage, there were still more GnRH users having cardiovascular risk factors, such as DM, hyperlipidemia, CKD, or receiving radiotherapies. Notably, a relatively higher incidence of VTE was observed in patients who received GnRH therapies than in those who did not receive GnRH (1.13 vs. 0.98%, $p = 0.4513$; **Table 1**). Among patients who developed VTEs, the incidences of DVT and PE were not significantly different between GnRH users and non-users (**Supplementary Table 3**).

The Risks of VTEs in Prostate Cancer Patients Receiving GnRH Therapies

In the Cox regression analysis, the 5-year risk VTEs were higher among GnRH users than among non-users at a borderline level of statistical significance (adjusted HR: 1.51; CI: 1.03–2.22, $p = 0.0367$; **Table 2**). There was no significant impact of age on the risk of VTEs. Interestingly, compared with patients at cancer stage IV, those at earlier stages had lower risks of VTEs. For example, the risk of VTEs was reduced in patients with stage I/II (adjusted HR: 0.69; CI: 0.47–1.01, $p = 0.0568$). In terms of cardiovascular risk factors, after adjusting for age and comorbidities, only hyperlipidemia showed a significant

TABLE 1 | Demographic information of prostate cancer patient treated with gonadotropin-releasing hormone therapy (GnRH) or not after matching.

	Non-GnRH $N = 5,420$	GnRH $N = 5,420$	*P*-value
Age groups			
70<	1,776 (32.77)	1,776 (32.77)	>0.9999
70≧	3,644 (67.23)	3,644 (67.23)	
Clinical stage			
I, II	3,323 (61.31)	3,323 (61.31)	>0.9999
III, IV	2,097 (38.69)	2,097 (38.69)	
Overall follow-up period, years			
Median (Q1–Q3)	4.16 (2.33–6.55)	3.51 (2.18–5.25)	<0.0001
5 year follow-up period			
VTE	53 (0.98)	61 (1.13)	0.4513
Time to VTE, years	1.88 (0.90–3.16)	1.75 (0.99–2.93)	0.7943
Mortality	1,323 (24.41)	1,265 (23.34)	
Comorbidities			
DM	1,104 (20.37)	1,200 (22.14)	0.0242
Hyperlipidemia	1,118 (20.63)	1,215 (22.42)	0.0234
HTN	2,902 (53.54)	2,969 (54.78)	0.1965
PAD	63 (1.16)	79 (1.46)	0.1765
Valvular heart disease	151 (2.79)	134 (2.47)	0.3075
Asthma	263 (4.85)	225 (4.15)	0.0784
AF	182 (3.36)	147 (2.71)	0.0500
CKD	458 (8.45)	534 (9.85)	0.0114
CAD	1,008 (18.60)	982 (18.12)	0.5189
COPD	464 (8.56)	443 (8.17)	0.4663
Radiation	1,492 (27.53)	2,441 (45.04)	<0.0001
Chemotherapy	43 (0.79)	53 (0.98)	0.3053
Drug used			
ACEI	524 (9.67)	441 (8.14)	0.0051
ARB	1,422 (26.24)	1,571 (28.99)	0.0014
All beta blockers	1,173 (21.64)	1,217 (22.45)	0.3080

Value of p was derived from Pearson's chi-square test and Wilcoxon test.
DM, diabetes mellitus; HTN, hypertension; PAD, peripheral arterial disease; AF, atrial fibrillation; CKD, chronic kidney disease; CAD, coronary arterial disease; COPD, chronic obstructive pulmonary disease; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers.

TABLE 2 | Risk factors of 5 years venous thromboembolic events (VTEs) between prostate cancer patients with or without gonadotropin-releasing hormone therapy (GnRH).

	Crude HR (95% C.I.)	*P*–value	Adjusted HR (95% C.I.)	*P*–value
GnRH v.s. non-GnRH	1.33 (0.92–1.93)	0.1285	1.51 (1.03–2.22)	0.0367
Age groups				
70<	Ref.		Ref.	
70≧	1.30 (0.87–1.95)	0.2012	1.22 (0.81–1.85)	0.3443
Clinical stage				
I, II	0.59 (0.41–0.85)	0.0045	0.69 (0.47–1.01)	0.0568
III, IV	Ref.		Ref.	
Comorbidities				
DM	1.10 (0.71–1.72)	0.6683	1.09 (0.68–1.76)	0.7101
Hyperlipidemia	0.72 (0.44–1.18)	0.1944	0.49 (0.27–0.89)	0.0194
Valve	1.06 (0.34–3.33)	0.9231	0.94 (0.30–2.99)	0.9152
Asthma	1.66 (0.81–3.40)	0.168	1.78 (0.86–3.67)	0.1205
CKD	1.26 (0.68–2.35)	0.4611	1.18 (0.62–2.22)	0.6195
CAD	1.10 (0.69–1.74)	0.7019	0.93 (0.56–1.55)	0.7905
HTN	0.94 (0.65–1.36)	0.7516	0.80 (0.51–1.26)	0.3402
COPD	1.45 (0.80–2.64)	0.2242	1.44 (0.78–2.65)	0.2416
Radiation	1.15 (0.79–1.67)	0.4624	1.10 (0.75–1.60)	0.6308
Chemotherapy	1.58 (0.22–11.31)	0.6498	1.33 (0.19–9.61)	0.7746
Drug used				
ACEI	1.10 (0.59–2.05)	0.7584	1.13 (0.59–2.18)	0.7141
ARB	1.21 (0.81–1.80)	0.3544	1.28 (0.79–2.06)	0.3215
All beta blockers	1.05 (0.68–1.63)	0.8248	1.03 (0.64–1.67)	0.8926

Adjusted HRs were adjusted for age group, clinical stage, comorbidities, cancer treatment types, and history of drug used.

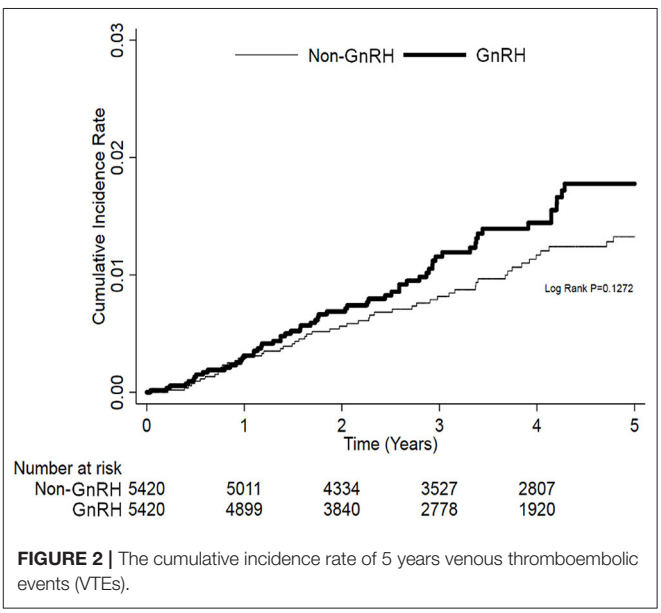

FIGURE 2 | The cumulative incidence rate of 5 years venous thromboembolic events (VTEs).

association with the development of VTEs (adjusted HR: 0.49; CI: 0.27–0.89, $p = 0.0194$); in contrast, DM, hyperlipidemia, CKD, or receiving radiotherapies did not correlate with VTEs. Likewise, the use of cardiovascular medications did not show differences in VTE risks between GnRH users and non-users. In the Kaplan-Meier plot, despite no significant differences in VTEs between prostate cancer patients who received different treatments, a statistically non-significant increase of VTE incidence in patients who received GnRH therapies indicated a potentially higher risk than in those who did not receive GnRH (**Figure 2**).

Subgroup Analysis of 5-Year VTEs in Prostate Cancer Patients Receiving GnRH Therapies

Upon our findings of increasing incidences of VTEs in patients who received GnRH therapies, we sought to identify the specific populations that are at a high risk. Through the subgroup analysis among patients receiving GnRH therapy, interestingly, those younger than 70 years old or at an earlier cancer stage (Stage I/II)

TABLE 3 | Subgroups analysis of risk factors of 5 years venous thromboembolic events (VTEs) between prostate cancer patients with and without gonadotropin-releasing hormone therapy (GnRH) uses.

Subgroup of patient	*N*	Crude HR (95% C.I.)	*P*–value	Adjusted HR (95% C.I.)	*P*–value
Age <70	3,552				
GnRH v.s. Non-GnRH		2.04 (1.00–4.16)	0.0488	2.58 (1.21–5.53)	0.0147
Age 70≧	7,288				
GnRH v.s. Non-GnRH		1.13 (0.73–1.74)	0.5965	1.20 (0.76–1.90)	0.4357
Clinical stage I, II	6,646				
GnRH v.s. Non-GnRH		1.86 (1.10–3.16)	0.0209	1.80 (1.05–3.10)	0.0332
Clinical stage III, IV	4,194				
GnRH v.s. Non-GnRH		0.93 (0.55–1.57)	0.7752	1.37 (0.76–2.47)	0.2924
Age <70 and stage I, II	2,106				
GnRH v.s. Non-GnRH		7.73 (1.73–34.57)	0.0075	8.73 (1.90–40.23)	0.0054
Age <70 and stage III, IV	1,446				
GnRH v.s. Non-GnRH		0.96 (0.39–2.37)	0.9323	1.34 (0.50–3.61)	0.5647
Age ≧70 and stage I, II	4,540				
GnRH v.s. Non-GnRH		1.31 (0.73–2.38)	0.3692	1.21 (0.66–2.23)	0.5376
Age ≧70 and stage III, IV	2,748				
GnRH v.s. Non-GnRH		0.91 (0.48–1.74)	0.7771	1.30 (0.63–2.71)	0.4814

Adjusted HRs were adjusted for age group, clinical stage, comorbidities, cancer treatment types, and history of drug used.

were at higher risks of VTEs (adjusted HR: 2.58; 95% CI: 1.21–5.53, $p = 0.0147$ and adjusted HR: 1.80; CI: 1.05–3.10, $p = 0.0332$, respectively). In addition, the interaction subgroup of patients who were younger than 70 years old and were at an early-stage had 8.73-fold risk of VTEs (95% CI: 1.90–40.23, $p = 0.0054$) in patients who received GnRH therapy compared with those who did not receive GnRH therapy (**Table 3**).

DISCUSSION

In this nationwide cohort focusing on prostate cancer patients, we observed that the risk of VTEs was higher among GnRH users than among non-users. Notably, different from our concept that older patients were prone to a higher risk of VTEs, our findings indicated that those younger than 70 years old or at an earlier cancer stage (Stage I/II) were at higher risk of VTEs. In addition to patients at old age or higher cancer stages, who may be prone to higher risks of thrombosis events, this study highlighted the risk to younger patients at earlier stages of cancer. However, given that the incidences of VTEs increase with age, the results did not encourage GnRH use in older patients or patients at advanced stages but emphasized critical concerns regarding the cardiac safety of GnRH therapy in all population of prostate cancer patients that include those who were younger or were at an early stage of cancer.

Androgen deprivation therapy is the standard treatment for prostate cancer (2, 3). Most doctors in our country treat patients with prostate cancer based on the National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) guidelines (3, 19). On both two guidelines and clinical practice, ADT is equal to orchiectomy or GnRH therapy. Upon achieving castration levels, ADT has efficacies in cancer control (2, 3, 20, 21). However, with the decline in testosterone levels, adverse effects, such as flushes, weight gain, bone fractures, and metabolic dysfunction, develop (20, 21). Most importantly, the suppression of testosterone may also contribute to fatal cardiovascular events, such as VTEs (22, 23). The SEER database reported that prostate cancer *per se* and its treatment both contribute to increased risks of VTEs (24, 25). Notably, ADT use was associated with a 1.54-fold higher risk of VTEs than non-ADT use (25). Similarly, a Swedish study also indicated that compared with the general population, the risk of VTEs was increased in patients with prostate cancer, but the risk was incrementally higher in patients treated with ADT (26). In another large cohort of prostate cancer patients, the risk was found to be twice higher in ADT users than non-users, and ADT was recommended to be reserved for patients whose benefits outweigh risks (5).

Although compared with orchiectomy, GnRH therapy has been reported with higher risks of VTEs in patients with prostate cancer. In a meta-analysis, Guo indicated that the uses of GnRH agonists alone but not orchiectomy were associated with a higher risk of DVT but controversially, both uses of GnRH agonists and orchiectomy increased the risks of PE. Back to our study, we found that after age and cancer stage were adjusted, incidences of both DVT and PE were increased among GnRH users compared with non-users. Different from previous studies showing a higher incidence of VTEs in ADT users who were older or at advanced cancer stages, using a multivariable Cox regression to adjust comorbidities, we found a persistently increasing risk of VTEs in overall prostate cancer patients who received GnRH therapies compared with non-users. Notably, among patients who received GnRH therapy, those younger than 70 years old or at an earlier cancer stage (Stage I/II) presented with a higher risk of VTEs.

Interestingly, as focusing on the interaction subgroup of patients who were both younger than 70 years old and at cancer stage I or II, there was a significantly higher risk of VTEs (HR: 8.73, 95% CI: 1.90–40.23, $p = 0.0054$) in GnRH users compared with non-users. Our findings, for the first time, highlighted the critical concerns regarding the cardiac safety of GnRH therapy in prostate cancer patients at a relatively younger age or at an earlier cancer stage.

Given that androgen receptor dampens tissue factor, a pivotal mediator of coagulation and VTEs, expression via nuclear factor-kappa B (NF-κB) and early growth response protein 1, increased tissue factor expression is expected in androgen-deprived prostate cancer patients (27). In another *in vitro* study, androgen receptor-positive prostate cancer cell lines did not trigger platelet aggregation. Instead, suppressing androgen receptors in cell lines triggered platelet aggregation with enhanced invasion and matrix metalloproteinase (MMP)-2 and MMP-9 expressions (28). This may explain a plausible mechanism regarding the correlation between ADTs and VTEs. Interestingly, our subgroup analysis showed that GnRH users who were younger than 70 years old presented with a higher risk of VTE. Given that androgen levels declined with aging, androgen deficiency is prevalent in men older than 65 years. In comparison, the androgen deprive therapy may contribute to a more significant impact on thrombosis in younger patients who were supposed to have more endogenous androgens (29). In contrast to the androgen deprive therapy, testosterone supplement has been also observed with an increase in short-term risk for VTE among men with and without hypogonadism. Notably, the association was more prominent among younger men. It implied that in addition to a deficiency of sex hormones, the fluctuations of hormone levels may be even more detrimental in the vascular health and result in the development of thrombosis (30). These findings highlight that the concerns of VTEs should not only focus on the older patients but also on the relatively younger ones as hormone or hormone derive therapies are prescribed.

Androgen deprive therapies have been found to contribute to insulin resistance and hyperlipidemia. Previous studies showed that hyperlipidemia could be a risk factor for the development of VTEs (31). To note, in our study after being matched with age and comorbidities, hyperlipidemia showed a significant reducing risk with VTEs. Given that the national health insurance in Taiwan reimburses statin uses in large numbers of patients diagnosed with hyperlipidemia, it implied a high prevalence of statin use in the studied population. Through anti-inflammatory effects, several studies reported that statin use reduced the risk of VTEs (32, 33). Thus, the reducing risk of VTEs observed in GnRH users who have hyperlipidemia is suspected owing to the potential use of statins. In contrast, although radiotherapies did not represent a significant correlation with VTEs after being adjusted with age and comorbidities, in this cohort, there were still more GnRH users who have received radiotherapies. Previous studies have observed a significant correlation between radiotherapy and VTE in patients with cancer (34, 35). Analysis from the Registro Informatizado de Enfermedad TromboEmbólica (RIETE) registry revealed that 13% of patients with cancer-associated thrombosis received radiotherapy treatments (34). Therefore, early detection and aggressive management in case of suspicious VTEs in prostate cancer patients, especially those who received GnRH therapies or radiotherapies, is necessary.

Although Chiang et al. have reported a lower incidence of VTE in Asia than in Western countries, the risks of VTEs in Asia have risen (36). Compared with an incidence of approximately 100 cases per 100,000 patient-years in the western countries, using a proportional meta-analysis with a random-effects model (37), Kok found that VTE incidence in the East Asian population was 20.3 (95% CI, 11.2–32) per 100,000 person-years (38). In addition, the risk of VTE recurrence was increased in patients with cancer (38). However, the impact of ADT on the development of VTEs remains largely uncertain in the Asia population. Hereby, as focusing on Asian men subjected to GnRH therapy for prostate cancer, we found that the risks of VTEs were considerably increased. With a shorter duration of testosterone suppression and lack of testosterone surge, the recently launched GnRH antagonists have been found with fewer adverse effects compared with the long-acting GnRH agonists. A real-world analysis from the UK primary care system indicated that GnRH antagonist was associated with lower risks of cardiac events than GnRH agonists (39). Likewise, Chen et al. reported that GnRH antagonists presented with reduced risk CV events compared with the GnRH agonists, which is possible through the effects on the matrix invasion of macrophages (12). In this study, however, given that GnRH antagonists have yet been covered by Taiwan National Health Insurance until recent years, only a small population of patients received GnRH antagonists. Despite limitations, our findings confer a concept that the optimal strategy to lower ADT-associated complications is to limit its use to patients having more benefits than the potential adverse effects. For patients already on ADT, physicians should be more alert regarding the possible development of VTEs. To date mitigating the consequences of ADT remains a major challenge.

In conclusion, despite the substantial benefit of ADT on prostate cancer control, its potential negative effects in terms of the development of subsequent VTEs should be carefully evaluated. Although previous studies reported that GnRH therapies may be less associated with VTEs (4, 40), in this national cohort, after adjustment for age and comorbidities, we still observed a significantly higher risk of VTEs among GnRH users than among non-users, especially in patients who were younger or at an earlier cancer stage. Our findings emphasized concerns regarding the cardiac safety of GnRH therapy in prostate cancer patients not only at older ages but also at relatively younger ages.

DATA AVAILABILITY STATEMENT

The data belongs to NHIRD. Requests to access these datasets should be directed to W-TC, cmcvecho@gmail.com.

ETHICS STATEMENT

This study was approved by the Local Institutional Review Committee of Clinical Research Center in Chi-Mei Medical Center, Tainan, Taiwan (IRB no. 11005-E03), and they granted a waiver of informed consent. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

W-TC: study concept and design and supervision. Y-CC and C-HH: data analysis and statistical analysis. C-SH, K-LH, and W-TC: drafting of the manuscript. C-SH, K-LH, Y-CC, C-HH, C-YC, MC, J-YS, Z-CC, and W-TC: critical revision. C-SH and W-TC: obtaining funding. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.794310/full#supplementary-material

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REVIEW
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Big Data in Cardiology: State-of-Art and Future Prospects

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Cardiological disorders contribute to a significant portion of the global burden of disease. Cardiology can benefit from Big Data, which are generated and released by different sources and channels, like epidemiological surveys, national registries, electronic clinical records, claims-based databases (epidemiological Big Data), wet-lab, and next-generation sequencing (molecular Big Data), smartphones, smartwatches, and other mobile devices, sensors and wearable technologies, imaging techniques (computational Big Data), non-conventional data streams such as social networks, and web queries (digital Big Data), among others. Big Data is increasingly having a more and more relevant role, being highly ubiquitous and pervasive in contemporary society and paving the way for new, unprecedented perspectives in biomedicine, including cardiology. Big Data can be a real paradigm shift that revolutionizes cardiological practice and clinical research. However, some methodological issues should be properly addressed (like recording and association biases) and some ethical issues should be considered (such as privacy). Therefore, further research in the field is warranted.

Keywords: Big Data, epidemiological registries, high-throughput technologies, wearable technologies, non-conventional data streams, cardiology

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CARDIOVASCULAR DISEASE: EPIDEMIOLOGY AND GLOBAL BURDEN OF DISEASE

The global burden of disease (GBD) is the quantitative estimation of the health loss because of a disorder, risk factor, or injury. It is modeled and computed as the epidemiological, clinical, and societal burden generated by a given disease, in terms of its economic-financial and humanistic impact, if ineffectively managed and inadequately treated. Such a quantitative approach enables practitioners and scholars as well as all relevant stakeholders, including public and global health decisions- and policymakers, to compare the burden of different diseases, risk factors, or injuries, robustly and consistently over a temporal period and across various spatial settings and territories/nations. Moreover, these data can inform policies in a pure data-driven and evidence-based fashion, allowing prioritization and allocation of resources, especially in developing countries and in other resource-limited contexts (1). This approach enables to monitor the effects of a given

policy or intervention and verifies if sufficient progress has been made toward the achievement of the Sustainable Development Goals (SDGs) set up by the United Nations (UN) General Assembly (2). In particular, SDG 3.4.1 has the ambitious goal of achieving a 30% reduction in premature mortality due to non-communicable diseases, including cardiovascular disease (CVD), by 2030 (2).

To track such a target, the GBD initiative as well as other similar taskforces and groups, like the Global Health Estimates (GHE) initiative led by the World Health Organization (WHO), have devised and implemented a set of validated and reliable indicators. These measures include the years of life lost (YLLs), the years lived with disability (YLDs), and the disability-adjusted life years (DALYs), which allow researchers to quantitatively evaluate life lost due to death (casualty or premature death) or disability, respectively, which hinder to live life at 100% health.

As previously mentioned, GBD- and GHE-related metrics are of paramount importance in providing stakeholders with data, especially in those settings where there is a dearth of data, or data are not properly updated and/or reliable, because they would be too much time- and resource-consuming to collect. CVD contributes to a significant portion of the GBD (3). CVD, especially stroke and ischemic heart disease (IHD), is the leading cause of mortality and disability. Prevalent CVD cases have nearly doubled from 271 million in 1990 to 523 million in 2019, globally. Similarly, the number of CVD deaths has increased from 12.1 million to 18.6 million, with DALYs and YLLs increasing as well. YLDs have doubled from 17.7 million to 34.4 million. Despite scholarly achievements and technological advancements, especially concerning the management of acute coronary artery disease, chronic ischaemic heart disease, and heart failure, CVD still imposes a dramatically high burden, which is increasing even in those settings in which it was previously decreasing (3, 4), pointing out the urgent need of implementing effective public health policies at a global and local level. This burden is still dramatically high for diseases, like atrial fibrillation, acute heart failure, or sudden cardiac death (3, 4).

In the present review paper, we will show how cardiology can benefit from the use of the so-called "Big Data", especially in the efforts of counteracting and mitigating against the burden of CVD. In the next paragraphs, we will overview the changes cardiological research and practice have undergone in the last decades and we will make some examples of potential applications of Big Data in the cardiological arena, broken down according to their sources/channels (**Tables 1**–**3**), as well as their current major shortcomings and limitations (**Table 4**).

TOWARD A NEW WAY OF PRACTICING CARDIOLOGY AND DOING CARDIOLOGICAL RESEARCH

Healthcare provision delivery has changed dramatically in the last decades. New models and pathways of managing and treating diseases have emerged. A new biomedical approach termed "P4 medicine" (preventative, predictive, personalized, and participatory) has been introduced by Doctor Leroy Hood, a pioneering and inspiring figure in the arena of systems biology, pointing out the shift from a "one-size-fits-all" theoretical framework to one in which the individual signature of the disease matters (5–9).

Moreover, thanks to its latest scientific and technological improvements, medicine, including cardiology, is entering a new, unprecedented era, characterized by the production and release of an incredible amount of data, termed as Big Data. They are characterized by several key dimensions, including velocity (Big Data can be generated, processed, and analyzed in real-time), volume (referring to the wealth of data, the magnitude of which challenges classical storage, processing, and analytical capacities and infrastructures), variety (referring to the diversity of data sources, administrative, patient-reported, healthcare-generated, etc.), veracity (credibility, reliability, and accuracy of data), and value (raw data that, once processed, become smart, applicable, and actionable).

Different channels and sources can produce Big Data: from large-scale surveys, databases, repositories, and registries (epidemiological/clinical Big Data) to next-generation sequencing and high-throughput technologies (molecular Big Data) and computational approaches (infodemiological or digital Big Data). Big Data is deeply transforming clinical practices into disruptive ones and informing data-driven approaches (**Figures 1**, **2**).

The "American College of Cardiology (ACC) Task Force on Health Policy Statements and Systems of Care" designed the 2017 Roadmap for Innovation in the cardiological arena, identifying three major pillars: namely, i) digital health, ii) Big Data, and iii) precision health (10, 11).

ROLES AND APPLICATIONS OF EPIDEMIOLOGICAL/CLINICAL BIG DATA IN CURRENT CARDIOLOGICAL RESEARCH AND PRACTICE

Epidemiological/clinical Big Data can come from large-scale, often nationwide surveys. These data can inform public and global health policies as well as evidence-based medicine and, more specifically, cardiology.

Whilst randomized controlled clinical trials represent the gold standard for building a body of rigorous and clinically relevant evidence, they may not always reflect real-life patient populations, as such limiting the generalizability and external validity of their findings. Real-life or real-world evidence, collected during daily clinical practice, provides a complementary perspective to rigorously and strictly randomized controlled clinical trials (12, 13). In this respect, Big Data-based studies can add to well-designed "small data"-based investigations and randomized controlled clinical trials (13).

A major example of real-life or real-world data is TriNetX, which is the largest global research network providing real-world evidence. It contains tens of billions of clinical facts diagnosis, laboratory findings, treatment received, procedures performed, on more than 250 million patients worldwide, including subjects suffering from hypertensive disease, type 2 diabetes, or chronic

TABLE 1 | Types of big data and their sources/channels in the field of cardiology.

Type of big data	Sources/channels
Epidemiological/clinical big data	Epidemiological survey
	Claims-based database (administrative database)
	Electronic health records (EHRs)/electronic medical records (EMRs)
	Large clinical registries (the "Society of Thoracic Surgeons (STS) National Database," the "American Heart Association (AHA) Get With The Guidelines (GWTG) Database," the "American College of Cardiology (ACC) National Cardiovascular Data Registry" (NCDR), the "Hospital Compare Database," the "National Heart Lung and Blood Institute (NHLBI) Percutaneous Transluminal Coronary Angioplasty (PTCA) Registry," the "STS/ACC Transcatheter Valve Therapy (TVT) database," the "Hypertrophic Cardiomyopathy Registry," and the "Cooperative Cardiovascular Project")
Molecular big data	Microarray chips, next-generation DNA and RNA sequencing and whole-exome sequencing, chromatin-immunoprecipitation-coupled sequencing, and mass-spectrometry-based proteomics analysis
Big data generated by information and communication technologies (ICTs)	Smartphones, apps, and gamified mobile apps Smartwatches Sensors and wearable devices/technologies Imaging techniques (i.e., radiography, radiomics, and radiogenomics)
Computational/digital big data	"Non-conventional data streams"
	Web searches (Google Trends)
	Website page consultation (i.e., Wikipedia)

TABLE 2 | Some select examples of big data-based registries/databases for cardiovascular disease.

Country/territory	Database name/acronym	Major details
Japan	Japanese Registry Of All cardiac and vascular Diseases-Diagnostic Procedure Combination (JROAD-DPC)	Governed by the Japanese Circulation Society (JCS), more than 700,000 health records' data as of 2012 from 610 certificated hospitals
	Japan Acute Myocardial Infarction Registry (JAMIR)	>20,000 patients
Korea	Prospective Cohort Registry for Heart Failure in Korea (KorAHF)	>5,000 patients
Denmark	Danish Cardiac Rehabilitation Database (DHRD)	Collecting data from all hospitals in Denmark
	Danish Heart Registry	Collecting data from five cardiology centers, eight cardiology satellite centers, four surgical centers, and a private hospital
Sweden	Swedish Primary Care Cardiovascular Database (SPCCD)	>70,000 patients
	SWEDEHEART	>2 million subjects
USA	National Cardiovascular Data Registry (NCDR)	Governed by the American College of Cardiology (ACC), it consists of 10 registries, eight inpatient/procedure-based and two outpatient-based from more than 2,400 hospitals and 8,500 providers with more than 60 million patient records

kidney disease. Specifically, concerning the cardiological arena, this network has been exploited to shed light on the safety profile and cardiovascular outcomes of drugs (14, 15), the effectiveness of rehabilitation protocols (16, 17), and the cardiovascular implications of the still ongoing "Coronavirus Disease 2019" (COVID-19) pandemic (18, 19), among others.

To paraphrase what Doctor Lukas Kappenberger, pioneering father of the so-called "computational cardiology," has stated in 2005, the science (i.e., randomized controlled clinical trials) tells scholars and practitioners what they can do, the guidelines and checklists implement what they should do, and clinical registries/databases tell them what they are doing and observing (20, 21).

Currently, there are lots of sources generating epidemiological Big Data, such as surveys, medical insurance data, vital registration data, cohort data, inpatient and outpatient data, among others (20).

These data can be retrospectively or prospectively collected: prospective clinical registries can be defined as large/very large datasets of observational data which have been collected prospectively and systematically and in a structured fashion, to reflect real-world clinical practices and outcomes of a given procedure (treatment, or surgical intervention) across large patient populations, including specific clinical/demographic (sub-)populations (20).

Furthermore, besides being complementary, randomized controlled clinical trials can be embedded within clinical registries (20): this enables to save time and resources and strengthens the generalizability of the findings (20). For instance, the "Coronary Artery Surgery Study (CASS) registry," which is

TABLE 3 | Types of big data and examples of potential uses/applications in the field of cardiology.

Type of big data	Examples of potential uses/applications
Epidemiological/clinical big data	Epidemiological assessment (incidence, prevalence, co-morbidities, and mortality rates)
	Epidemiological nowcasting/forecasting for funding and resources allocation optimization
	Economic assessment (costs evaluation)
	Evaluation and comparison of different cardiological treatment and management options
	Identification of diagnostic and prognostic markers
	Evaluation and assessment of mid-term and long-term clinical outcomes
Molecular big data	Patient profiling and stratification
	Personalized/individualized cardiology
	Characterization of the effects and actions of drugs at the cellular and molecular levels
	Identification of potential druggable targets
Big data generated by information and communication technologies	Collection of patient-reported outcomes
	Customization and personalization of healthcare provision delivery
Computational/digital big data	Patient health-related literacy assessment
	Patient education and empowerment

TABLE 4 | Major shortcomings and limitations of big data in current cardiological practice and clinical research.

Type of big data	Limitation/issue
Epidemiological/clinical big data	Discrepancies between registry-based studies and individual (single- or multi-center) investigations
	Discrepancies among database-based studies
	Privacy and bioethical issues
Molecular big data	Conflicting results among studies (depending on the type of tissue studied, the type of molecular technique used, etc.)
	"False discovery" of markers
Big data generated by information and communication technologies	Privacy and bioethical issues due to the pervasive and ubiquitous nature of the devices
Computational/digital big data	Lack of transparency concerning the algorithm

also one of the early examples of clinical registries, is a database embedded within a clinical trial (the CASS investigation) (22).

In the cardiological arena, there exist very large clinical databases and registries, whose origins can be dated back to the eighties (20). The most popular ones include societal registries, that is to say, databases endorsed, funded, and sponsored by scientific societies, like the "Society of Thoracic Surgeons (STS) National Database," which collects clinical outcomes for patients undergoing cardiothoracic surgery (23), and the "American Heart Association (AHA) Get With The Guidelines (GWTG) Database," which is based on a hospital-based initiative, led by the AHA and the American Stroke Association (ASA), collecting data from >2,000 hospitals, aimed at improving the quality of care of patients suffering from CVD, including heart failure, atrial fibrillation, and stroke (24). Another major societal database is the "ACC National Cardiovascular Data Registry" (NCDR), which is composed of 10 registries (eight of which are inpatient/procedure-based and the remaining two are outpatient-based), collecting data from >2,400 hospitals and 8,500 healthcare providers with >60 million patient records (25).

Other databases include the "Hospital Compare Database", which collects data concerning the quality of care (overall star rating and other quality measures) from >4,000 Medicare-certified hospitals (26), and the "Cooperative Cardiovascular Project" (27, 28), which is one of the early examples of a clinical registry.

Some datasets and registries are devoted to specific cardiovascular medications or surgical procedures, like the "National Heart Lung and Blood Institute (NHLBI) Percutaneous Transluminal Coronary Angioplasty (PTCA) Registry", collecting outcomes data for patients undergoing PTCA (29, 30), the "STS/ACC Transcatheter Valve Therapy (TVT) database", which collects outcomes data for patients undergoing transcatheter valve replacement and repair procedures from >650 reporting sites (31), and the CathPCI registry from the NCDR, collecting outcomes data for patients undergoing diagnostic catheterization and/or percutaneous coronary intervention (PCI) procedures (32).

Some registries and databases are specifically devoted to particular CVD, like the "Hypertrophic Cardiomyopathy Registry" led by the University of Virginia (USA) and the University of Oxford (UK), aimed at identifying biomarkers of hypertrophic cardiomyopathy (33).

Epidemiological/clinical big data can be utilized for a variety of purposes and aims, including i) performing an epidemiological assessment of CVD (in terms of incidence, prevalence, and mortality rates), ii) quantifying and forecasting epidemiological trends, iii) investigating the determinants of CVD and related underlying co-morbidities, iv) identifying diagnostic and prognostic markers and signatures, v) devising risk score tools to better stratify CVD patients, vi) exploring the mid-term and long-term clinical outcomes of a given (pharmacological or surgical) procedure and its superiority over another one (the competitor), vii) verifying the implementation of recommendations and decision-making processes, setting benchmarks, and viii) computing the economic-financial costs of a given CVD (34, 35).

Big data can help uncover relationships between diseases and/or co-morbidities, in that they tend to co-cluster. The diseasome is the "human disease network": a Big Data-based study of the diseasome can contribute to a better understanding of the so-called "system or network medicine" (36). Several CVDs, including heart failure, frequently coexist with various

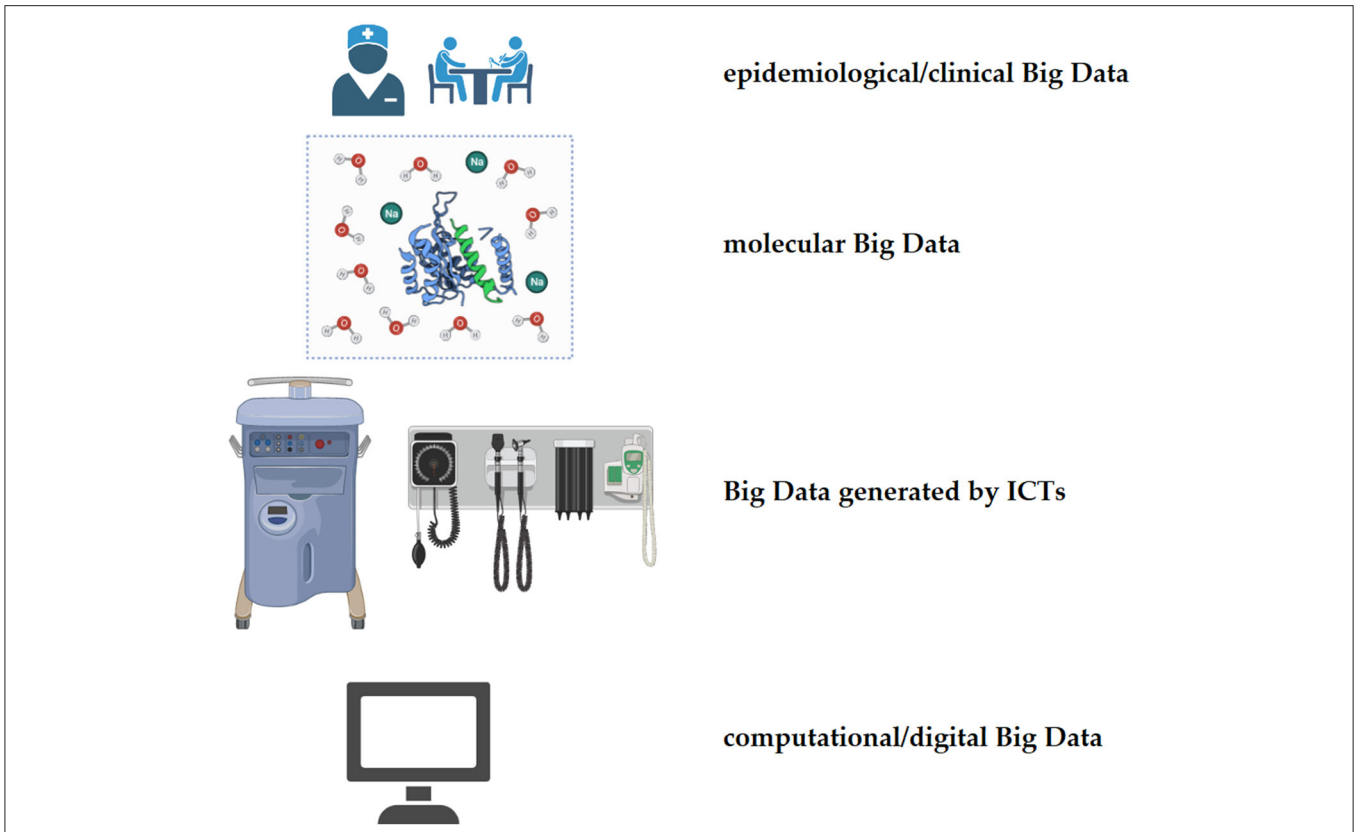

FIGURE 1 | Types and sources/channels of big data.

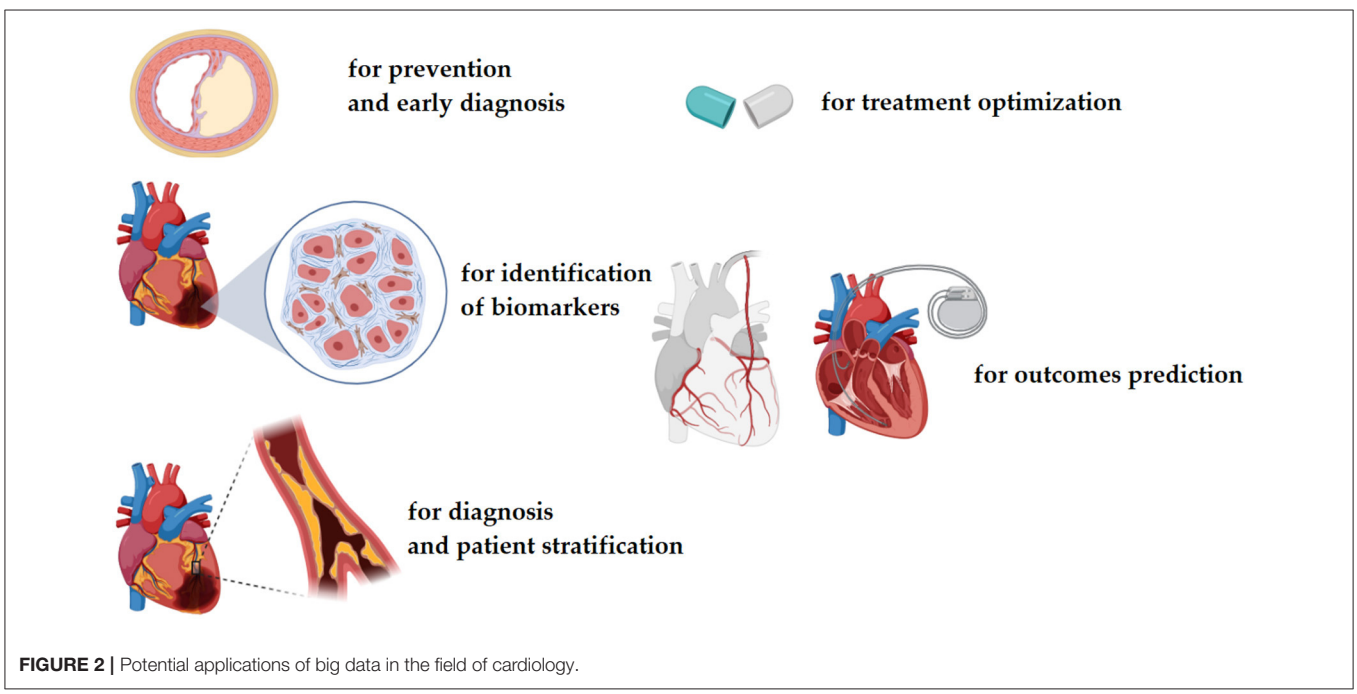

FIGURE 2 | Potential applications of big data in the field of cardiology.

comorbidities. Meireles et al. (37) assessed the prognostic role and impact of several underlying comorbidities on the risk of developing acute heart failure. A set of 229 patients suffering from acute heart failure was compared vs. a set of 201 patients with

chronic heart failure. The number of comorbidities was slightly higher in the acute heart failure patient group: these included metabolic impairments such as hyperuricemia, and obesity, other CVDs like atrial fibrillation, or peripheral artery disease as well as chronic kidney disease. Investigating the comorbidome could allow the implementation of "precision cardiology" by devising *ad hoc* multi-dimensional interventions targeting the specific patient sub-population.

There exist several risk tools, ranging from the Framingham score to the SCORE, the "Global Registry of Acute Coronary Events" (GRACE), the "Thrombolysis In Myocardial Infarction" (TIMI), the "Congestive Heart Failure, Hypertension, Age (≥75 years), Diabetes, Stroke, Vascular disease, Age (65 to 74 years), and Sex category" (CHA_2DS_2VASc), and the "Meta-Analysis Global Group in Chronic Heart Failure" (MAGGIC) risk-score, among others (38).

These risk calculators are fundamental components of the so-called "personalized cardiology," in that they enable to stratify patient cohorts and provide the patient with the treatment they need the most. Examples of precision and personalized management include the customized assessment of the risk factor for a variety of cardiovascular diseases, such as atrial fibrillation, chronic myocardial ischemia, heart failure, and hypertension, given the individual biological makeup (genetic) and family history for cardiovascular disease. Also, pharmacological provisions, for instance, the usage of anticoagulants, can be tailored, in such a way to minimize the insurgence of potential side-effects (6–8).

There are, however, few published comparisons among the different risk scores, which remains a field open to further research and investigation (38).

Some emerging applications of Big Data-based databases are: i) addressing cardiovascular-related iniquities and disparities, also from a gender perspective, ii) performing post-marketing analysis of different cardiovascular treatments and medications (39).

Finally, Big Data is particularly helpful when the studied cardiological disease is rare, such as congenital CVD (40): pediatric cardiology is anticipated to benefit a lot from large datasets and the deployment of artificial intelligence (41).

Artificial intelligence is anticipated to fully leverage and harness Big Data-based databases, potentially overcoming the issue of "classical" and "conventional" statistical techniques, including propensity score analysis and multivariate regression modeling (42). Ahn et al. (43) developed CardioNet, a manually curated, standardized, and validated, comprehensive CVD-related database based on clinical information (either structured or unstructured) collected from 748,474 patients, that can be utilized for Artificial intelligence analyses and provide insights on the care of patients with CVD. Barbieri et al. (44) combined the classical survival analysis (Cox proportional hazard modeling) with a deep learning approach on a cohort of 2,164,872 New Zealanders aged 30–74 years. Predictors of CVD events were found to be tobacco use in women and chronic obstructive pulmonary disease (COPD) with acute lower respiratory infection in men, besides well-established risk factors like high blood pressure, chest pain, diabetes, and metabolic impairment.

On the other hand, despite the use of sophisticated statistical tools, as previously mentioned, there are still open issues that need to be addressed and solved. Big Data-based studies can offer a different point of view, but some conflicting findings of randomized controlled clinical studies and small, well-conducted investigations can be found.

Such discrepancies could be due to the unique nature of the database used in the study: each cardiological database significantly varies in the methods deployed to collect and capture data and the population(s) it specifically represents (13). Also, the format of the database (structured vs. unstructured) could impact data quality. For instance, Hernandez-Boussard et al. (13) mined a dataset inclusive of 10,840 clinical notes and found lower recall and precision rates (51.7 and 98.3%, respectively) in the case of structured electronic health records (HER), concerning unstructured EHR (95.5 and 95.3%, respectively), warranting the routine measurement of recall for each database/registry, before proceeding with data processing and analysis.

Summarizing, Big Data repositories, registries, and databases are increasingly common in the field of cardiological practice and clinical research: there are, however, significant considerable variations in socio-demographic characteristics, co-morbidities, and major complication rates between individual (single- or multi-center) and database-based studies, and even among registry-studies themselves (for example, clinical vs. administrative database). This should be accounted for when critically appraising cardiological research and in risk adjustment modeling (20).

In particular, administrative databases (20) can provide researchers and scholars, as well as practitioners and policy- and decision-makers with a lot of information concerning disease epidemiology, co-morbidities, disparities, and inequalities in access to healthcare and clinical outcomes. Furthermore, they can inform in a data-driven fashion the decision-making processes underlying cardiological pharmacological treatments or surgical procedures, in terms of pre-operative risk stratification parameters to significantly curb/minimize perioperative morbidity and mortality rates. On the other hand, administrative databases (20) may suffer from clerical inaccuracies, recording bias (due to the very nature of the database and secondary to economic-financial incentives underlying the collection, and maintenance of the dataset), temporal changes in nosology and nomenclature systems as well as in billing codes, and, finally, a dearth of several clinically relevant parameters, including cardiology-specific variables and outcomes.

A major issue seriously limiting the deployment of databases and registries is related to their inter-operability and sometimes inconsistent use of definitions. Moreover, not all databases meet regulatory standards (13) and are enough curated/validated. As such, data standardization and meta-data are urgently warranted (20).

Conversely, clinical studies, especially those relying on "Small Data," even though well-designed and well-conducted,

are generally statistically underpowered and are plagued by several biases, including participants sampling and selection bias, which hinders the generalizability of the findings, with samples being not representative of the entire population. It is also difficult to stratify according to a given cardiological pharmacological treatment or surgical procedure if the sample is particularly heterogeneous and the sample size does not allow to make sufficiently statistically robust and reliable calculations. Confidence and certainty can increase with "Big Data," paralleling, however, the growth of complexity and associated computational costs (45, 46). Also, Big Data-based databases can be affected by biases, as previously mentioned, such as recording or association biases and other statistical artifacts, like "reverse epidemiology" or "reverse causality" (47). For instance, some database-based studies have found that body mass index (BMI), lipid profile, and blood pressure, which usually predict a poor clinical outcome in the general population, become inverse prognostic predictors in chronic heart failure patients. Greater survival has been, indeed, linked to overweight and obesity, hypercholesterolemia, and high values of blood pressure, which is rather counter-intuitive. Several hypotheses have been formulated, including the presence of the "malnutrition-inflammation complex syndrome" or "malnutrition–inflammation–cachexia syndrome". However, some scholars think that it is more likely (and biologically/clinically plausible) that these findings are statistical artifacts.

ROLES AND APPLICATIONS OF MOLECULAR BIG DATA IN CURRENT CARDIOLOGICAL PRACTICE AND RESEARCH

Wet-lab and high-throughput technologies, including microarray chips, next-generation DNA and RNA sequencing and whole-exome sequencing, chromatin-immunoprecipitation-coupled sequencing, chromatin interaction analysis by paired-end tag sequencing (ChIA-PET), chromatin conformation capture with sequencing, assay for transposase-accessible chromatin with high-throughput sequencing (ATAC-Seq), and mass-spectrometry-based proteomics analysis can generate a wealth of molecular big data, paving the way for a personalized/individualized rather than "one-size-fits-it-all" cardiology (48, 49).

Molecular big data can elucidate the mechanisms underlying the etiopathogenesis of a given heart disease and identify new potential druggable targets for the development of *ad hoc* pharmacological therapies. Personalized cardiology can benefit from genome-wide association and post-genomics studies (50, 51), aimed at the identification of new cardiogenic transcription factors, genotypic and phenotypic validations of potential transcriptional regulators, and molecular/cellular mechanisms.

CardioGenBase (50) is a literature-based, comprehensive online resource tool, which extensively collects gene-disease associations (over 1,500) for major CVD, including cerebrovascular disease, ischemic heart disease, coronary artery disease (CAD), inflammatory heart disease, rheumatic heart disease, and hypertensive heart disease, among others.

Vakili et al. (51) made efforts to combine all the OMICS-based specialties within a highly integrated, coherent, multi-OMICS approach termed as "panomics," to shed light on the multi-factorial pathogenesis of CVD. The authors systematically mined the literature and were able to find 104 CVD-related OMICS-based databases, 72 of which provided genomics/post-genomics and clinical measurements. Of these datasets, 59 and 65 databases were transcriptomic, epigenomic/methylomic, 41 proteomic, 42 metabolomic, and 22 microbiomic.

Combing the scholarly literature, clinical and OMICS-based information, and exploiting the "diseasome" approach, Sarajlić et al. (52) assessed the structure of the human protein-protein interaction (PPI) network to discover new CVD-related genes, that could be potential druggable targets. The authors found that these new genes were involved in intracellular signaling cascades, signaling transducing activity, enzyme binding, and intracellular receptor-mediated signaling pathways.

Moreover, the unique and unprecedented convergence between different disciplines, such as nano-(bio-) engineering, three-dimensional (3D) printing and computational simulation, molecular and mathematical modeling, and advanced and sophisticated biostatistical techniques and Artificial Intelligence (Data Mining, Machine, and Deep Learning), are shaping new paths and opportunities in the field of cardiological practice and clinical research, enriching it, making it more multi- and inter-disciplinary and complex, and more able to address the biomedical challenges. Similarly, Dr. Elias Zerhouni (53–55), who has served as Director of the National Institutes of Health (NIH) from 2002 to 2008, has indicated such a unique convergence as the future roadmap in the field of scholarly research, including the cardiological arena.

3D printing is being increasingly utilized in biomedicine, and, in particular, in cardiology. Generally, mainly rigid anatomic models are produced, but the incorporation of dynamic functionality is expected to dramatically advance preoperative cardiovascular surgical planning as well as hemodynamics (56). 3D models can shed light on different CVD-related pathophysiological conditions, thus complementing information obtained using classical imaging.

Moreover, molecular Big Data, alone or combined/integrated with epidemiological Big Data, can capture the landscape of several cardiological diseases and events, either idiopathic or congenital, including dilated cardiomyopathy and heart failure (57, 58), among others.

ROLES AND APPLICATIONS OF BIG DATA GENERATED BY IMAGING TECHNIQUES AND WEARABLE TECHNOLOGIES/SMART SENSORS IN CURRENT CARDIOLOGICAL PRACTICE AND RESEARCH

Latest technological achievements in the field of mobile health (mHealth) and ubiquitous health (uHealth), with

smartphones, smart devices, smartwatches, and other wearable sensors (59) are revolutionizing the field of cardiology, directly involving, and engaging the patient, improving their therapeutical adherence and compliance, and also enabling remote patient monitoring.

Wearable sensors of different types (bioelectric, mechano-electric, optoelectronic, and ultrasonic wearable devices) enable collecting cardiovascular vital signs (such as blood pressure, heart rate and heart rhythm, blood oxygen saturation, and blood glucose, as well as brain waves, air quality, exposure to radiations, and other metrics) continuously, allowing early intervention (60).

Gandhi et al. (61) conducted a systematic review of the literature, investigating the effectiveness of mHealth Interventions for the secondary prevention of CVD. The authors pooled 27 studies together, totaling 5,165 patients. mHealth was found to increase therapeutic adherence (with an odds ratio, OR, of 4.51) as well as overall compliance, either pharmacologic or non-pharmacologic (with an OR of 3.86). Different targets were more likely to be met: namely, blood pressure (OR 2.80), exercise and physical activity with reduced sedentary time and sitting (OR 2.55), but not smoking cessation (OR 1.42), and lipid profile (OR 1.16). However, the mHealth group did not differ from the standard-of-care group in terms of hospitalizations and hospital readmissions (OR 0.93). Few studies showed a statistically significant reduction in angina (OR 0.23) and transient ischemic attack/stroke recurrence in cerebrovascular disease patients (OR 0.18). The cardiovascular mortality rate was computed to be lower, even though not achieving the significance threshold (OR 0.19). Similar results could be replicated in a more updated systematic review and meta-analysis conducted by Akinosun et al. (62) and in the systematic review of the literature by Spaulding et al. (63).

Wali et al. (64) showed that mHealth interventions can be particularly useful in reaching vulnerable and underserved communities, including aboriginal and indigenous individuals or subjects residing in low- and middle-income countries. Usually, these individuals are excluded or are under-represented in clinical trials.

Gamification and gamified mobile applications (apps) represent another interesting and promising ramification of the digital health arena. Davis et al. (65) have performed a systematic literature review, synthesizing seven studies, totaling 657 patients. The authors found that gamification resulted in improved adoption of healthier lifestyles and behaviors (for instance, in terms of the practice of exercise and physical activity), better biochemical profile, enhanced mood, and motivation. Interestingly, also CVD-related health literacy and knowledge improved in a significant way, even though some parameters, such as blood pressure, body mass index, self-management, and therapeutical compliance, were comparable with standard-of-care.

To summarize, mHealth and digital health-based interventions, including telemonitoring (telecardiology) or text messaging, can be customized, meeting the needs of "personalized cardiology," also becoming culturally sensitive and targeting specific populations, which are disproportionately affected by non-communicable diseases, including CVD.

Concerning smart devices, such as smartwatches and smartphones, Prasitlumkum et al. (66) have conducted a systemic review and meta-analysis to quantitatively evaluate the accuracy of utilizing wearable devices for screening, detecting, and properly diagnosing atrial fibrillation. The authors were able to compute excellent areas under the summary receiver operating characteristic (SROC) curves at 0.96 and 0.94, for smartphones and smartwatches, respectively. Sensitivity and specificity were in the range of 94–96 and 93–94% for the two kinds of smart/wearable devices, respectively: they proved to be as diagnostically accurate and reliable as gold standards, like photoplethysmography and single-lead electrocardiography.

Signals and data generated by imaging techniques, like electrocardiography, computed tomography, or magnetic resonance imaging, can be further processed, analyzed, and refined using artificial intelligence (67, 68). For instance, MOCOnet (69) is a next-generation convolutional neural network that can significantly enhance and improve quantitative cardiovascular magnetic resonance T1 mapping, making it more robust, reliable, clinically meaningful, less prone to motion artifacts, and in a time-efficient manner. MOCOnet, being purely data-driven, outperforms currently available methods for motion correction, which are model-driven.

Finally, radiomics and radiogenomics are highly innovative translational fields of research aimed at mining, retrieving, merging, processing, analyzing, and extracting clinically meaningful patterns and interpretations from large-scale, high-dimensional datasets generated by clinical imaging techniques and tools (70), including cardiac computed tomography angiography and cardiac magnetic resonance. Latest advancements concerning more and more sophisticated protocols enable the integration of imaging features and molecular profiling to identify relevant and clinically meaningful biomarkers and signatures (such as atherosclerotic lesions, coronary plaques, and myocardial structural abnormalities) related to diagnosis, prognosis, and response to treatment. Supervised and unsupervised artificial intelligence, including deep and machine learning, can further combine and aggregate data and assist the development of risk models and tools that can facilitate clinical diagnostic and prognostic procedures.

In the field of cardiological research, radiomics, and radiogenomics can be utilized for the characterization, profiling/phenotyping, and risk stratification of coronary heart disease (CHD), hypertrophic cardiomyopathy, ischemic heart disease, and cerebrovascular disease (70–73), among others. However, also given its recency, still too much has to be explored in this field. On the other hand, it can be anticipated that radiomics, radiogenomics, and other Big Data generated by wearable/smart devices and sensors will profoundly impact both cardiological practice and research.

ROLES AND APPLICATIONS OF INFODEMIOLOGICAL BIG DATA IN CURRENT CARDIOLOGY RESEARCH

Infodemiology (a *portmanteau* of "information" and "epidemiology") and infoveillance (a combination of the words "information" and "surveillance") represent a highly innovative discipline, at the intersection of computer, data, and behavioral science, aimed at shedding light on the determinants of computational and digital activities (such as web queries, use of social media, posting on social networks, and production/consumption of online material) (74, 75).

Researchers in the field of infodemiology and infoveillance make use of resources that enable to assess information demand and consumption, such as Google Trends, which is an open-source tool that enables to track and monitor web searches conducted using the Google search engine.

Infodemiology and infoveillance enable to track the effectiveness of awareness campaigns, such as the "Go Red for Women" (76), which is a social initiative aimed at improving and enhancing CVD- and stroke-related literacy among women. Suero-Abreu et al. (77) investigated the impact of "Go Red for Women" on health information-seeking behavior, utilizing Google Trends. Authors found increased search volumes related to the awareness campaign and various CVD-related terms over 15 years. However, stroke-related digital searches were not found to be increased over the study period.

Dzaye et al. (78) have exploited infodemiology and infoveillance techniques to assess public interest toward CVD and related comorbidities during the "Coronavirus Disease 2019" (COVID-19) pandemic. According to some studies, attention to CVD would have decreased, despite the negative relationship between CVD and infection. Patients suffering from CVD or with risk factors for CVD have been consistently reported to exhibit worse outcomes than their CVD-free counterparts. Authors found that digital interest in terms like exercise or physical activity and cigarettes had increased (by 18%) and decreased (by 52.5%), respectively. Noteworthy, interest in terms like statin, lipid profile, low-density lipoprotein (LDL), and hemoglobin A1C, had significantly increased at well, after a previous decline over time.

On the other hand, according to a research study by the same group (79), the first months of the COVID-19 pandemic were paralleled by a decrease in search interest for myocardial infarction and acute coronary syndrome (ACS), potentially explaining the excess cardiovascular mortality despite a marked reduction in hospitalization for ACS.

To summarize, search engines and other non-conventional data streams appear to be valuable and promising tools that can provide insights on health information-seeking behaviors and evaluate the effectiveness of social campaigns and other interventions.

The quality of cardiology-related websites and, more in general, online material is highly heterogenous and variable both in terms of content and information provided. For instance, Azer et al. (80) assessed the quality, accuracy, and readability of Wikipedia pages concerning CVD. About 83% of Wikipedia pages were deemed of moderate quality, with 8.5% being of good and poor quality, respectively. Despite clinical presentation and etiopathogenesis of CVD being treated and discussed, several sections, including the pathophysiology, signs and symptoms, diagnosis, and management, were not always accurate and adequately scholarly referenced. Several entries exhibited errors and omissions. The readability was at the level of collegiate subjects.

CVD patients use the internet as a low-cost and easily available source of personal healthcare information, to learn more about their condition/disorder, as well as about potential treatment options and CVD physicians and surgeons (81). According to a recent survey by Jones et al. (81), 74.3% of the interviewees surfed the internet, with 63% utilizing it daily. In the case the patient could not directly access the web, a family member was willing to do so on their behalf. The authors concluded that most patients (∼85%) utilized the internet, being particularly interested in local information.

Practitioners and residents in the field of cardiology should be aware of these findings in that the web is often consulted by patients with CVD. Locally delivered Web-based information service is particularly requested and appreciated by CVD patients. The web can be used to deliver high-quality, educational material and empower the patient, by enhancing their literacy, collecting patient-generated/reported outcomes (PROMs), and health-related behaviors and attitudes, devising *ad hoc* social campaigns and monitoring their impact on health-related digital seeking behaviors.

"PARTICIPATORY CARDIOLOGY": INTEGRATING BASIC AND TRANSLATIONAL CARDIOLOGY AND CITIZEN SCIENCE

Big Data can also contribute to an emerging super-specialization within the field of cardiology: the so-called "participatory cardiology", in such a way promoting public participation in the field of cardiological practice and clinical research, creating "global collaborative social networks", and integrating basic and translational cardiology and citizen science (82, 83). This is of paramount importance especially in low- and middle-income countries and would help curb/reduce health disparities and iniquities.

A systematic review conducted by Wali et al. (64) has shown that establishing collaborative partnerships and relationships with community members – especially those from underserved and vulnerable populations – would significantly improve and enhance the effectiveness of the cardiological intervention by ensuring it was devised and implemented within the appropriate context.

Participatory cardiology, as a branch of participatory medicine, gives a new value and importance to the patient, who is the "real teacher," quoting a famous statement of the Canadian physician and cardiologist Sir William Osler (1849–1919) enunciated in 1903. Latest scientific and technological advancements and current trends in clinical practice and

research, especially in the cardiological arena, have gradually shifted the practitioners' attention and interest toward patient's "subjective" outcomes (satisfaction, pain, quality of life, etc.), besides "objective" clinical outcomes (healthcare resources uptake and consumption, healthcare processes and provisions delivery, morbidity and mortality rates).

However, for most cardiologists and cardiological surgeons, the world of PROMs represents a still "unchartered health care environment" (84), the navigation of which, by incorporating "mission, values and culture" (85, 86), can advance cardiological practice and research. There are several gaps in the implementation and full incorporation of PROMs within the daily routine cardiological practice. According to the "International Consortium for Health Outcomes Measurement" (ICHOM), while there exist several national, international, and trial registries for heart failure, very few of them can be considered as patient-centered and standardized guidelines and checklists guiding the process of properly, effectively, and meaningfully using PROMs are lacking. To fill in this gap, the ICHOM has developed a 17-item dataset, which consists of several domains (functional-, psycho-social-, burden of care-, and survival-related outcomes). This set, which also includes PROMs besides clinical/objective measurements, and administrative data, enables to compare consistently heart failure management and treatment across several healthcare providers and various regions, globally (87).

LIMITATIONS AND SHORTCOMINGS OF BIG DATA IN THE FIELD OF CARDIOLOGY

Table 4 overviews the major limitations and shortcomings of Big Data in the field of cardiology based on the type of source/channel that generates them. Basically, these pitfalls are of a two-fold nature: legal/bioethical (in terms of legal requirements and restrictions, legislation, privacy, and data sharing policies) and methodological.

Epidemiological/clinical Big Data can be affected by inconsistencies according to the type of study and its design (registry-based *vs.* individual – single or multi-center – investigations). Also, database-based studies may give rise to contrasting findings based on the reason and scope data were collected (clinical, administrative, or financial purposes). Optimizing databases and ensuring inter-operability could overcome these issues. Moreover, datasets can also be publicly uploaded and shared, enabling other scholars and researchers to replicate findings. However, there exist some privacy and bioethical issues. Data de-identification or anonymization or pseudonymization or masking can ensure re-use of potentially sensitive, personal, and legally restricted data, preserving scalability and performance, also if this technique could be challenging and not trivial to implement (88).

Molecular big data require extensive processing of data, which can be quite expensive, time- and resource-consuming. Moreover, the results of the various studies have to be reconciled, depending on the type of tissue/cell studies, the molecular technique applied, etc. This can lead to a "false discovery" of biomarkers. Recently, meta-analyses of molecular big data pooling together various samples have enabled to increase the statistical power and, thus, the reliability and trustworthiness of the discovery. Ensuring reproducibility and clinical meaningfulness of results should be a research priority (89).

Big data generated by information and communication technologies can be affected by privacy and bioethical issues due to the pervasive and ubiquitous nature of the devices.

Finally, concerning computational/digital big data, there are some issues affecting their usage, like the lack of transparency related to the algorithm deployed to retrieve, collect, process, and store data.

CONCLUSIONS AND FUTURE PROSPECTS

Big Data is increasingly having a more and more relevant role, being highly ubiquitous and pervasive in contemporary society, permeating it and paving the way for new, unprecedented perspectives in biomedicine, including cardiology. Big Data can be a real paradigm shift that revolutionizes cardiological practice and clinical research. However, some methodological issues should be properly addressed, and some ethical issues should be considered. Therefore, further research in the field is urgently warranted.

AUTHOR CONTRIBUTIONS

HD and NB conceived and drafted the paper. All other authors critically revised it. All authors contributed to the article and approved the submitted version.

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Dynamic Secondary Mitral Regurgitation: Current Evidence and Challenges for the Future

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Heart failure (HF) is a challenging situation in healthcare worldwide. Secondary mitral regurgitation (SMR) is a common condition in HF patients with reduced ejection fraction (HFrEF) and tends to be increasingly associated with unfavorable clinical outcomes as the severity of SMR increases. It is worth noting that SMR can deteriorate dynamically under stress. Over the past three decades, the characteristics of dynamic SMR have been studied. Dynamic SMR contributes to the reduction in exercise capacity and adverse clinical outcomes. Current guidelines refer to the indication of transcatheter edge-to-edge repair (TEER) for significant SMR based on data from the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial if symptomatic despite optimal guideline-directed medical therapy (GDMT) and cardiac resynchronization therapy (CRT), but nonpharmacological treatment for dynamic SMR remains challenging. In HFrEF patients with LV dyssynchrony and dynamic SMR, CRT can improve LV dyssynchrony and subsequently attenuate SMR at rest and during exercise. Also, a recent study suggests that TEER with GDMT and CRT is more effective in symptomatic patients with HFrEF and dynamic SMR than GDMT and CRT alone. Further studies are needed to evaluate the safety and efficacy of nonpharmacological treatments for dynamic SMR. In this review, current evidence and challenges for the future of dynamic SMR are discussed.

Keywords: dynamic secondary mitral regurgitation, heart failure with reduced left ventricular ejection fraction, guideline-directed medical therapy, cardiac resynchronization therapy, transcatheter edge-to-edge repair

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INTRODUCTION

Heart failure (HF) is a challenging situation in healthcare worldwide (1–3). HF with reduced ejection fraction (HFrEF) is seen in approximately half of the patients with HF (4). Secondary mitral regurgitation (SMR) with structurally normal leaflets is a common disease in patients with HFrEF (5, 6). Moreover, as the severity of SMR increases, the condition significantly tends to be incrementally associated with unfavorable clinical outcomes (6). As for the treatments for HFrEF with severe SMR, maximally tolerated guideline-directed medical therapy (GDMT) s is recommended (7–10). In patients with an ischemic etiology of the condition, the revascularization of significant coronary artery disease is recommended if applicable. Also, cardiac resynchronization therapy (CRT) for left ventricular (LV) dyssynchrony should be considered when the condition is refractory to the treatments above. Moreover, current guidelines recommend transcatheter edge-to-edge repair (TEER) if feasible when patients with HFrEF and severe SMR have symptoms despite optimal GDMT and CRT.

It is worth noting that SMR can deteriorate dynamically according to changes in hemodynamics (**Figure 1**). The characteristics of dynamic SMR have been investigated during the past three decades (11–13). Dynamic SMR contributes to reductions in exercise capacity and adverse clinical outcomes (14–19). Although there are evidence-based nonpharmacological approaches for symptomatic SMR, the optimal treatment of dynamic SMR remains a matter of debate. In HFrEF patients with LV dyssynchrony and dynamic SMR, CRT can ameliorate LV dyssynchrony and subsequently attenuate dynamic SMR during exercise (20–22). Also, a recent study has demonstrated that TEER may be effective for dynamic severe SMR (23). Therefore, it is time to renew our knowledge of dynamic SMR and reconsider the optimal therapy of symptomatic dynamic SMR.

This review summarizes current evidence and challenges for the future of dynamic SMR in light of the mechanisms of dynamic SMR, its prognostic value, and its potentially effective treatment options.

MECHANISM OF DYNAMIC SMR

The mitral valve apparatus is intricately comprised of several components, including the mitral annulus, anterior and posterior mitral leaflets, chordae tendinae, anterolateral and posteromedial papillary muscles, and adjacent LV wall. MR can be regulated based on an exquisite balance among these components during systole. In SMR, tethering and closing forces of the mitral valve during systole are essential to understand the intricate mechanism. The tethering force is affected by LV dilatation, LV sphericity, LV regional wall motion abnormalities, papillary muscle displacement, papillary muscle dyssynchrony, papillary muscle asymmetry, annular dilatation, and annular flattening. The closing force is decreased due to LV contractility impairments, LV dyssynchrony, increased left atrial (LA) pressure, and decreased mitral annular contraction.

Over the past three decades, the characteristics of dynamic SMR have been studied (11–13). Previous reports have elucidated that changes in LV dyssynchrony, LV sphericity, LV regional wall motion abnormality, increased mitral valve coaptation depth and

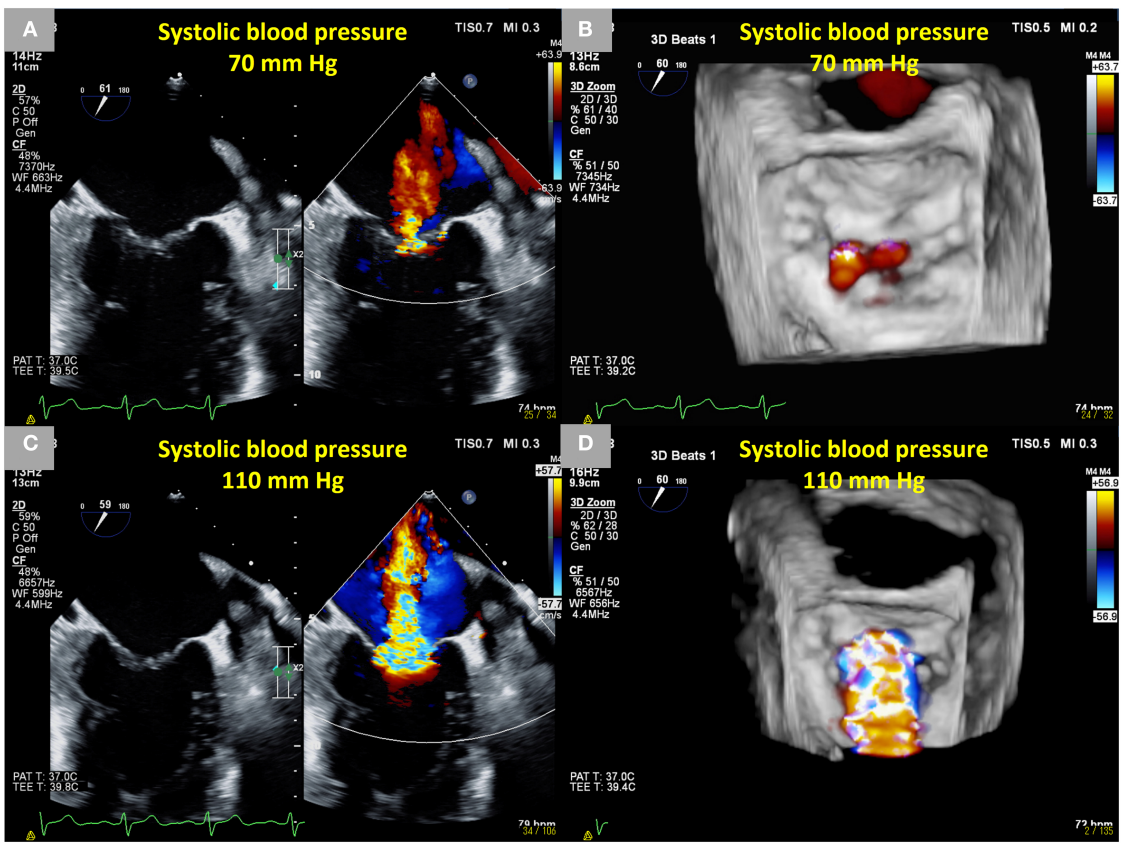

FIGURE 1 | Dynamic changes in SMR during transesophageal echocardiography in a 66-year-old male patient who had an anterior old myocardial infarction and heart failure with reduced ejection fraction. Mild SMR (EROA 0.10 cm^2) under sedation using midazolam under a systolic blood pressure of approximately 70 mm Hg. **(A)** Two-dimensional B-mode and color Doppler images from the intercommissural view and **(B)** a three-dimensional color Doppler image from the en-face view. Dynamic severe SMR (EROA 0.51 cm^2) under an elevated systolic blood pressure of approximately 110 mm Hg using norepinephrine. **(C)** Two-dimensional B-mode and color Doppler images from the intercommissural view and **(D)** a three-dimensional color Doppler image from the en-face view. SMR, secondary mitral regurgitation; EROA, effective regurgitant orifice area.

tenting area, and mitral annular dilatation during exercise are crucial in light of the mechanism of dynamic SMR (24–32). It is worth noting that when comparing ischemic cardiomyopathy with apical and inferobasal scars, the coaptation depth is important in the case of an anterior myocardial infarction while the tenting area and LV regional wall motion abnormality are crucial in the case of an inferior myocardial infarction (24). There is a paucity of data on resting factors associated with dynamic SMR although only LV dyssynchrony at rest is suggested to be related to dynamic SMR (31). It may be because mitral valve tethering and closing forces change based on complicated combinations of dynamic changes of LV and LA geometry and MV apparatus during exercise.

EXERCISE CAPACITY AND CLINICAL OUTCOMES IN DYNAMIC SMR

SMR can deteriorate dynamically during exercise (**Figure 2**). Dynamic SMR is expected to affect a patient's exercise tolerance due to the abruptly deteriorated severity, leading to a reduction in the forward stroke volume and an increase in the overload on the LA and pulmonary circulation during exercise. Izumo et al. elucidated that changes in the effective regurgitant orifice area (EROA) of SMR during exercise stress echocardiography (ESE) are significantly associated with the peak VO_2 and VE/VCO_2 slope and that the rate of exercise termination is higher in patients with dynamic SMR (ΔEROA $\geq$0.13 cm^2 during exercise) than in those without dynamic SMR (18). Also, Bandera et al. investigated the exercise capacity of patients with HFrEF via cardiopulmonary exercise testing combined with ESE and reported that the exercise tolerance of patients with dynamic severe SMR (EROA $\geq$0.20 cm^2 during exercise) was less than that of patients without dynamic severe SMR (19).

Lancellotti et al. initially reported that dynamic SMR with changes in the EROA $\geq$0.13 cm^2 during exercise was independently associated with adverse clinical outcomes at mid-term (14, 15). Moreover, long-term clinical outcomes in patients with dynamic severe SMR (EROA $\geq$0.20 cm^2 during exercise) were shown to be unfavorable by Suzuki et al. (16). Also, Piérard et al. (33) investigated the association of dynamic SMR with acute pulmonary edema in patients who recently suffered from acute pulmonary edema and underwent ESE after the improvement of pulmonary edema. Then, changes in the EROA

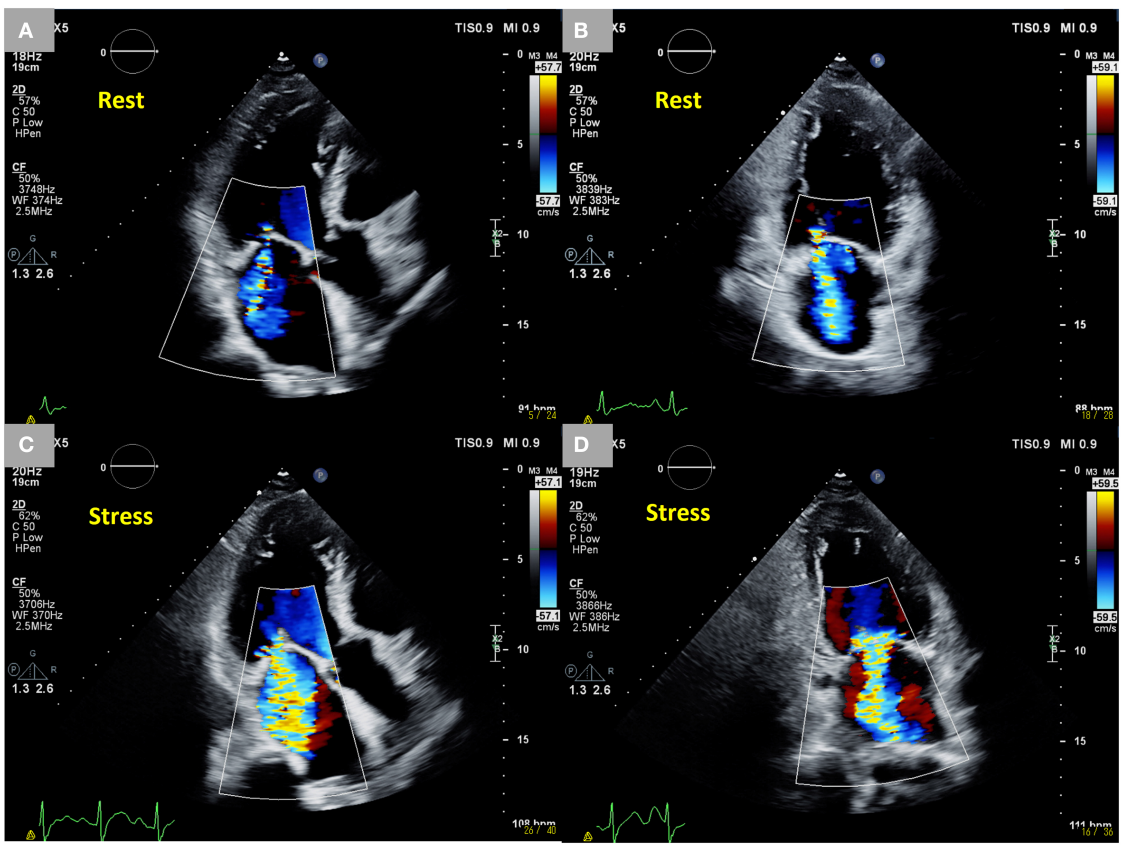

FIGURE 2 | Dynamic changes in SMR during exercise stress echocardiography in an 85-year-old male patient who had an anterior old myocardial infarction and heart failure with reduced ejection fraction. Moderate SMR (EROA 0.22 cm^2) at rest. **(A,B)** Two-dimensional color Doppler images from three- and two-chamber views. Dynamic severe SMR (EROA 0.46 cm^2) under stress. **(C,D)** Two-dimensional color Doppler images from three-chamber and two-chamber views. SMR, secondary mitral regurgitation; EROA, effective regurgitant orifice area.

on exercise were reported to be significantly associated with recent acute pulmonary edema. Furthermore, in patients that require hospitalization for acute decompensated HF, dynamic severe SMR on hospitalization is expected to be similar to persistent severe SMR in light of favorable outcomes (17).

PHARMACOLOGICAL TREATMENT FOR DYNAMIC SMR

The four classes of drugs that constitute GDMT in HFrEF are angiotensin-converting enzyme inhibitors (ACEi)/angiotensin II receptor blockers (ARB)/angiotensin receptor-neprilysin inhibitors (ARNI), beta-blockers (BB), mineralocorticoid receptor agonists (MRA), and sodium-glucose cotransporter 2 inhibitors (SGLT2i); these drugs should be titrated to the maximum tolerated doses in all patients with HFrEF regardless of the presence of SMR (7–10). The optimization of GDMT using ACEi/ARB, BB, and MRA in HFrEF patients is expected to reduce the severity of SMR (34, 35). Also, ARNI has recently received attention as an effective basic HF drug and is recommended prior to ACEi/ARB in patients with HFrEF if applicable according to current guidelines (7–10). ARNIs are effective for LV and LA reverse remodeling (36–39). Moreover, ARNIs are reported to reduce the SMR (40). Also, according to data from a previous meta-analysis, the new "golden triangle" consisting of ARNIs, BBs, and MRAs is the most effective remedy for LV reverse remodeling among several combinations using some GDMT drugs (ACEi, ARB, ARNI, BB, and MRA) (41), which may be expected to bring about further improvements in the dynamic SMR.

A meta-analysis of three cardiac magnetic resonance imaging trials reported that SGLT2i therapy in patients with HFrEF was not significantly associated with reverse cardiac remodeling, including left ventricular ejection fraction, end-systolic volume, and end-diastolic volume; however, there was a tendency toward the improvement of these parameters (42).

NONPHARMACOLOGICAL TREATMENT FOR DYNAMIC SMR

In HFrEF patients with persistent severe SMR, GDMT should be optimized as much as possible; however, such patients often suffer from either residual or worsening HF symptoms or undergo repeat HF hospitalization. Thus, when these patients have symptoms despite optimal GDMT, current guidelines recommend nonpharmacological treatment, including CRT and TEER (if applicable), after appropriate revascularization for significant coronary artery disease. However, there remains a matter for consideration in terms of nonpharmacological treatment for dynamic SMR in patients with HFrEF. Then, the nonpharmacological treatment of dynamic SMR is discussed below with a focus on CRT and TEER.

CRT FOR DYNAMIC SMR

In HFrEF patients with LV dyssynchrony, CRT can suppress LV dyssynchrony and subsequently improve LV hemodynamics

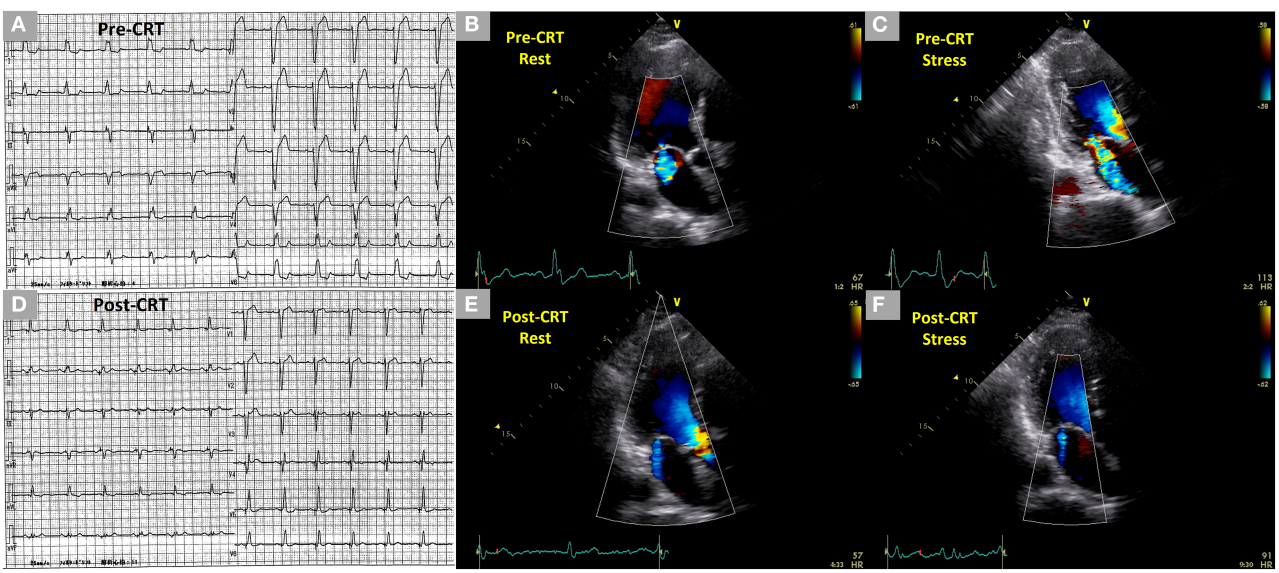

FIGURE 3 | Dynamic changes of SMR during exercise stress echocardiography before CRT and controlled SMR following CRT during exercise stress echocardiography in a 71-year-old male patient who had an anterior old myocardial infarction and heart failure with reduced ejection fraction. **(A)** Complete left bundle branch block with a QRS duration of 154 ms in the electrocardiogram before CRT. **(B,C)** Mild SMR (EROA 0.14 cm^2) at rest and dynamic moderate-to-severe SMR (EROA 0.32 cm^2) under stress in two-dimensional color Doppler images from the three-chamber view before CRT. **(D)** Non-left bundle branch block with a QRS duration of 128 ms in the electrocardiogram after CRT. **(E,F)** Trivial SMR at rest and under stress 1 year after the CRT in two-dimensional color Doppler images from the three-chamber view after CRT. SMR, secondary mitral regurgitation; CRT, cardiac resynchronization therapy, EROA, effective regurgitant orifice area.

while attenuating MR at rest and during exercise (**Figure 3**) (20, 22). Madaric et al. elucidated the time course of changes in LV dyssynchrony, LV contractility, and SMR at rest and during exercise following CRT (21). Approximately 1 week after CRT, LV dyssynchrony and SMR during exercise did not adequately improve despite ameliorations in LV dyssynchrony and SMR at rest. However, approximately 3 months after CRT, LV dyssynchrony and dynamic SMR were controlled even during exercise with resting SMR and in LV volumes progressively reduced despite there being no additional improvement in the resting LV dyssynchrony. Moreover, the cardiopulmonary performance after CRT improved at late follow-up in HFrEF

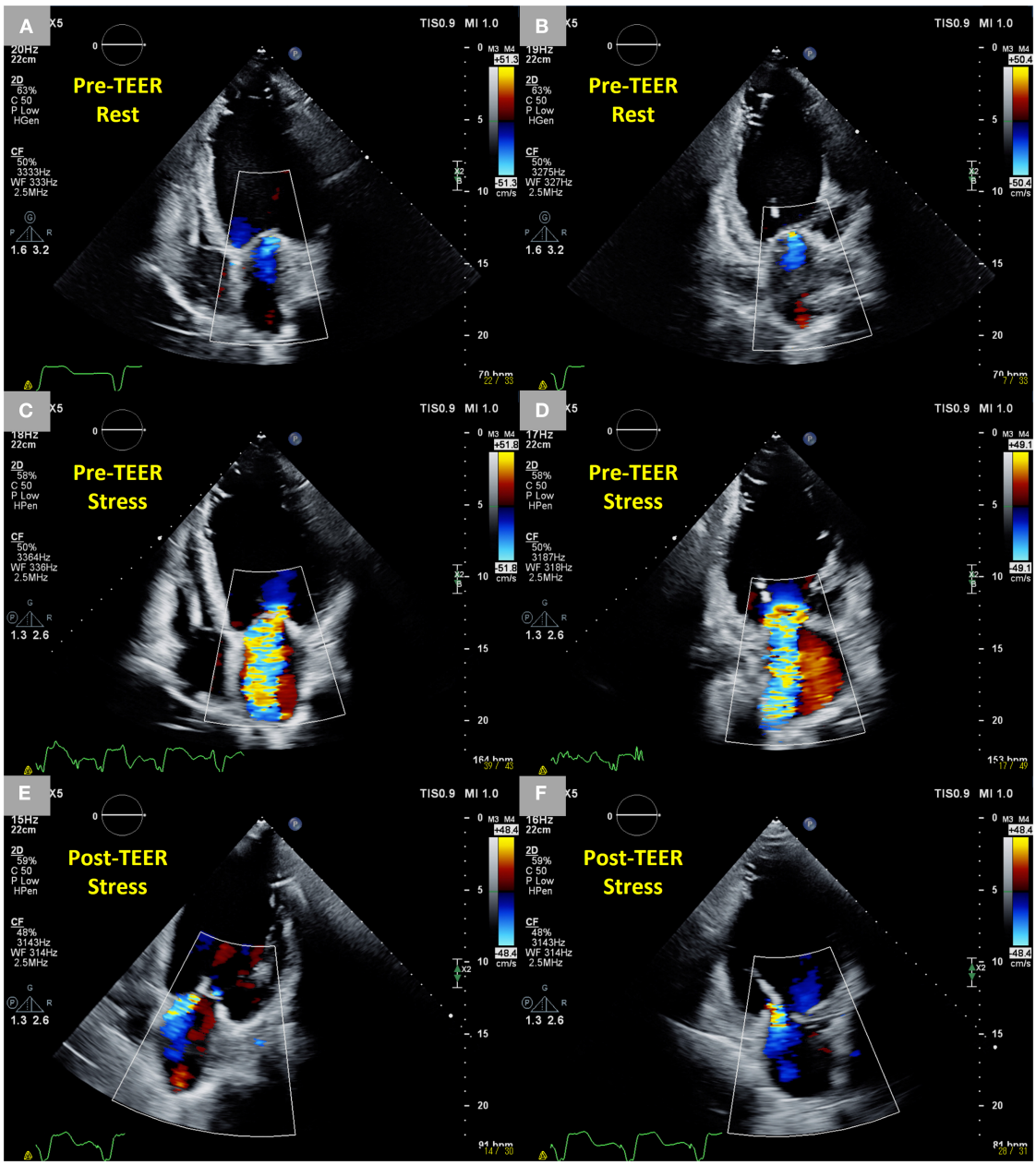

FIGURE 4 | Dynamic changes in SMR during exercise stress echocardiography before TEER and controlled SMR following TEER during exercise stress echocardiography in an 83-year-old male patient who had an anterior and inferior old myocardial infarction and heart failure with reduced ejection fraction after CRT. **(A,B)** Trivial SMR at rest in two-dimensional color Doppler images from four-chamber and two-chamber views. **(C,D)** Dynamic severe SMR (EROA 0.52 cm^2) under stress in two-dimensional color Doppler images from four-chamber and two-chamber views. **(E,F)** Mild MR under stress 6 months after the TEER in two-dimensional color Doppler images from four-chamber and two-chamber views. SMR, secondary mitral regurgitation; TEER, transcatheter edge-to-edge repair; CRT, cardiac resynchronization therapy; EROA, effective regurgitant orifice area; MR, mitral regurgitation.

patients with dynamic SMR although no reports showed a prognostic value of CRT.

Also, it was (reportedly) possible to induce a left bundle branch block (LBBB) during exercise by increasing the heart rate of HFrEF patients with non-LBBB at rest (43). Rate-related LBBB may be accompanied by LV dyssynchrony and dynamic SMR, subsequently leading to deteriorated hemodynamics and worsening HF symptoms. In the case report, the patient underwent CRT to correct rate-related LBBB, LV dyssynchrony, and dynamic SMR and had favorable clinical outcomes during follow-up (43). Thus, dynamic SMR with rate-related LBBB may be assessed using ESE in unexplained symptomatic patients with HFrEF despite resting non-LBBB, no dyssynchrony, and non-significant SMR.

TEER FOR DYNAMIC SMR

In patients with HFrEF and dynamic SMR, it may be possible that HF symptoms remain or recur with dynamic SMR refractory to optimal GDMT and CRT. In such patients, TEER can control not only the SMR at rest but also the dynamic change during exercise (**Figure 4**). Previously, Lancellotti et al. suggested that dynamic SMR should be considered in HFrEF patients with moderate SMR at rest and unexplained dyspnea under optimal GDMT and nonpharmacological treatments, including CRT and revascularization, if indicated, and TEER might be indicated when dynamic SMR was performed during exercise (44). Recently, Izumo et al. reported that TEER is suggested to be safe and effective in light of HF symptoms and clinical outcomes during follow-up in symptomatic HFrEF patients with dynamic SMR (ΔEROA $\geq$0.13 cm^2 during exercise) refractory to treatment with optimized GDMT and CRT if applicable (23). Of note, the patients in the non-TEER group, who had no significant SMR (the EROA of 0.20 $\pm$ 0.08 cm^2) at rest but significant SMR (the EROA of 0.38 $\pm$ 0.10 cm^2) during exercise, had a significantly higher rate of HF-related hospitalization and all-cause mortality than those in the TEER group. This suggested that resting SMR in patients with HFrEF is potentially underestimated unless ESE is performed and, consequently, even a non-significant resting SMR can bring about adverse clinical events if medically treated. In addition, this study addressed the association of EROA of SMR with left ventricular end-diastolic volume at rest and during exercise. In the study patients, EROA and left ventricular end-diastolic volume increased significantly during exercise, and as a result, the relationship between EROA in the study and left ventricular end-diastolic volume during exercise was similar to that in the COAPT study. Thus, ESE may be useful to figure out symptomatic patients with HFrEF who have potentially disproportionate dynamic SMR and are expected to receive adequate benefit from TEER.

TEER can reduce the intensity of the symptoms of SMR and its prevalence because of the acute changes in mitral valve geometry as follows; improved coaptation area and mitral valve tethering, decreased anteroposterior diameter and area of the mitral annulus, and increased sphericity of the mitral annulus (45–50), all of which lead to a persistent reduction of the SMR and improvement of the functional status (45, 46). Such acute changes following TEER seem to resist dynamic SMR derived from changes in the mitral valve geometry during exercise. Therefore, TEER could be a reasonable treatment for dynamic SMR in patients with HFrEF. Further studies are required to evaluate the safety and efficacy of TEER for dynamic SMR.

CHALLENGES FOR THE FUTURE IN DYNAMIC SMR

Optimal GDMT reduces the severity of SMR in patients with HFrEF (34, 35, 40). Current guidelines recommend TEER for SMR in patients with HFrEF if they had HF symptoms despite the uptitration of HF drugs as long as tolerated (7, 8). However, a previous study reported that optimal GDMT before TEER was not necessarily achieved (51). Less than 50% of the overall population received >50% of the target dose of ACEi/ARB/ARNI and BB, which suggests the difficulty in the maximal optimization of GDMT in clinical practice. This might be because of hypotension, worsening HF, drug intolerance, and worsening kidney function.

The study also reported that 67% of the patients who underwent TEER had either unchanged or uptitrated GDMT (51). Such patients showed a lower rate of recurrent MR $\geq$3+, more reduced LV end-systolic volumes, and lower NYHA classes during follow-up than those with downtitrated GDMT. Moreover, unchanged or uptitrated GDMT following TEER was associated with favorable clinical outcomes, which was defined as freedom from death and heart transplantation.

TEER for dynamic SMR may be expected to improve hemodynamics, mitral valve geometry, and HF symptoms, subsequently enabling patients to avoid downtitrated GDMT and gain clinical benefits as with TEER for persistent severe SMR. Thus, optimal GDMT even after TEER for dynamic SMR is also considered the crucial cornerstone of HF management considering its effect in further cardiac reverse remodeling and SMR reduction (45–53). Further studies are needed in light of the importance of optimal GDMT after TEER as well as the safety and efficacy of TEER in patients with HFrEF and dynamic SMR.

Also, there are issues with ESE in patients with HFrEF and SMR; such patients can not exercise long enough to reach peak stress. Therefore, it may be difficult to compare dynamic SMRs among different patients based on certain stress criteria. Then, low-load ESE, which can be performed for a shorter time and under lower stress than conventional ESE, may be reasonable to evaluate the dynamic changes of SMR under specific stress in HFrEF patients. In such patients, it is expected that the usefulness of low load ESE will be examined in future.

CONCLUSION

Dynamic SMR is associated with exercise performance impairments and adverse clinical outcomes in patients with HFrEF. In such patients, optimal GDMT and CRT are expected to ameliorate the deteriorated mitral valve apparatus, which subsequently leads to improvements in the dynamic

SMR. Dynamic SMR can be residual or recurrent even after administering the appropriate treatments above. In such cases, other invasive treatment options, including TEER, may be indicated considering the effectiveness of TEER for dynamic SMR. CRT and TEER, along with GDMT, can improve deteriorated mitral valves and LVs, left ventricular dynamics, HF symptoms, exercise tolerance, and clinical outcomes. Even after obtaining such clinical benefits from CRT and TEER, GDMT regimens should be re-evaluated and reinforced as long as patients are tolerated to aim at further cardiac reverse remodeling and the reduction and prevention of dynamic SMR, subsequently leading to the amelioration of exercise tolerance and clinical outcomes.

AUTHOR CONTRIBUTIONS

HO and MI drafted the manuscript and prepared the figures. TN, SN, and YA revised the manuscript. All authors read and approved the final manuscript.

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Myocardial Injury Predicts Risk of Short-Term All-Cause Mortality in Patients With COVID-19: A Dose–Response Meta-Analysis

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Objective: Predictive value of myocardial injury as defined by elevated cardiac tropnins (cTns) in patients with COVID-19 has not been fully investigated. We performed a meta-analysis to evaluate the dose–response relationship between myocardial injury and short-term all-cause mortality.

Methods: Pubmed, Embase, and the Cochrane Library database were searched for all the studies which evaluated the relationship between cTns and the risk of short-term all-cause mortality in patients with COVID-19.

Results: Compared with patients without myocardial injury, the group with elevated cTns was associated with increased short-term mortality (11 studies, 29,128 subjects, OR 3.17, 95% CI 2.19–4.59, $P = 0.000$, $I^2 = 92.4\%$, P for heterogeneity 0.00). For the dose–response analysis, the elevation of cTns 1 × 99th percentile upper reference limit (URL) was associated with increased short-term mortality (OR 1.99, 95% CI 1.53–2.58, $P = 0.000$). The pooled OR of short-term mortality for each 1 × URL increment of cTns was 1.25 (95% CI 1.22–1.28, $P = 0.000$).

Conclusion: We found a positive dose–response relationship between myocardial injury and the risk of short-term all-cause mortality, and propose elevation of cTns > 1 × 99th percentile URL was associated with the increased short-term risk of mortality.

Keywords: cardiac troponin, myocardial injury, short-term mortality, meta-analysis, COVID-19

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INTRODUCTION

COVID-19 pandemic caused by the SARS-COV-2 is responsible for an immense burden of morbidity and mortality globally. As of 13 December 2021, over 270.52 million confirmed cases have been identified and more than 5.32 million people died from COVID-19[1]. Patients affected by COVID-19 experience varied clinical presentations and outcomes. The majority of patients experience mild or moderate symptoms and resolve within a few weeks of initial infection, while other minorities develop acute respiratory distress syndrome (ARDS), or even multiple organ dysfunction with

[1]https://www.worldometers.info/coronavirus/

a high risk of mortality (1–3). The key element to reduce the mortality of COVID-19 has been recognized as identifying high-risk patients and providing earlier intervention (4, 5). However, it is still challenging to improve risk stratification.

According to the Fourth Universal Definition of Myocardial Infarction (UDMI), myocardial injury is defined as an increase of cardiac troponins (cTns, including cTnI and cTnT) values over the 99th percentile upper reference limit (URL). cTns, as a sensitive biomarker, could be detected not only in cardiac conditions, but also in non-cardiac conditions including sepsis, aortic dissection, end-stage renal disease, etc., (6–8). What's more, elevated cTns are often associated with adverse outcomes and are helpful for risk stratification in both cardiac and non-cardiac conditions (9–11). Till now, the predictive value of myocardial injury in patients with COVID-19 during the in-hospital term or short term is mixed. A series of studies have shown that myocardial injury in patients with COVID-19 is very common and associated with higher mortality (12–22). However, other studies indicated that the influence of myocardial injury is attenuated after adjusting multiple severe diseases (23, 24). Therefore, we performed a comprehensive dose–response meta-analysis to investigate the relationship between myocardial injury and short-term all-cause mortality in patients with COVID-19 with the following objectives: (1) to provide a quantitative assessment of the association between myocardial injury and short-term all-cause mortality; (2) to explore the potentially modifiable factors related to myocardial injury and short-term all-cause mortality; (3) to define an optimal threshold of elevated cTns that is associated mortality; (4) to quantify the dose–response relationship of the magnitude of myocardial injury and risk of short-term all-cause mortality.

METHODS

Search Strategy

We reported this meta-analysis following the guidance of the MOOSE (Meta-analysis of Observational Studies in Epidemiology) statement (25). We searched PubMed (from 2019 to December 2012), Embase (from 2019 to December 2012), and the Cochrane Library database (http://www.cochrane.org). We also manually searched reference lists of the retrieved articles and reviews. The keywords used in the search were (troponin or myocardial injury) paired with (COVID-19). No language restriction was applied.

Study Outcomes and Selection

The primary endpoint was short-term all-cause mortality. Inclusion criteria for the retrieved studies were as follows: (1) prospective or retrospective design; (2) inclusion of the outcome of short-term/in-hospital mortality; (3) inclusion of multivariable-adjusted or undusted relative risk (RR) or odds ratio (OR) and their corresponding 95% CI or provided the number of events and total population in each group; (4) inclusion of different level of elevated cTns and the related mortality. To conduct a dose–response meta-analysis, studies with three or more categories of URL were included (studies with $<3^{\circ}$, e.g., with only positive or negative cTns were excluded); (5) the referent group with cTns $<$ 99th percentile URL or provided the number of events and cases within cTns $<$ 99th percentile URL.

Data Extraction

Data were extracted by two independent authors (Yuehua Li and Hanjun Pei). Discrepancies were resolved by group discussion. The extracted data included the source of study (author, publication year, country), population characteristics [mean age, male proportion, number of subjects, percentage of elevated cTns, hypertension, diabetes mellitus (DM), coronary artery diseases (CADs), heart failure (HF), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), cancer], follow-up term, the different threshold of cTns, ORs, or RRs and their corresponding 95% CI. We assessed study quality by the Newcastle–Ottawa quality assessment scale which is a validated scale for non-randomized studies in meta-analyses. This scale assigns a maximum of nine points to each study: four points for selection, two points for comparability, and three points for the assessment of outcomes and adequacy of follow-up. We assigned scores of 0–3, 4–7, and 8–9 for low-, moderate-, and high-quality studies, respectively.

Statistical Analysis

We considered RRs as ORs in the retrospective studies. We pooled the ORs from the group with the lowest URL and >99th percentile of URL in each study. If the study did not provide the ORs, we calculated the ORs by the number of events and total subjects in the non-elevated and elevated group. If different reference categories were reported, we chose a category with cTns $<$ 99th percentile of URL as reference. We pooled the OR by combining all the categories of elevated cTns for comparing the category with cTns $\geq$ 99th and <99th percentile of URL by DerSimonian and Laird random-effects model (26). If the study provided more than 3 categories, we would calculate the ORs using data on the number of cases and non-cases in all the elevated categories and referent groups. The random-effects model was also used in the pooled analysis for the potential clinical heterogeneity. The heterogeneity was assessed by Q statistic, I-squared, and P-value ($P < 0.05$ was considered to be statistically significant). Univariable meta-regression analyses (including all population characteristics, such as follow-up term, age, percentage of male, DM, hypertension, CAD, HF, COPD, CKD, cancer, and NOES points) were conducted to explore the potential sources of heterogeneity (27). For the dose–response analyses, the degree of elevated cTns was categorized into $<$ 99th percentile of URL, 1–2 URL, 2–3 URL, 3–5 URL, >5 URL. If the study provided the elevated cTns by numerical value, we converted it into the corresponding URL according to the upper reference value in each study. We assigned the ORs from each study into standardized intervals according to the range or median of the degrees of elevated cTns in each category. The average URL of elevated cTns in each category was estimated by mean of the lower and upper levels. If the highest category of cTns had an open upper level, the mean URL was estimated to be 1.5 level of the lower level. The weighted linear regression model was

used to explore the dose–response relationship between elevated cTns and the risk of short-term all-cause mortality (28). To determine whether cTns was an independent risk factor for the short-term all-cause mortality, we performed sensitivity analysis restricted to the studies with multiple-variable adjusted OR.

Publication bias was assessed by the Begg's test and Egger's test. Two-sided $P < 0.05$ was considered to be significant (29). All the data analyses were performed by STATA software (10.0 version, StataCorporation, TX, USA) and REVMAN software (version 5.0; Cochrane Collaboration, Oxford, United Kingdom).

RESULTS

Search Results

We initially identified 11,277 studies by database and manual searching. After the exclusion of duplicates and non-relevant studies, 34 potential articles were selected for detailed evaluation. We further excluded 23 articles as shown in **Figure 1**. Finally, 11 retrospective studies involving 29,128 subjects were included in our meta-analysis (12–16, 18–23). Among them, nine had reported outcomes for cTnI (12, 14–16, 18, 20–23), 1 for cTnT (19), and 1 for combined cTnI and T (13).

Study Characteristics

Table 1 showed the main characteristics of the data extracted from the included studies. All the studies had a retrospective study design. A total of eight studies were conducted in the USA and three in other countries. The mean age ranged from 49.0 to 68.0 years old, the follow-up time varied from 7 to 40 days. The incidence of myocardial injury in patients with COVID-19 ranged from 14.9 to 63.5%. The NOES points ranged from 6 to 9 (**Supplementary Figure 1**).

Myocardial Injury and Risk of Short-Term All-Cause Mortality

Compared with the group without myocardial injury, the group with myocardial injury was associated with an increased risk of short-term mortality (29,128 subjects, 11 studies, OR 3.17, 95% CI 2.19–4.59, $P = 0.000$, $I^2 = 92.4\%$, P for heterogeneity 0.00) in patients with COVID-19 (**Figure 2**). In univariable meta-regression, none of the variables including follow-up term, gender, age, percentage of DM, hypertension, CHD, HF, COPD, CKD, cancer, and NOES points was related to the risk of short-term death (**Supplementary Table 2**).

Dose–Response Analysis of Myocardial Injury and Risk of Short-Term All-Cause Mortality

Table 2 showed the elevated cTns > 99th percentile URL was associated with increased risk of short-term mortality in patients with COVID-19 (OR 1.99, 95% CI 1.53–2.58, $P = 0.000$, $I^2 =$

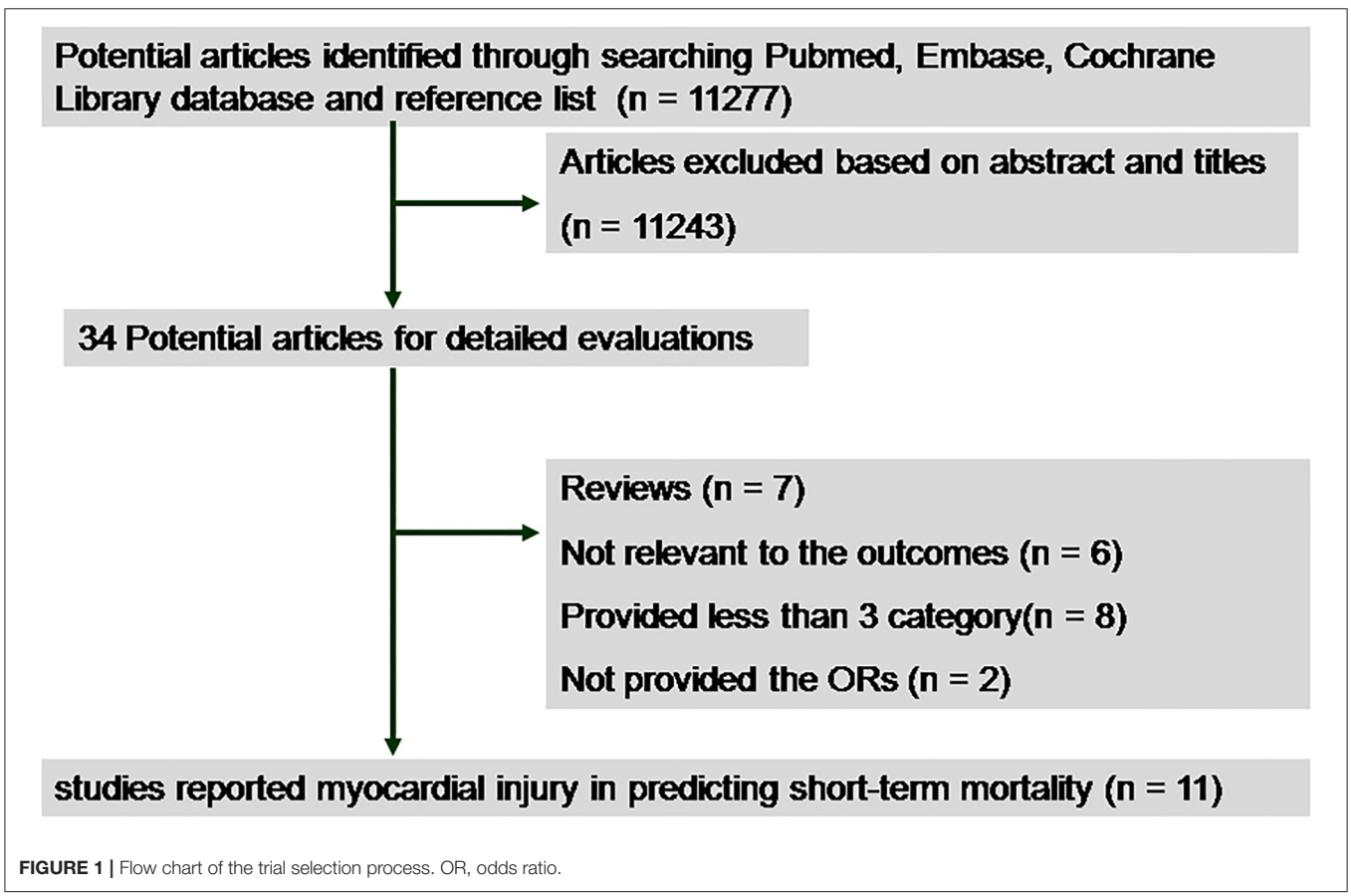

FIGURE 1 | Flow chart of the trial selection process. OR, odds ratio.

TABLE 1 | Characteristics of included studies.

References	Country	Category	Subjects	cTnI/T	Age (y)	Male %	Factory	Follow-up term
Salvatici et al. (15)	Italy	<-99th %URL, 1–2 × 99th URL, >2 × 99th %URL	523	hs-cTnI	68.0	64	Beckman Coulter	7d
Almeida Junior et al. (19)	Brazi	≤0.006 ng/dl, 0.007–0.01 ng/dl, 0.011–0.029 ng/dl, ≥0.03 ng/dl	183	hs-cTnT	66.8	65.6	Roche Laboratory	7d
Franks et al. (20)	USA	<-99^{th}%URL, 1-3×99^{th} URL,> 3×99^{th} %URL	182	cTnI	64.0	56.6	Abbott Architect i2000	In-hospital
Lala et al. (18)	USA	<-99th %URL, 1–3 × 99th %URL, > 3 × 99th %URL	2,736	cTnI	66.4	59.6	Abbott Architect i2001	14d
Metkus et al. (23)	USA	<99th %URL, 1–5 × 99th %URL, 5–10 × 99th % URL, >10 × 99th %URL	243	cTnI	62.8	60.9	Abbott Architect i2002	40d
Majure et al. (13)	USA	<99th %URL, 1–3 × 99th %URL, >3 × 99th %URL	6,247	cTnI, T	66.0	60	Siemens,Roche	7d
Raad et al. (16)	USA	<99th %URL, 1–5.5 × 99th %URL, >5.5 × 99th %URL	1,020	hs-cTnI	63.0	50	Beckman Coulter	30d
Tanboga et al. (12)	Turkey	<0.5 × 99th %URL, <99th %URL, 1–2 × 99th %URL, 2–5 × 99th %URL, 5–10 × 99th %URL, 10–50 × 99th % URL, >50 × 99th %URL	14,855	hs-cTnI	49.0	54	Abbott Architect i2000	30d
Chorin et al. (21)	USA	<99th %URL, 1–2 × 99th %URL, >2 × 99th %URL	204	hs-cTnI	64.0	76	Abbott Park	24.2 ± 7.4d
Smilowitz et al. (14)	USA	<99th %URL, 1–2.1 × 99th %URL, >2.1 × 99th %URL	2,163	hs-cTnI	64.1	63.3	Siemens, Abbot Architect	in-hospital
Ruge et al. (22)	USA	<99th %URL, 1–2 × 99th %URL, >2 × 99th %URL	772	cTnI	58.3	59.1	NA	in-hospital

References	HT %	DM %	CAD %	HF %	Cancer %	CKD %	COPD %	cTn(+) %	Adjusted variable
Salvaticia et al. (15)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Almeida Junior et al. (19)	53.6	19.7	19.1	NA	9.8	2.2	NA	63.5	Age, CAD, oxygen saturation, lymphocytes, D-Dimer, CRP, creatinine, BNP
Franks et al. (20)	NA	NA	NA	NA	NA	NA	NA	55.9	NA
Lala et al. (18)	38.9	10.1	16.6	10.1	7.1	10	5.8	36	Age, sex, BMI, race, ethnicity, history of CAD, history of AF, HF, HT, CKD, DM, statin use, ACEI or ARB use, and CURB-65 score
Metkus et al. (23)	60.9	19.2	NA	28.8	NA	20.2	22.2	51	Age, sex, creatinine, bilirubin, Pao2/Flo2 ratio, vasopressor use, lactate, organ failures
Majure et al. (13)	60	36	13	9	7	NA	6	29.2	Age, sex, race, ethnicity, HT, CAD, HF, peripheral vascular disease, COPD, and DM, use of ACEI/ARBs, alanine aminotransferase, and creatinine
Raad et al. (16)	73	44	12	13	NA	30	10	38.2	Age, sex, BMI, HT, CAD, Heart Failure, AF, cerebrovascular disease, COPD, CKD, cirrhosis, immunosuppressed state
Tanboga et al. (12)	36.3	19.9	15.3	5.1	3.1	3.2	21.6	6.9	Age, sex, NLR, D-Dimer, LDH, CRP, hemoglobin, platelet count, CAD, HF, COPD, cerebrovascular disease, HT, DM, CKD
Chorin et al. (21)	56	30	12	3		8	6	41	Age, CKD, DM, gender, race, CAD, HF, HT,COPD,HF, creatinine, abnormal LFTs
Smilowitz et al. (14)	NA	NA	NA	NA	NA	NA	NA	30.7	Age, sex, race, BMI, smoking, HT, hyperlipidemia, DM, CKD, previous myocardial infarction, HF, AF or malignancy, temperature, pulse oximetry at presentation, outpatient prescriptions for antiplatelets, statin and β-blocker use, CRP, creatinine, D-dimer, absolute lymphocyte count, and platelet count
Ruge et al. (22)	64.2	45.2	28	NA	11.3	14.8	8.2	14.9	NA

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; cTn, cardiac troponin; hs-cTn, hypersensitive –cTn; DM, diabetes mellitus; HF, heart failure; HT, hypertension; LDH, lactate dehydrogenase; LFT, liver function test; NA, not available; NLR, neutrophil-lymphocyte ratio.

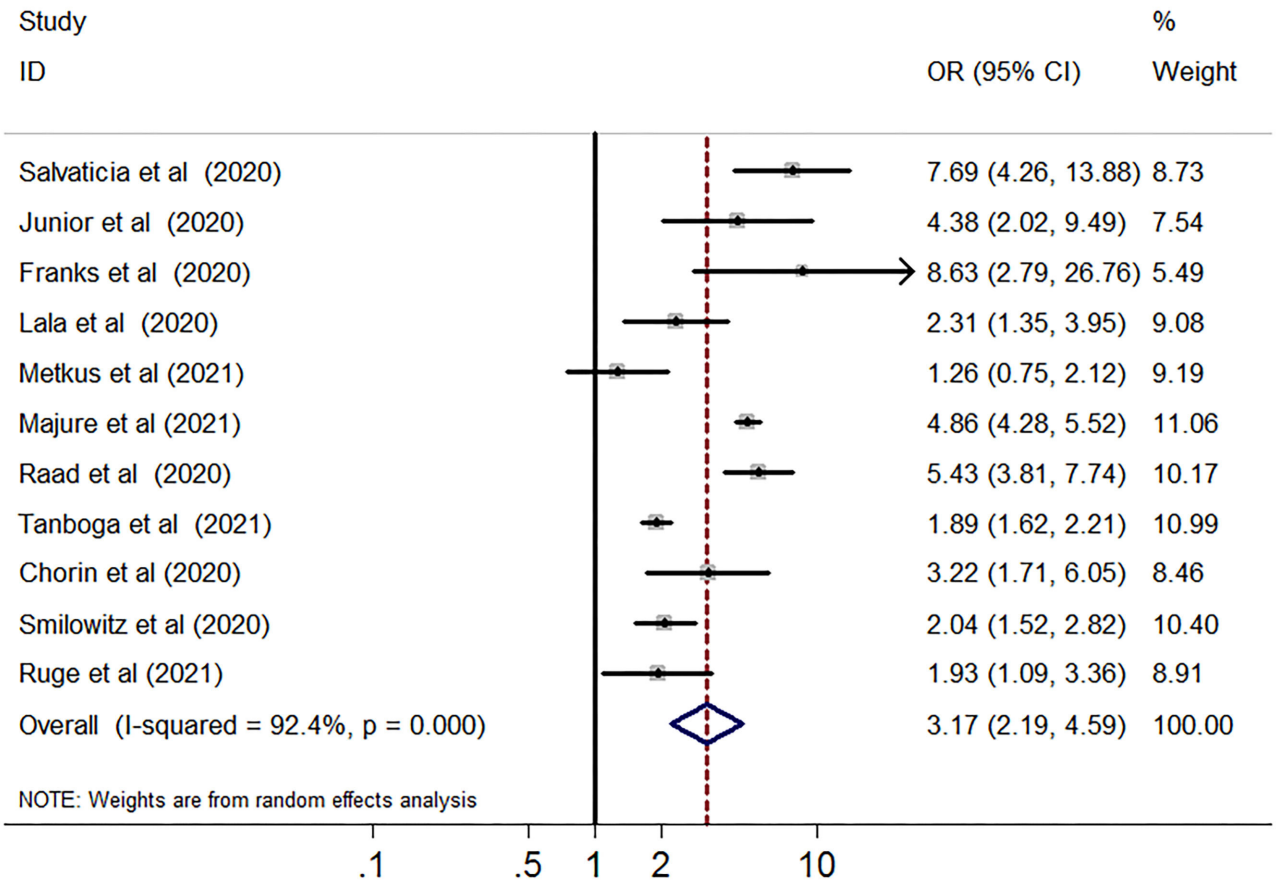

FIGURE 2 | Funnel plot of myocardial injury and risk of short-term all-cause mortality in patients with COVID-19. Meta-analysis of elevated vs. non-elevated cardiac troponin levels and risk of short-term all-cause mortality in patients with COVID-19. CI, confidence interval; OR, odds ratio.

TABLE 2 | Risk of short-term mortality by categories of cardiac troponin I in patients with COVID-19.

Category (URL)	No. of studies	OR 95% CI	*P*	*P* for heterogeneity
1 to < 2x	9	1.96 (1.53–2.58)	0.000	0.007
≥2 to <3x	9	2.92 (1.97–4.33)	0.000	0.000
≥ 3x to <5x	5	3.45 (2.27–5.22)	0.000	0.000
≥ 5x	4	2.48 (1.09–5.67)	0.000	2.93

CI, confidence interval; OR, odds ratio; URL, upper reference limit.

62.3%, *P* for heterogeneity 0.007). The dose–response analysis showed that for every 1x99th percentile URL increment in cTns elevation, the pooled OR was 1.25 (95% CI 1.22–1.28, $P = 0.000$) for the risk of all-cause mortality in patients with COVID-19 (**Figure 3**).

Sensitivity Analysis

When restricted to studies with the multivariable-adjusted results [13–15, 17, 19, 22–24), we found that cTns was also associated with the short-term death (eight studies, 28,240 subjects, OR 2.09, 95% CI 1.72–2.53, $P = 0.000$, $I^2 = 33.8\%$, *P* for heterogeneity 0.158) (**Supplementary Figure 1**). The dose–response analysis showed that for every 1 × 99th percentile URL increment in cTns elevation, the pooled OR was 1.23(95% CI 1.20–1.26, $P = 0.000$) for the risk of short-term all-cause mortality in patients with COVID-19 (**Supplementary Figure 2**).

Publication Bias

Publication bias was not observed by Begg's adjusted rank correlation test ($P = 0.436$) and Egger's test ($P = 0.832$) (**Supplementary Figure 3**).

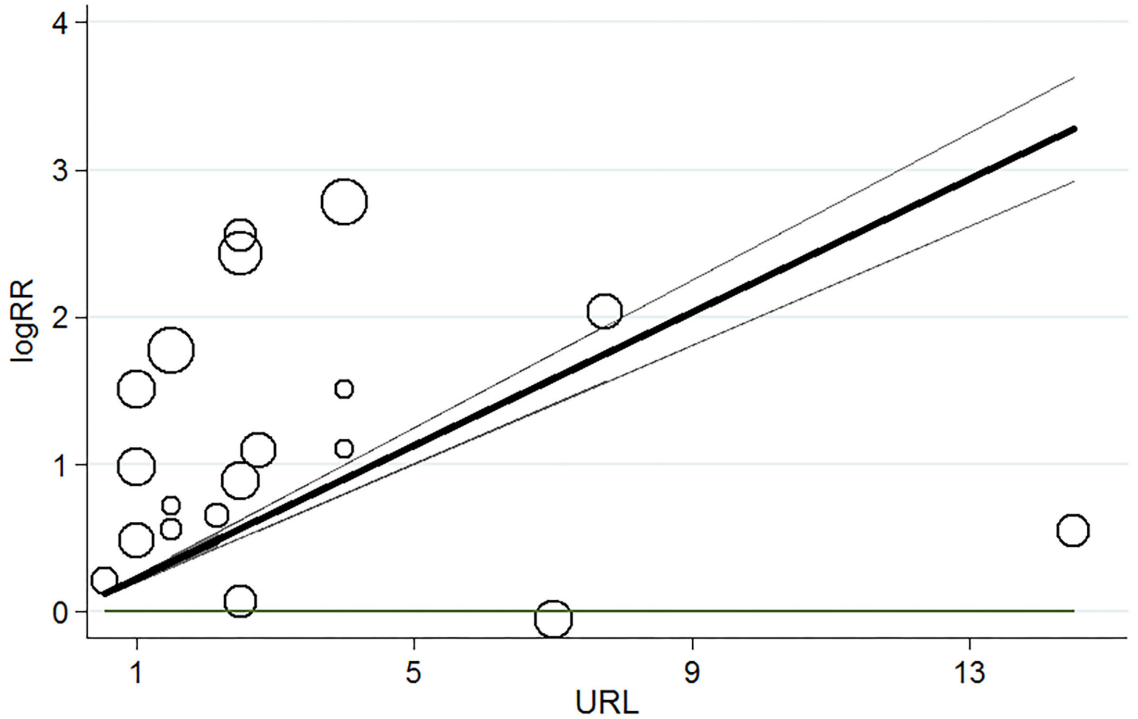

FIGURE 3 | Dose–response relationship for myocardial injury and risk of short-term all-cause mortality in patients with COVID-19. Each black small circle indicates logOR for each category of cardiac troponin levels which is proportional to its statistical weight; solid line represents weighted logOR, and it is two accompanying dashed lines represent its lower and upper CIs. Horizonal solid line indicates the null hypothesis (logOR = 0). CI, confidence interval; OR, odds ratio.

DISCUSSION

In this dose–response meta-analysis of retrospective studies, we found that myocardial injury as defined by elevated cTns above the 99th percentile URL was associated with a 3.17-fold increased risk of short-term mortality in patients with COVID-19. This association was not modified by the factors including age, gender, follow-up term, percentage of DM, hypertension, CAD, HF, COPD, CKD, and cancer. More importantly, above 1 × 99th percentile URL for cTns was related to the risk of short-term mortality. Crucially, the short-term mortality was increased by 25% for each 1 × 99th percentile URL increment for cTns.

Accumulating evidence has indicated that myocardial injury is very common in patients with COVID-19 and often predicts poor prognosis. Bangalore et al. (30) have reported that in a case series with ST-segment elevation affected by COVID-19, 9 of 10 patients with myocardial injury died in the hospital even without coronary involvement, compared with the group with confirmed myocardial infarction deemed less death (4/8). Shi et al. (31) have shown that higher cTnI predicted in-hospital death in severe patients with COVID-19 [hazard ratio (HR) 4.26] and the author also reported that the predictive value of myocardial injury ranged during the time from symptom onset (HR, 4.26) and from admission to endpoint (HR 3.41) (32). Our study was in line with the previous researches and showing that myocardial injury was associated with the short-term mortality. What's more, our meta-analysis has provided new insights. Our study has provided a cut-off value for myocardial injury and indicated that elevated cTns above the 1 × 99th percentile URL were associated with the risk of short-term mortality. Of note, our dose–response analysis also revealed a positive linear association between myocardial injury and short-term mortality in patients with COVID-19 (OR 1.25). Therefore, it would be helpful to risk-stratify the patients with COVID-19 by routine screening for cTns at admission.

The association of myocardial injury and risk the short-term all-cause mortality might be modified by combined diseases such as cardiovascular diseases, respiratory disease, kidney disease, or malignancy. Zhou et al. (33) have indicated that myocardial injury was associated with in-hospital mortality in unadjusted model and the predicted value was attenuated after adjusted age, gender, current smoking, combined diseases including DM, hypertension, CAD, lung diseases, kidney diseases, and inflammatory factors. However, Shi et al. (32) have reported that myocardial injury is an independent risk factor for the risk of mortality after adjusting the mentioned variables. Our meta-regression analyses were consistent with the latter study and showed that the predictive value of myocardial injury was not modified by the mentioned factors. What is more, our sensitivity analysis restricted to the multiple-variable adjusted studies has also shown the positive dose–response relationship between cTns and short-term death. Our results suggested that

myocardial injury was an independent risk factor for short-term mortality in patients with COVID-19. Nevertheless, large prospective trials are necessary to investigate the modifiable factor for myocardial injury.

The present meta-analysis has important strengths. First, our meta-analysis indicated that myocardial injury is an independent risk factor for short-term mortality in patients with COVID-19. Our meta-analysis suggested that routine screening cTns at admission would be helpful for risk-stratification and guide further management for patients with COVID-19. Second, we have provided a cut-off value for elevated cTns about the risk of short-term mortality, that is cTns above the 1 × 99th percentile URL. Using this cut-off value, patients at a higher risk of death could be identified. Last but not the least, our dose–response results have shown that each increment of 1 × 99th percentile URL, results in increase in short-term mortality by 25%. The patients with a high level of cTns should be paid attention and may benefit from a prolonged hospital stay, closer monitoring, more intensified treatment, or more intensive outpatient follow-up to improve outcomes. Future research to aim at preventing or reducing the development of myocardial injury warrants further investigation, given the dose–response between cTns release and adverse outcomes.

The present meta-analysis also has some limitations. First, our meta-analysis was based on retrospective studies, so the recalling and selective bias might be a concern. Second, not all studies have provided the multi-variable adjusted ORs, so the residual confounders could not be ruled out. However, we performed sensitivity analysis restricted to the studies with multi-variable adjusted and found that there was also a positive dose–response relationship between cTns and short-term death in patients with COVID-19. Third, we have excluded some studies without providing more than three categories of cTns, so the unpooled data might affect the results. Fourth, heterogeneity is often a concern of meta-analysis. We tried to explore the potential heterogeneity but were limited by other data such as cardiac function, heart rate, respiratory rate, atrial fibrillation, cough, lung involvement by CT scanning, etc. Fifth, the potential different blood sampling regimens for cTns levels may result in some inherent heterogeneity. Sixth, although the two tests showed no obvious publication bias, we could not rule out the potential effect on the results. Seventh, for few studies, have provided the results of cTn above 10 × 99th percentile URL, thereby the dose–response relationship in a higher level of cTn is limited. Finally, our meta-analysis used pooled data, rather than individual data, which restricted the potential confounding factors.

CONCLUSION

Our dose–response meta-analysis of 11 studies comprising 29,128 patients with COVID-19 has demonstrated that myocardial injury was an independent risk factor for the risk of short-term mortality. We provided the optimal cut-off value of myocardial injury which is the 99th percentile URL about short-term mortality. Each increment of 1 × 99th percentile URL of cTns, the short-term mortality was increased by 25%. Routine screening of cTns at admission is helpful to risk stratification and to guide therapy for patients with COVID-19.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

CZ conceived the idea and supervised the study. YL and HP acquired and analyzed the data and took the responsibility for the accuracy and integrity of the data. YL and YL drafted the manuscript. CZ, YL, YL, and HP contributed to writing, reviewing, or revising the article. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.850447/full#supplementary-material

Supplementary Figure 1 | Funnel plot of myocardial injury and risk of short-term all-cause mortality in COVID-19 patients. Meta-analysis of elevated vs. non-elevated cardiac troponin levels and risk of short-term all-cause mortality in COVID-19 patients for studies with multiple-variable adjusted results. CI, confidence interval; OR, odds ratio.

Supplementary Figure 2 | Dose-response relationship for myocardial injury and risk of short-term all-cause mortality in COVID-19 patients for studies with multiple-variable adjusted results. Each black small circle indicates logOR for each category of cardiac troponin levels which is proportional to its statistical weight; solid line represents weighted logOR, and its two accompanying dashed lines represent its lower and upper CIs. Horizonal solid line indicates the null hypothesis (logOR = 0). CI, confidence interval; OR, odds ratio.

Supplementary Figure 3 | Begg's funnel plot (with pseudo 95% CIs) of myocardial injury and risk of short-term all-cause mortality with all individual studies. Studies that evaluated the association of myocardial injury and risk of short-term all-cause mortality were plotted with weighted lnOR on the vertical axis and the se of the lnOR along the horizontal axis. CI, confidence interval; OR, odds ratio; SE, standard error.

Supplementary Table 1 | Summarized Newcastle–Ottawa quality assessment scale of the included randomized trials.

Supplementary Table 2 | Meta-regression of baseline characteristics for elevated cardiac troponin and risk of short-term all-cause mortality for COVID-19 patients.

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Comparative Risks of Fracture Among Direct Oral Anticoagulants and Warfarin: A Systematic Review and Network Meta-Analysis

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Importance: Previous studies have shown the effectiveness and safety of direct oral anticoagulants (DOACs), including lower fracture risks, compared to warfarin. However, direct or indirect comparisons between different DOACs are scarce in the literature.

Objective: This study aims to compare fracture risks among different DOACs and warfarin, including apixaban, rivaroxaban, dabigatran, and edoxaban, in patients with non-valvular atrial fibrillation (NVAF) or venous thromboembolism (VTE).

Methods: We searched PubMed/MEDLINE, Embase, Cochrane CENTRAL, and Web of Science for randomized controlled trials and cohort studies comparing the fracture risks among patients who used warfarin or DOACs, up to March 2021. Two authors extracted data and appraised the risk of bias of included studies. The primary outcome was fracture risk. We performed pairwise meta-analyses to compare differences between medications and network meta-analyses using frequentist random-effects models to compare through indirect evidence. We used surface under the cumulative ranking curve (SUCRA) and mean ranks to determine the probability of a DOAC ranking best in terms of fracture risk.

Results: Thirty-one studies were included in the final analysis. Twenty-four randomized controlled trials and seven cohort studies with 455,343 patients were included in the systematic review and network meta-analysis. Compared to warfarin, the risk of any fractures was lowest with apixaban [relative risk (RR) = 0.59; 95% confidence interval (CI): 0.48–0.73], followed by rivaroxaban (RR: 0.72; 95% CI: 0.60–0.86), edoxaban (RR: 0.88; 95% CI: 0.62–1.23), and dabigatran (RR = 0.90; 95% CI: 0.75–1.07). No substantial inconsistency between direct and indirect evidence was detected for all outcomes.

Conclusions: All DOACs were safer than warfarin concerning the risk of fracture; however, apixaban had the lowest relative risk of fracture within the class of DOACs. Further head-to-head prospective studies should confirm the comparative safety profiles of DOACs regarding fractures.

Keywords: non-vitamin K antagonist oral anticoagulants, fracture, network meta-analysis, direct-acting oral anticoagulant (DOAC), warfarin, osteoporosis, atrial fibrillation, venous thromboembolism

KEY POINTS

Question: What is the comparative risk of fractures in patients using different direct oral anticoagulants (DOACs) and warfarin?

Findings: This systematic review with network meta-analysis including 31 studies with 463,495 patients found that, compared to warfarin, the risk of fracture was lowest with apixaban, followed by rivaroxaban, edoxaban, and dabigatran. Our results suggested that among DOACs, apixaban carried the lowest fracture risk.

Meaning: DOACs were safer than warfarin with regard to the risk of fracture. Among the DOACs, apixaban had the lowest relative risk of fracture. Healthcare professionals should be informed about different fracture risk profiles associated with different DOACs in order to select the most appropriate DOACs for patients.

INTRODUCTION

As society ages, the prevalence of musculoskeletal and cardiovascular comorbidities increases. Osteoporosis, increasing with age (1), can increase the risk of osteoporotic fracture and subsequent death and disability in the older population (2). The incidence of non-valvular atrial fibrillation (NVAF), another concern in the elderly, continues to increase globally (3). Oral anticoagulants, including vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs), are recommended for patients with NVAF for the treatment or prevention of stroke and thromboembolism (4).

Warfarin, a classic VKA, has been the mainstay treatment for stroke prevention in patients with AF for decades. Of note, VKA use has been associated with an increase in osteoporotic fragility fractures (5–9). Great concern has been raised by a Medicare population-based study (5), in which AF patients using warfarin for longer than one year show an elevated risk of fragility fracture, compared to those not using warfarin. Bone quality is compromised due to the inhibition of vitamin K-dependent carboxylation of bone metabolism-associated proteins such as osteopontin and matrix Gla (10–15). Despite the potential risk of fragility fracture, warfarin has remained necessary for decades due to the lack of alternatives.

Abbreviations: CI, confidence interval; DOAC, direct oral anticoagulants; NVAF, non-valvular atrial fibrillation; PICO, Patient-Intervention-Comparison-Outcome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RR, relative risk; VKA, vitamin K antagonists.

DOACs, recently approved for stroke prevention in AF patients, have been introduced for use as an alternative to warfarin. Given at least equal efficacy in stroke prevention and additional advantages including lower bleeding risk and reduced monitoring requirement compared to warfarin (4), the guidelines of the American College of Cardiology/American Heart Association and the Heart Rhythm Society currently recommend DOACs over warfarin for stroke prevention in NVAF patients (16–18). Consequently, in the United States, DOACs are now more common than VKAs in cardiovascular management (4). Furthermore, DOACs have not been reported to affect bone metabolism proteins (19). Binding et al. report that among 37,350 patients receiving DOACs for over 180 days with no previous use of osteoporotic medications, DOACs are associated with a significantly lower risk of any major osteoporotic fractures, compared to VKAs (6).

As DOACs continue to be a commonplace medication among elderly patients, it is essential to assess the comparative safety profiles, most notably with regard to fractures, within this drug class. Although recent studies have compared fracture risks among the OACs (20–22), the optimal choice of DOAC remains uncertain. Therefore, we performed this systematic review and network meta-analysis to evaluate the network, direct and indirect effects of fracture risk among different DOAC users.

METHODS

Research Protocol and Search Question

The PICO search protocol framework was followed to address the hypothesis: DOAC use in patients with NVAF or VTE (Population of interest), can lead to a varying reduction in the risk of fractures, depending on which individual DOAC medication is used (Comparator/Intervention). Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines were followed for study protocol review and the study was registered in PROSPERO (CRD42020206788).

Eligibility Criteria and Primary Outcome

Studies were eligible if they met the following criteria: (1) They included adult patients using DOACs for NVAF or VTE. (2) They were observational studies or randomized controlled trials (RCTs). (3) They compared the fracture risk between DOACs and warfarin or other DOACs. Relevant exclusion criteria included: (1) single-arm studies, case reports, small case series of <10 patients, reviews, basic science experiments and animal- or cadaver studies; (2) studies including patients with severe

infection or under immunosuppression; and (3) conference abstracts without corresponding full-length papers.

Search Strategy and Study Selection

On March 27th, 2021, we systematically searched PubMed/MEDLINE, Embase, Ovid, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and Scopus for articles using the combination of keywords and medical subject heading (MeSH), adjusted for each database, including: "atrial fibrillation," "anticoagulant," "direct oral anticoagulant," "non-vitamin K antagonist oral anticoagulants," "vitamin K antagonist oral anticoagulants," " warfarin," "Dabigatran," "Pradaxa," "Rivaroxaban," "Xarelto," "Apixaban," "Eliquis," "Edoxaban," "Savaysa," "non-vitamin K antagonist oral anticoagulants," "novel oral anticoagulants," "new oral anticoagulants," "factor Xa inhibitors," "factor IIa inhibitors," "fracture," "osteoporosis" and "osteoporotic fractures." We also searched the reference lists of the included studies to identify additional studies, and the trial register (clinicaltrials.gov) for any ongoing trials. In addition, we contacted specialists in the field for any ongoing trials or unpublished data. We applied no language restrictions. The detailed search strategy is presented in the **Supplementary Table 1**.

Two reviewers (SHLT, CWH) independently evaluated eligible studies by their titles and abstracts and then reviewed the full text of relevant articles for further qualification. All disagreements between reviewers were resolved by reaching a consensus through discussion, and a third reviewer (LTK) was consulted where necessary.

Data Collection and Quality Assessment

Two independent reviewers (SHLT, CWH) extracted all data onto a pre-planned Microsoft Excel spreadsheet (version 16.32). Data fields included study characteristics (authors, year of publication, region of study, data source, study design, period of study), study arms, sample size of overall study and, by study arms, patient age, outcome as defined above, inclusion criteria of each study, specific definition of treatment arm, and source of funding.

The quality of included studies was assessed by two independent reviewers (SHLT, CWH). We evaluated all included RCTs via the RoB (Cochrane risk-of-bias tool for randomized trials) (23), and the non-RCTs via the Newcastle-Ottawa Scale (24). Grade assessment was also performed (25). All discrepancies were resolved by discussion, and a third reviewer (LTK) was consulted where necessary.

Statistical Analysis and Quantitative Data Synthesis

All statistical analyses were undertaken using Network commands for statistical software package Stata (Version 15). A pairwise function was first used to transform raw data to a contrast-based format and generate treatment effect and standard error for each pairwise comparison. A network meta-analysis was then performed to estimate network meta-analysis models with a frequentist approach derived from graph theoretical methods. The random-effects model was incorporated by adding the estimated heterogeneity $\tau 2$, based on the Dersimonian-Laird estimator (26). Subsequently, we examined the structure of our network comparison by applying the netgraph function, with vertices demonstrating treatments and the thickness of edges corresponding to the number of studies.

As a conservative assumption, a random-effects pooled relative risk (RR) with a 95% confidence interval (CI) was calculated to summarize the efficacy of each treatment. Forest plots were constructed to display findings with VKAs as the reference group. Given the I^2 value increased with the larger populations included in the meta-analysis, τ^2 was used to measure heterogeneity; 0.04, 0.16, and 0.36 corresponded to a low, moderate, and high degree of heterogeneity, respectively. Subgroup analysis based on treatment comparison was conducted to evaluate heterogeneity within studies. Sensitivity analysis was also performed in the presence of publication bias or significant heterogeneity. We also estimated the probabilities of each treatment being at each rank for each outcome. We obtained a treatment hierarchy using the surface under the cumulative ranking curve (SUCRA) and mean ranks; the SUCRA value is 0 when a treatment is the worst option and 1 when a treatment is the best option (27).

Furthermore, we assessed the potential inconsistency between direct and indirect comparisons using the design-by-treatment interaction model (28), and side-splitting models (29). The design-by-treatment interaction model provides a global assessment of consistency across the entire network. The side-splitting method separates evidence into direct and indirect evidence and then evaluates differences between them (28, 29). We used the Egger's test and a funnel plot to assess small-study bias (30, 31). Symmetry around the effect estimates line indicated lower chance of publication bias or small study effects (32).

Subgroup Analyses

Where data were available, we planned to perform subgroup analyses including:

1. Fracture location: spinal fracture, hip fracture, and all fractures.
2. DOAC indications: NVAF or VTE/PE.
3. Type of study design: RCTs vs. Non-RCTs.
4. Studies with a given drug dose.
5. Studies with male predominance.
6. Studies with patients aged <65.

RESULTS

Literature Search and Selection Process

A total of 9,332 articles were identified through the database search. After the removal of duplicates, 1,149 articles remained. An additional 13 articles were identified after checking the reference lists of eligible studies. One thousand one hundred and seventeen articles were excluded by checking the titles and abstracts. After checking the full-text of the remaining 45 articles against the inclusion and exclusion criteria, 11 articles were excluded, whereby eight had the wrong study design, two had

the wrong patient population, and one had the wrong outcomes (**Supplementary Table 2**). Ultimately, 31 studies were included in the network meta-analysis (**Figure 1**).

Study Characteristics, Cohort Description and Treatment Definition

Our network meta-analysis included 24 randomized controlled trials and seven cohort studies with a total of 455,343 patients receiving five different anticoagulants. Two hundred twenty-one thousand two hundred three patients used warfarin, 78,810 used dabigatran, 106,996 used rivaroxaban, 35,359 used apixaban and the remaining 12,975 patients were edoxaban users. The network graphs are presented in **Figures 2A–C**, and the main characteristics of the included studies are reported in **Table 1**. The included studies were conducted in Asia (six studies; 50,203 patients), the Americas (three studies; 270,202 patients), Europe (one study; 14,376 patients), and multinational settings (21 studies; 120,562). The included patients had a median age of 69.05 years (range: 54 to 89 years). A smaller proportion of participants were female (median: 38%) (**Table 1**). AF and VTE prophylaxis were indications for DOAC use among 93.43% (N = 214,198) and 6.57% (N = 15,058) of patients, respectively, across the 31 studies. The assumption of transitivity was accepted because no variability was identified in the study and population baselines (**Supplementary Tables 3**, **4**). **Supplementary Figure 1** summarizes the detailed risk of bias assessments.

Methodological Quality and Assessment of Risk of Bias

The main sources of RoB in the included RCTs were blinding of participants, personnel, and incomplete outcome data. Connolly et al. (34), EINSTEIN Investigators et al. (38), and EINSTEIN–PE Investigators et al. (42) had a high risk of performance bias, while Gibson et al. (49), Hohnloser et al. (58), Piazza et al. (51) and Weitz et al. (37) had a risk of attrition bias (**Supplementary Figures 1A,B**). The quality of non-RCTs was fairly good (**Supplementary Table 5**). Most studies had funding from multinational pharmaceutical companies. Only Huang et al. (63) and Wang et al. (61) did not report external funding.

Fracture Risk

We summarized our random-effects network meta-analysis and pairwise comparison of fracture risks in **Figure 3**; **Supplementary Table 6**. We ranked the risk of any fractures of DOACs against warfarin and the SUCRA probability (**Supplementary Figures 3**, **4**; **Supplementary Table 7**).

Any Fracture Risk

This outcome was reported by 31 studies with 455,343 participants. The overall structure is shown in **Figure 2A**. VKA users had 5,553 fractures (5,553/2,21,203, 2.51%), dabigatran users had 2,578 fractures (2,578/78,810, 3.27%), rivaroxaban users had 2,025 fractures (2,025/1,06,996, 1.89%), apixaban users had 666 fractures (666/35,359, 1.88%) and edoxaban users had 254 fractures (254/12,975, 1.96%). Comparing network estimates of fracture risk between DOACs and warfarin, apixaban users (RR: 0.59; 95% CI: 0.50 to 0.71) and rivaroxaban users (RR: 0.72; 95% CI: 0.64 to 0.84) showed a statistically significant reduction in fracture risk, compared to warfarin users. No significant fracture risk reduction was observed among edoxaban, dabigatran, and warfarin users (**Figure 3A**). In terms of any fracture risk, apixaban (SUCRA = 98.0%) was most likely to be ranked the best, followed by rivaroxaban (SUCRA = 71.6%) (**Supplementary Figures 3A,B**, **4A**; **Supplementary Table 7**).

Spine Fracture Risk

This outcome was reported in 10 studies with 83,842 participants (34, 38, 40–46, 54). The overall structure is shown in **Figure 2B**. VKA users had 61 fractures (61/4,1849, 0.15%), dabigatran users had 5 fractures (5/6,839, 0.07%), rivaroxaban users had 15 fractures (15/11,920, 0.13%) and edoxaban users had 16 fractures (16/11,153, 0.14%). No spinal fracture event was reported among apixaban users. Pooled estimates revealed no significant differences among apixaban users (RR: 0.07; 95% CI: 0.01 to 0.57), rivaroxaban users (RR: 0.75; 95% CI: 0.34 to 1.69), edoxaban users (RR: 0.78; 95% CI: 0.33 to 1.81) and dabigatran users (RR: 1.72; 95% CI: 0.32 to 9.17), when compared to warfarin users (**Figure 3B**). Apixaban (SUCRA = 98.5%) was most likely to be ranked the best in terms of risks for spine fracture (**Supplementary Figures 3A,B**, **4B**; **Supplementary Table 7**).

Hip Fracture Risk

This outcome was reported in 16 studies with 228,133 participants (34, 35, 38, 40–42, 44–49, 51, 54, 60, 61). The overall structure is shown in **Figure 2C**. VKA users had 453 fractures (453/1,02,133, 0.44%), dabigatran users had 195 fractures (195/42,434, 0.46%), rivaroxaban users had 158 fractures (158/44,631, 0.35%), apixaban users had 69 fractures (69/27,726, 0.25%), and edoxaban users had 36 fractures (36/11,209, 0.32%). Overall, apixaban users generated the lowest pooled fracture risk estimate (RR: 0.56; 95% CI: 0.43 to 0.74), followed by rivaroxaban users (RR: 0.73; 95% CI: 0.60 to 0.88), edoxaban users (RR: 0.73; 95% CI: 0.47 to 1.12) and dabigatran users (RR: 1.06; 95% CI: 0.89 to 1.26), compared to warfarin users (**Figure 3C**). Apixaban (SUCRA = 90.4%) was most likely to be ranked the best in terms of risks for hip fracture (**Supplementary Figures 3A,B**, **4C**; **Supplementary Table 7**).

Subgroup Analyses

The detailed results of subgroup analyses were presented in **Supplementary Tables 8–10**. Of note, in 22 studies with the indication of NVAF, apixaban reported the lowest fracture risk compared to warfarin (RR: 0.59; 95% CI: 0.58 to 0.75), followed by rivaroxaban (RR: 0.70; 95% CI: 0.58 to 0.85, **Supplementary Table 10**). Eight studies reported the indication of VTE, none of the DOACs were statistically significant in fracture reduction compared to warfarin. The results were similar in the subgroup of patients older than 65 and male predominant studies. Advanced age and male sex are both common characteristics of the NVAF population, with both subgroups concluding the lowest fracture risk in apixaban users (**Supplementary Table 10**).

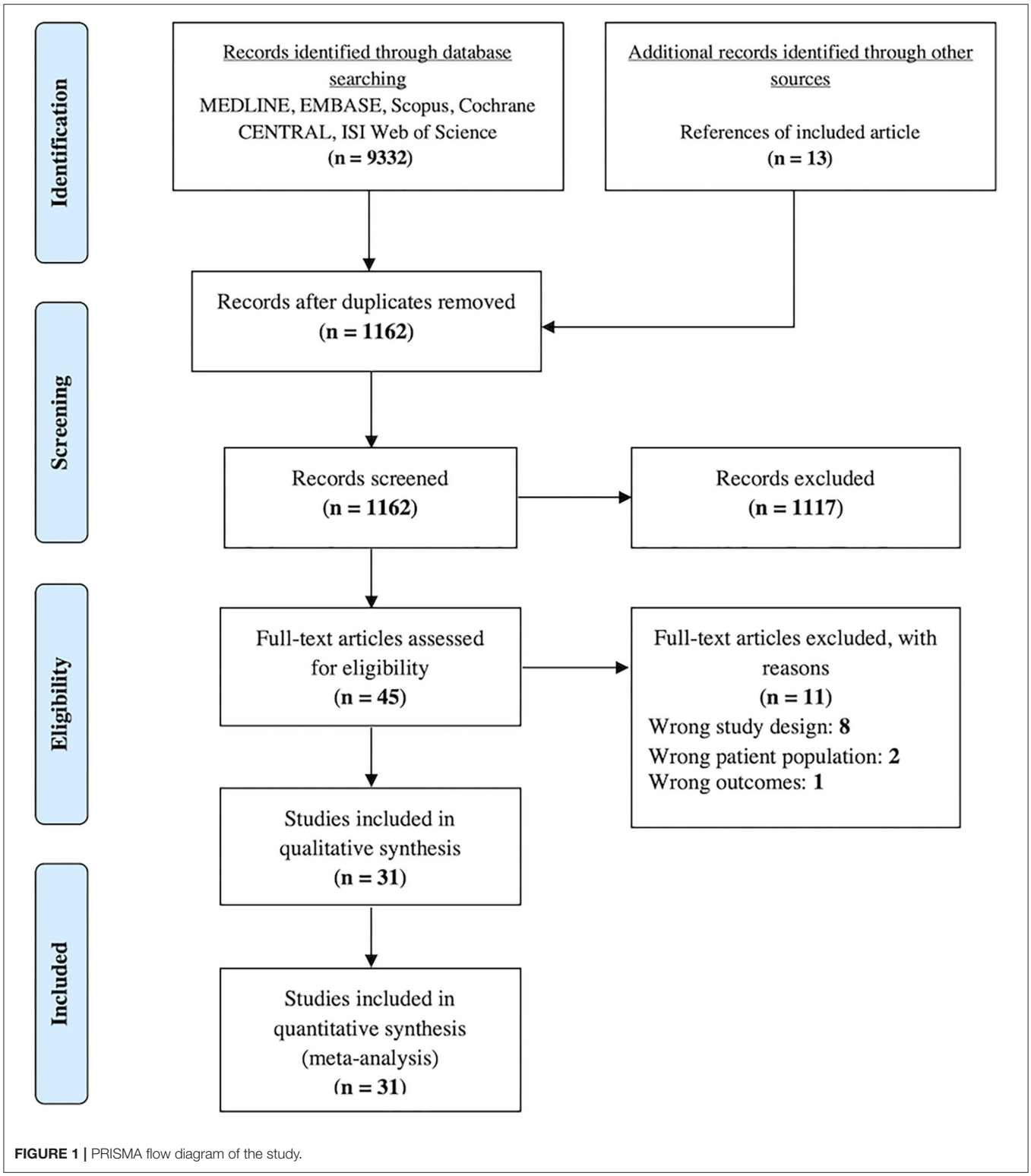

FIGURE 1 | PRISMA flow diagram of the study.

Exploration for Inconsistency and Publication Bias

We found no evidence of global inconsistency in any of the outcomes using the design-by-treatment interaction models (**Supplementary Table 11A**). Furthermore, no substantial inconsistency between direct and indirect comparisons was observed in the side-splitting models (**Supplementary Table 11B**). **Supplementary Figure 4A** shows

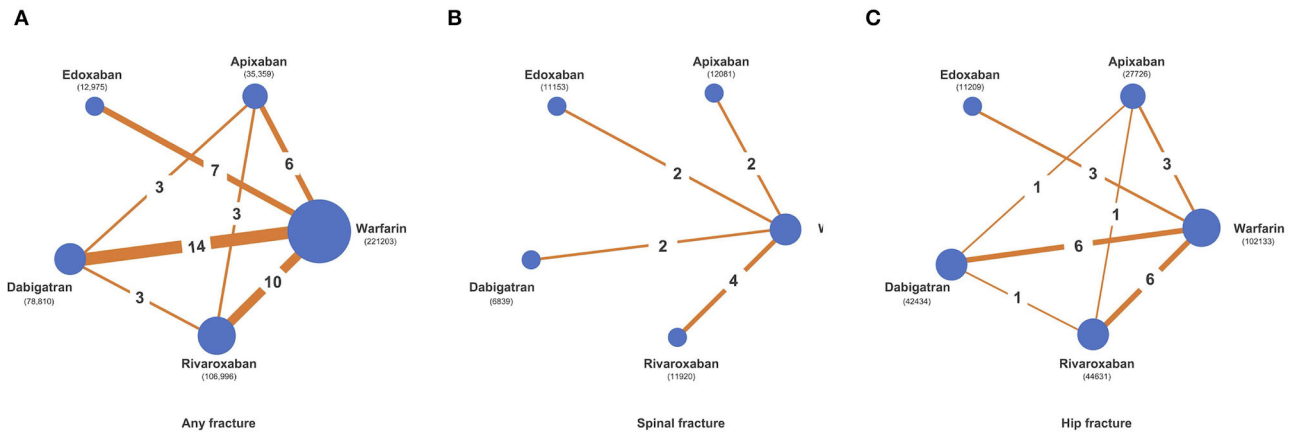

FIGURE 2 | Network diagrams of comparisons of different treatment outcomes in patients receiving warfarin and different direct oral anticoagulants (DOACs). **(A)** Comparisons of all fracture risks in patients receiving warfarin and DOACs. **(B)** Comparisons of spinal fracture risks in patients receiving warfarin and DOACs. **(C)** Comparisons of hip fracture risks in patients receiving warfarin and DOACs.

the comparison-adjusted funnel plots of fracture risks in the included studies, which revealed no significant funnel plot asymmetry. Lastly, the Egger test revealed no evidence of small-study bias (**Supplementary Figure 4A**).

GRADE

We incorporated the GRADE judgments for network estimates of fracture risks. The certainty of evidence for the risk between anticoagulants varied; it was moderate for most of the comparisons involving DOACs against warfarin with regards to risks for any fracture, spine fracture, and hip fracture. The certainty of evidence was mostly moderate to low for the comparisons between different DOACs (**Supplementary Tables 12**, **13A–C**).

DISCUSSION

The current study aimed to identify fracture risks among patients prescribed DOACs and warfarin. The principal findings of this study were that patients who were prescribed apixaban carried the lowest fracture risk, followed by rivaroxaban, edoxaban and dabigatran, compared to patients prescribed warfarin. When assessing future fracture risk, it is crucial to consider both patient medication and medical history, given that 30% of patients presenting with a proximal femoral fracture receive anticoagulation therapy (64). Owens et al. reported that dabigatran, rivaroxaban, and apixaban might be used safely in NVAF patients with specific valvular heart diseases including aortic stenosis, aortic regurgitation, and mitral regurgitation (65). By contrast, patients with moderate to severe mitral stenosis or mechanical valves should continue to receive warfarin, as these patients have routinely been excluded from NVAF clinical trials (65). Furthermore, NVAF or VTE patients may require long-term anticoagulation therapy. Previous studies have reported that long-term exposure to VKAs is associated with an increased risk of fractures (66). These findings could be an important reference for clinicians when evaluation of fracture risk is necessary for patients at high risk of fractures, such as the elderly, who need to be on anticoagulation for NVAF.

As regards DOAC use and fracture risk, the literature remains conflicted. Both Lau et al. and Lutsey et al. report that DOACs carry a lower risk of fractures in patients with NVAF in the US and Hong-Kong, respectively, compared to warfarin (21, 60). However, Lucenteforte et al. find no differences in fracture risk between DOACs and VKA in patients with NVAF in Italy (55). These discrepancies in results may be attributed to heterogeneity of the study populations and the studies' power to detect event rate differences, whereby new RCTs and cohort studies that have since appeared add to our understanding of DOACs, especially those new to us (apixaban). Our systematic review and network meta-analysis evaluated 24 RCTs and seven cohort studies and observed that DOAC use was associated with a 21% risk reduction in reported fractures, compared to patients receiving warfarin.

Physiologically, the difference in fracture risk between DOACs and VKAs may be attributed to pharmacologic bone mineral density. Extensive literature survey reveals that both hip and vertebral fractures are most common among osteoporotic patients (67). VKAs inhibit the carboxylation of vitamin K-dependent bone mineralization proteins, including osteocalcin, matrix Gla protein, and periostin, increasing fracture risk (10, 11, 14, 68). Inhibition of osteocalcin carboxylation reduces adherence to calcium and hydroxyapatite, decreasing bone mineral density (BMD) and increasing the risk of osteoporosis (69). In animal studies, Fusaro et al. determined that among rats administered warfarin, a significant decrease in histomorphometric bone volume and increase in trabecular separation was observed, compared to both Dabigatran and placebo groups (11). In human studies, Rezaieyazdi et al. observed a marked reduction in BMD (g/cm^2) and T-score of the lumbar spine among 70 rheumatic valvular heart disease patients taking warfarin, compared to controls ($P = 0.048$) (12). Warfarin

TABLE 1 | Characteristics of included studies.

References	Country	Study type, LOE	Funding	Diagnosis	Treatment	Dosage or INR/Frequency	Patient number	Fractures N (%)	Female (%)	Age (mean ± SD, or range)
Ezekowitz et al. (33)	Multinational	RCT, I	*Y	≥18 y/o with NVAF	Warfarin	2–3/QD	70	1 (1.43)	15.7	69 ± 8.3
					Dabigatran	50 mg/BID	105	0 (0)	20	70 ± 8.8
					Dabigatran	150 mg/BID	166	0 (0)	18.7	70 ± 8.1
					Dabigatran	300 mg/BID	161	0 (0)	17.4	69.5 ± 8.4
Connolly et al. (34)	Multinational	RCT, I	*Y	≥18 y/o with NVAF, or risk of stroke	Warfarin	2–3/QD	6022	34 (0.56)	36.74	71.6 ± 8.6
					Dabigatran	150 mg/BID	6076	87 (0.71)	36.8	71.5 ± 8.8
					Dabigatran	110 mg/BID	6015	44 (0.73)	35.93	71.4 ± 8.6
Schulman et al. (35)	Multinational	RCT, I	*Y	≥18 y/o with VTE	Warfarin	2–3/QD	1266	2 (0.32)	41.1	54.4 ± 16.2
					Dabigatran	150 mg/BID	1273	4 (0.16)	42	55.0 ± 15.8
U.S. National Library of Medicine (36)	Japan	RCT, I	*Y	≥20 y/o with NVAF	Warfarin	2–3/QD	62	1 (1.61)	8.1	67.4 ± 8.8
					Dabigatran	110 mg/BID	46	0 (0)	21.7	69.9 ± 7.5
					Dabigatran	150 mg/BID	58	0 (0)	8.6	68.3 ± 9.1
Weitz et al. (37)	Multinational	RCT, I	*Y	18–85 y/o with NVAF	Warfarin	NA/QD	250	1 (0.40)	39.6	66.0 ± 8.5
					Edoxaban	30 mg/QD	235	0 (0)	40.4	65.2 ± 8.3
					Edoxaban	30 mg/BID	244	0 (0)	38.5	64.8 ± 8.8
					Edoxaban	60 mg/QD	234	0 (0)	33.8	64.9 ± 8.8
					Edoxaban	60 mg/BID	180	0 (0)	36.7	64.7 ± 9.0
EINSTEIN Investigators et al. (38)	Multinational	RCT, I	*Y	≥18 y/o with VTE	Warfarin + enoxaparin	Warfarin/2–3/QD enoxaparin: Subcutaneous/1 mg/kg/BID	1711	8 (0.47)	43.7	56.4 ± 16.3
					Rivaroxaban	15 mg/BID (for 3 weeks, then 20 mg QD)	1731	6 (0.35)	42.6	55.8 ± 16.4
Chung et al. (39)	Hong Kong South Korea Singapore Taiwan	RCT, I	*Y	18–80 y/o with NVAF	Warfarin	2–3/QD	75	0 (0)	37.3	64.5 ± 9.5
					Edoxaban	30 mg/QD	79	0 (0)	35.4	64.9 ± 9.1
					Edoxaban	60 mg/QD	80	1 (1.25)	31.2	65.9 ± 7.7
Granger et al. (40)	Multinational	RCT, I	*Y	≥18 y/o with NVAF, or risk of stroke	Warfarin	2–3/QD	9052	148 (1.63)	35.0	^70
					Apixaban	2.5 mg or 5 mg/BID	9088	119 (1.30)	35.5	^70

(Continued)

TABLE 1 | Continued

References	Country	Study type, LOE	Funding	Diagnosis	Treatment	Dosage or INR/Frequency	Patient number	Fractures N (%)	Female (%)	Age (mean ± SD, or range)
Patel et al. (41)	Multinational	RCT, I	*Y	≥18 y/o with NVAF, or risk of stroke	Warfarin	2–3/QD	7133	116 (1.63)	39.7	^73
					Rivaroxaban	15 mg or 20 mg/BID	7131	82 (1.15)	39.7	^73
EINSTEIN-PE Investigators et al. (42)	Multinational	RCT, I	*Y	≥18 y/o with PE	Warfarin + enoxaparin	Warfarin/2–3/QD enoxaparin: Subcutaneous/1 mg/kg/BID	2413	9 (0.37)	48.3	57.5 ± 7.2
					Rivaroxaban	15 mg/BID (for 3 weeks, then 20 mg QD)	2419	15 (0.62)	45.9	57.9 ± 7.3
Hori et al. (43)	Japan	RCT, I	*Y	≥20 y/o with NVAF, or risk of stroke	Warfarin	2–3/QD	639	10 (1.56)	21.8	71.2 (43–90)
					Rivaroxaban	15 mg/BID	639	10 (1.56)	17.1	71.0 (34–89)
Hokusai-VTE Investigators et al. (44)	Multinational	RCT, I	*Y	≥18 y/o with PE or DVT	Warfarin	2–3/QD	4122	48 (1.16)	42.8	55.9 ± 16.2
					Edoxaban	60 mg/QD	4118	45 (1.09)	42.7	55.7 ± 16.3
Agnelli et al. (45)	Multinational	RCT, I	*Y	≥18 y/o with PE or DVT	Warfarin + enoxaparin	Warfarin/2–3/QD enoxaparin: Subcutaneous/1 mg/kg/BID	2704	13 (0.48)	40.9	56.7 ± 16.0
					Apixaban	10 mg/BID (for 1 week, then 5 mg BID)	2691	6 (0.22)	41.7	57.2 ± 16.0
Giugliano et al. (46)	Multinational	RCT, I	*Y	≥21 y/o with NVAF or risk of stroke	Warfarin	2–3/QD	7036	240 (3.41)	37.5	^72
					Edoxaban	30 mg/QD	7034	223 (3.17)	38.8	^72
					Edoxaban	60 mg/QD	7035	429 (2.93)	37.9	^72
Schulman et al. (47)	Multinational	RCT, I	*Y	≥18 y/o with PE or DVT	Warfarin	2–3/QD	1426	12 (0.84)	38.9	53.9 ± 15.3
					Dabigatran	150 mg/BID	1430	6 (0.42)	39.1	55.4 ± 15.0
Schulman et al. (48)	Multinational	RCT, I	*Y	≥18 y/o with PE or DVT	Warfarin	2–3/QD	1288	3 (0.23)	39.8	55.1 ± 16.3
					Dabigatran	150 mg/BID	1280	3 (0.23)	39	54.7 ± 16.2
Gibson et al. (49)	Multinational	RCT, I	*Y	≥18 y/o with NVAF and PCI	Warfarin + aspirin + clopidogrel	2–3/QD 75–100 mg/QD 75 mg/QD	706	6 (0.85)	26.6	69.9 ± 8.7

(Continued)

TABLE 1 | Continued

References	Country	Study type, LOE	Funding	Diagnosis	Treatment	Dosage or INR/Frequency	Patient number	Fractures N (%)	Female (%)	Age (mean ± SD, or range)
					Rivaroxaban + aspirin + clopidogrel	2.5 mg /BID 75–100 mg/QD 75 mg/QD	709	2 (0.28)	24.5	70.0 ± 9.1
					Rivaroxaban + clopidogrel	15 mg /QD 75 mg/QD	709	6 (0.85)	25.5	70.4 ± 9.1
Goette et al. (50)	Multinational	RCT, I	*Y	≥18 y/o with NVAF	Warfarin	2–3/QD	1104	0 (0)	35	64.2 ± 10.8
					Edoxaban	60 mg/QD	1095	1 (0.09)	34	64.3 ± 10.3
Piazza et al. (51)	Multinational	RCT, I	*Y	≥18 y/o with DVT	Warfarin	2–3/QD	28	2 (7.14)	25	53.1 ± 12
					Edoxapan	90 mg/QD (for 10 days, then 60 mg QD for 90 days)	56	0 (0)	26.8	55.6 ± 14.1
Bengtson et al. (52)	USA	CS, IIa	Y	Stroke prevention for non-AF	Warfarin	NA	37707	275 (0.73)	38.8	70.8 ± 12.1
					Dabigatran	75 mg or $^{+}$150 mg/NA	18981	108 (0.57)	36.2	68.5 ± 12.3
Calkins et al. (53)	Multinational	RCT, I	*Y	≥18 y/o with NVAF	Warfarin	2–3/QD	318	0 (0)	23	59.3 ± 10.3
					Dabigatran	150 mg/BID	317	0.32	27.4	59.1 ± 10.4
Cannon et al. (54)	Multinational	RCT, I	*Y	≥18 y/o with NVAF and PCI (within previous 120 h)	Warfarin + aspirin + clopidogrel	2–3/QD ≤100 mg/QD 90 mg/BID	981	13 (1.33)	23.5	71.7 ± 8.9
					Dabigatran + clopidogrel or ticagrelor	110 mg/BID 75 mg/QD 90 mg/BID	981	9 (0.92)	25.8	71.5 ± 8.9
					Dabigatran + clopidogrel or ticagrelor	150 mg/BID 75 mg/QD 90 mg/BID	763	6 (0.79)	22.4	68.6 ± 7.7
Lucenteforte et al. (55)	Italy	CS, IIa	Y	Patients with OACs	Warfarin	NA	13091	153 (1.17)	48.29	NA
					DOAC (D, R, A)	NA	3759	41 (1.09)	51.08	
					Direct Xa inhibitor (R,A)	NA	2474	26 (1.05)	51.70	
					Dabigatran	NA	1285	15 (1.16)	49.88	
Norby et al. (56)	USA	CS, IIa	Y	22–99 y/o with NVAF	Warfarin	NA	45496	408 (0.90)	40.1	71.1 ± 12.5
					Rivaroxaban	10 or 15 mg or 20 mg/NA	32495	194 (0.60)	38.7	69.3 ± 12.2
Ezekowitz et al. (57)	Multinational	RCT, I	*Y	≥18 y/o with NVAF within 48 h	Warfarin	2–3/QD	747	0 (0)	33.5	64.5 ± 12.8
					Apixaban	5 mg/BID	753	3 (0.40)	32.9	64.7 ± 12.2

(Continued)

TABLE 1 | Continued

References	Country	Study type, LOE	Funding	Diagnosis	Treatment	Dosage or INR/Frequency	Patient number	Fractures N (%)	Female (%)	Age (mean ± SD, or range)
Hohnloserm et al. (58)	Multinational	RCT, I	*Y	≥18 y/o with NVAF scheduled for first or repeated catheter ablation	Warfarin	2–3/QD	203	0 (0)	26.6	61 (52–67)
					Edoxaban	60 mg/QD	411	1 (0.24)	29.4	60 (53–67)
Ferro et al. (59)	Multinational	RCT, I	*Y	18–78 y/o cerebral venous thrombosis	Warfarin	2–3/QD	60	1 (1.67)	55	45.2 ± 13.8
					Dabigatran	150 mg/BID	60	0 (0)	55	45.2 ± 13.8
Huang et al. (20)	Taiwan	CS, IIa	NA	≥20 y/o with newly NVAF	Warfarin	NA	9707	1009 (10.39)	41.1	71.3 ± 11.5
					DOAC (D, R, A)	NA	9707	737 (7.59)	40.8	72.4 ± 10.7
					Warfarin	NA	5796	660 (11.39)	37.6	73.3 ± 11.2
					Dabigatran	NA	5796	535 (9.23)	36.6	73.6 ± 10.1
					Warfarin	NA	7287	831 (11.40)	42.7	73.2 ± 10.9
					Rivaroxaban	NA	7287	530 (7.27)	42.4	73.9 ± 10.3
					Warfarin	NA	1761	204 (11.58)	42.8	75.1 ± 11.1
					Apixaban	NA	1761	89 (5.05)	42.1	75.0 ± 10.0
Lutsey et al. (60)	USA	CS, IIa	Y	18–99 y/o with NVAF	Warfarin	NA	55826	2829 (5.07)	*W: 38.8 *D: 34.9 *R: 38.1 *A: 39.9	*W:70.2 ± 12.3 *D: 67.0 ± 12.4 *R: 67.7 ± 12.3 *A: 69.1 ± 12.6
					DOACs (D, R, A)	NA	55826	2685 (4.81)		
					Warfarin	NA	31612	1803 (5.70)		
					Dabigatran	75 mg or 150 mg/NA	31612	1764 (5.58)		
					Warfarin	NA	32440	1494 (4.60)		
					Rivaroxaban	10 or 15 mg or 20 mg/NA	32440	1124 (3.46)		
					Warfarin	NA	15645	521 (3.33)		
					Apixaban	2.5 mg or 5 mg/NA	15645	396 (2.53)		
					Dabigatran	75 mg or 150 mg/NA	12572	510 (4.06)		
					Rivaroxaban	10 or 15 mg or 20 mg/NA	12572	543 (4.32)		
					Apixaban	2.5 or 5 mg/NA	16621	401 (2.41)		

(Continued)

TABLE 1 | Continued

References	Country	Study type, LOE	Funding	Diagnosis	Treatment	Dosage or INR/Frequency	Patient number	Fractures N (%)	Female (%)	Age (mean ± SD, or range)
					Rivaroxaban	10 or 1 5mg or 20 mg/NA	16621	394 (2.37)		
					Apixaban	2.5 mg or 5 mg/NA	5112	153 (2.99)		
					Dabigatran	75 mg or 150 mg/NA	5112	160 (3.13)		
Wang et al. (61)	China	CS, IIa	NA	≥60 y/o with DM and NVAF	Warfarin	NA	383	13 (3.39)	45	68.69 ± 5.56
					Rivaroxaban	20 mg/QD	201	1 (0.50)	21	69.52 ± 4.55
Lau et al. (21)	Hong Kong	CS, IIa	Y	NVAF	Warfarin	NA	9541	196 (2.05)	45.2	73.1 ± 11.4
					Dabigatran	NA	6867	95 (1.38)	49.2	74.4 ± 10.0
					Rivaroxaban	NA	3866	57 (1.47)	49.5	75.0 ± 10.3
					Apixaban	NA	3241	53 (1.64)	51.8	77.9 ± 10.3

**Treatment group before characteristic match; $^{+}$: Majority; ^: Median; *Y: funding from pharmaceutical company.*

LOE, Level of evidence according to Halperin et al. (62); CS, cohort study; RCT, randomized controlled trial.

NVAF, non-valvular atrial fibrillation; PE, Pulmonary embolism; VTE, venous thromboembolism; PCI, Percutaneous coronary intervention; QD, Once daily; BID, Twice daily; INR, International normalized ratio; NA, not applicable; N, no; OACs, oral anticoagulants; DOAC, direct oral anticoagulant; D, dabigatran; R, rivaroxaban; A, apixaban; E, edoxaban; y/o, year-old.

use was the only risk factor of significant importance on spinal T-score ($P < 0.03$) (12). These findings support the utility of DOACs in decreasing fractures, compared to VKAs.

Kuo et al. (22) queried the Taiwan National Health Insurance database and reported that among 56,795 patients prescribed DOACs, dabigatran users show a lower incidence of osteoporotic fracture and spine fracture than patients receiving standard-dose rivaroxaban and apixaban. Our findings regarding the lower fracture risk of DOACs compared to warfarin have supported the already favorable clinical efficacy and side effect profiles of DOACs, compared to warfarin. Apixaban is superior to warfarin in the prevention of stroke and systemic embolism. The rates of stroke and ICH are both significantly lower in the ARISTOTLE trial (40). In a meta-analysis of 28 RCTs comparing DOACs with warfarin all DOACs have a higher rate of major GI bleeding, except apixaban (70). Our study findings also showed a statistically significant, lowered risk of fracture for apixaban, compared to warfarin. This lends support to the safety of apixaban use in elderly patients with regard to GI bleeding profiles, especially if these patients are at high risk of fracture.

Although DOACs have been reported to decrease fracture risk with protective bone mineralization properties compared to VKAs, not all fractures pose the same risk; therefore, subgroup analysis of anatomic fracture location is critical. Concerning hip fractures, our study determined that compared to warfarin, all of the DOACs except dabigatran exhibited a decreased hip fracture risk in the following descending order: apixaban, rivaroxaban, and edoxaban. Consistent with our findings, Huang et al. report a statistically significant risk reduction in hip fractures among adult users of DOACs, compared to VKAs, with varying risk reduction rates among the DOACs (63). Further research is required to determine the pharmacological mechanism of apixaban that contributes to fracture risk reduction in comparison to other DOACs.

Unlike osteoporotic hip and spine fractures among the elderly, trauma is typically associated with a high energy mechanism in the younger population with fewer comorbidities that do not require anticoagulation. Our findings showed that when only patients below 65 were included, no significant effect was seen among the DOACs, compared to warfarin. Most current literature focuses on patients with pre-existing comorbidities requiring anticoagulation treatment (71, 72). Second, most NVAF or VTE patients may require long-term anticoagulation therapy, and previous studies have indicated that long-term exposure to VKAs is associated with an increased risk of fractures (69, 73). In our study, we found that long-term DOAC exposure of at least one year also decreased the risk of fractures by 21%, compared to warfarin. Although the fracture types, treatment duration, and patients' sex or age varied among the included studies, the resulting overall robustness was proven by the subgroup analyses. The older female population is already known to be associated with increased fracture risk (74). We found that the female- and male population achieved similar effects when using DOACs to decrease fracture risks. Apixaban had the lowest fracture risks (RR: 0.55; 95% CI: 0.46 to 0.65), compared to warfarin, in the predominantly male studies. When we included only studies with younger patients (aged < 65), no significant effect was

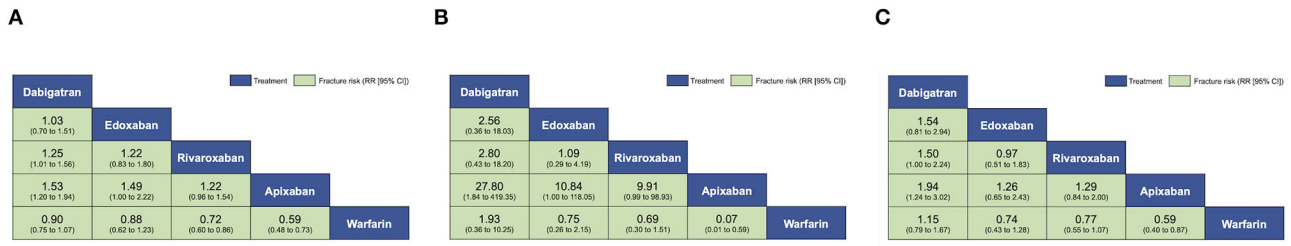

FIGURE 3 | Pooled estimates of the network meta-analysis. Comparisons, column vs. row, should be read from left to right and are ordered relative to overall effectiveness. **(A)** Pooled risk ratios (95% confidence intervals [CI]) for all fractures. **(B)** Pooled risk ratios (95% CI) for spinal fractures. **(C)** Pooled risk ratios (95% CI) for hip fractures.

seen among the DOACs, compared to warfarin, which may be explained by the diminished overall sample size as a result of including only these studies. Most studies evaluated patients older than 65.

To the best of our knowledge, at present, this is the most comprehensive, up-to-date network meta-analysis to analyze the fracture risk among patients receiving DOACs and VKA. However, some limitations must be addressed. It should be noted that there was cohort heterogeneity among the studies. Although over 90% of studies analyzed involved AF patients, some study cohorts included trauma patients who received oral anticoagulation for thromboprophylaxis. Reassuringly, our sensitivity analysis revealed consistent results in patients with varying indications for anticoagulation. It should also be noted that potential confounders, including age, sex, race, and comorbidities, were adjusted for, using propensity score matching to allow for robust, accurate data comparison. Additionally, most studies did not provide BMD data as it rarely was a primary or secondary outcome; therefore, further research is required to quantify the association of oral anticoagulants with measured changes in T-score. Future meta-analyses on individual-level participant data and head-to-head prospective studies will be beneficial to confirm the findings above.

CONCLUSION

In summary, this network meta-analysis demonstrated that apixaban had the lowest pooled fracture risk, compared to other DOACs, and that the four major DOACs had lower fracture risk than warfarin. Similar results were found in sensitivity analyses with lower heterogeneity and inconsistency. These findings might benefit clinical practice for the individualized use of anticoagulants; however, future, large head-to-head prospective studies are required to validate these findings.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

ST, C-WH, S-CS, and L-TK conceived and designed the study, interpreted data, and contributed to the final version of this report. ST and C-WH selected the articles and extracted the data. ST and L-TK analyzed the data. ST, C-WH, and L-TK wrote the draft. ET, OO, DV, WC, and J-RH made critical revisions. All authors agreed with the results and conclusions reported. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.896952/full#supplementary-material

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Risk of cardiovascular disease among different fluoropyrimidine-based chemotherapy regimens as adjuvant treatment for resected colorectal cancer

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Background: Patients with colorectal cancer (CRC) are more likely to develop cardiovascular disease (CVD) than those without cancer. Little is known regarding their CV risk after operative chemotherapy. We aimed to compare the risk of CV disease among different fluoropyrimidine derivatives.

Methods: We assembled a nationwide cohort of patients with newly diagnosed CRC between 2004 and 2015 who received fluoropyrimidine-based adjuvant chemotherapy for resected CRC by linking the Taiwan Cancer Registry (TCR), National Health Insurance Research Database (NHIRD), and Taiwan Death Registry (TDR). All eligible patients were followed from CRC diagnosis (index date) until a CV event, death, loss to follow-up, or December 31st 2018, whichever came first. CV outcomes included acute myocardial infarction (AMI), life-threatening arrhythmia (LTA), congestive heart failure (CHF), and ischemic stroke (IS). We used stabilized inverse probability of treatment weighting using propensity score (SIPTW) to balance all covariates among the three chemotherapy groups: tegafur-uracil (UFT), non-UFT, and mixed. In addition, survival analysis was conducted to examine the association between study outcomes and chemotherapy groups.

Results: From 2004 to 2015, 10,615 (32.8%) patients received UFT alone, 14,511 (44.8%) patients received non-UFT, and 7,224 (22.3%) patients received mixed chemotherapy. After SIPTW, the UFT group had significantly lower all-cause mortality and cancer-related death rates than the other two chemotherapy groups. However, the UFT group had significantly higher rates

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of cancer death, ischemic stroke, and heart failure than those of the other two chemotherapy groups. The UFT group also had a significantly higher AMI rate than the mixed group. There was no significant difference in LTA among the three groups. Similar findings were observed in the subgroup analysis (stage II and age <70 years, stage II and age ≥70 years, stage III and age <70 years, stage III and age ≥70 years) as the overall population was observed.

Conclusion: Higher heart failure and ischemic stroke rates were found in the UFT group than in the other two chemotherapy groups, especially those with stage III CRC and ≥70 years of age. Careful monitoring of this subset of patients when prescribing UFT is warranted.

KEYWORDS

cardiovascular disease, fluoropyrimidine, colorectal cancer, mortality, adjuvant chemotherapy

Introduction

Over the past two decades, early-stage cancer detection and treatment improvements have significantly improved the prognosis of several major cancers, such as colorectal cancer (CRC), prostate cancer, and breast cancer (1). It has been postulated that the population of cancer survivors in the USA will increase to eighteen million by 2022 (2). Within the population of cancer survivors, the awareness of health problems that can occur after cancer survival is increasing. Among these, treatment-related cardiovascular diseases are a major concern (3). The US Surveillance, Epidemiology, and End Results (SEER) study showed that cardiovascular (CV) death was the most common cause of non-cancer deaths among cancer patients in

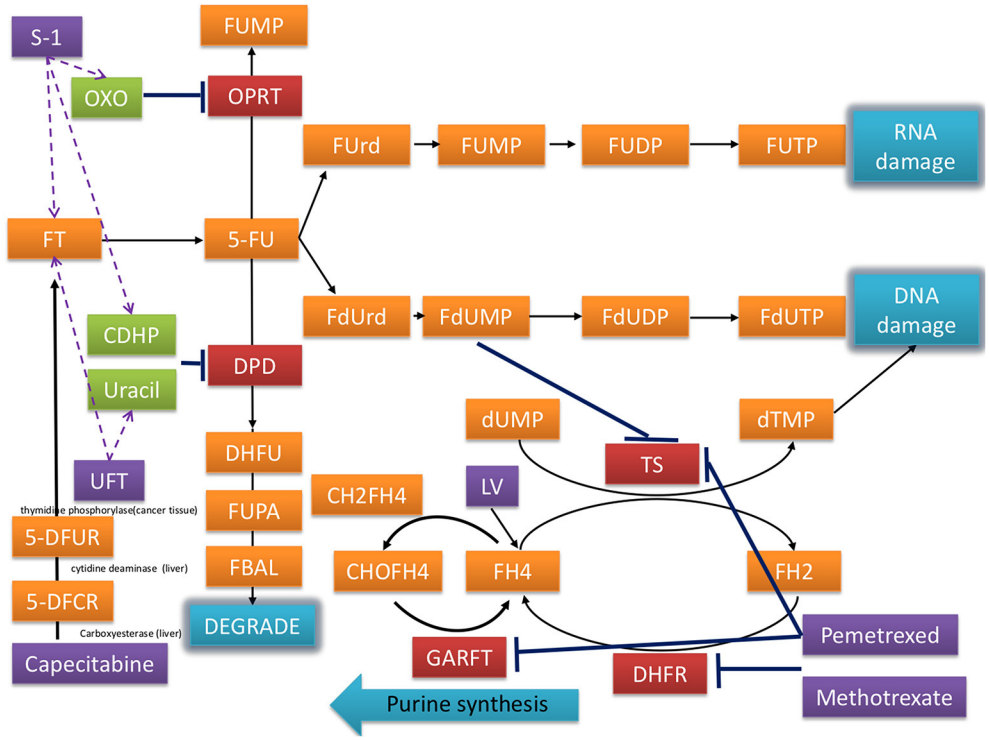

FIGURE 1
Mechanisms of fluorouracil-related medications including UFT, capecitabine, S-1, and others in the treatment of CRC.

1973–2012 (4). One cohort study, with 36,232 2-year survivors from 2000 to 2007 who were followed up until 2012, found that cancer survivors had significantly more CV adverse events than non-cancer controls (5).

Patients with colorectal cancer are more likely to develop cardiovascular disease (CVD) than those without cancer (6). Kenzik et al. conducted a US population-based study to determine the long-term risk of cardiovascular disease (including stroke and myocardial infarction) and congestive heart failure (CHF) in stage I–III CRC survivors aged 65 years. The 10-year cumulative incidence of new-onset cardiovascular disease and CHF was 57.4 and 54.5% for patients with stage I–III CRC compared with 22 and 18% for the matched cohort without cancer, respectively ($p < 0.001$) (7). Correspondingly, a Korean cohort study reported 141 (4.9%) patients who developed new-onset CVD among postoperative CRC patients (8). These studies raised the increasing concern of CV-related adverse events among CRC survivors.

Postoperative chemotherapy is associated with an increased risk of CVD (7, 8). Fluoropyrimidine is the backbone of chemotherapy in the adjuvant setting in patients with CRC. In addition to intravenous 5- fluorouracil (FU), oral fluoropyrimidine including UFT, TS-1 and capecitabine were commonly used in Asian countries (9, 10). While these oral prodrugs were finally metabolized to 5-FU, their adverse events were somewhat different, which may be due to the components of prodrugs (Figure 1). For example, gimeracil (the compoenent of TS-1) and uracil (the component of UFT) inhibit dihydropyrimidine dehydrogenase, which degrades 5-FU, leading to enhance cytotoxic effects.

Notably, exposure to fluoropyrimidine increases the risk of CV in patients with cancer (11). However, whether

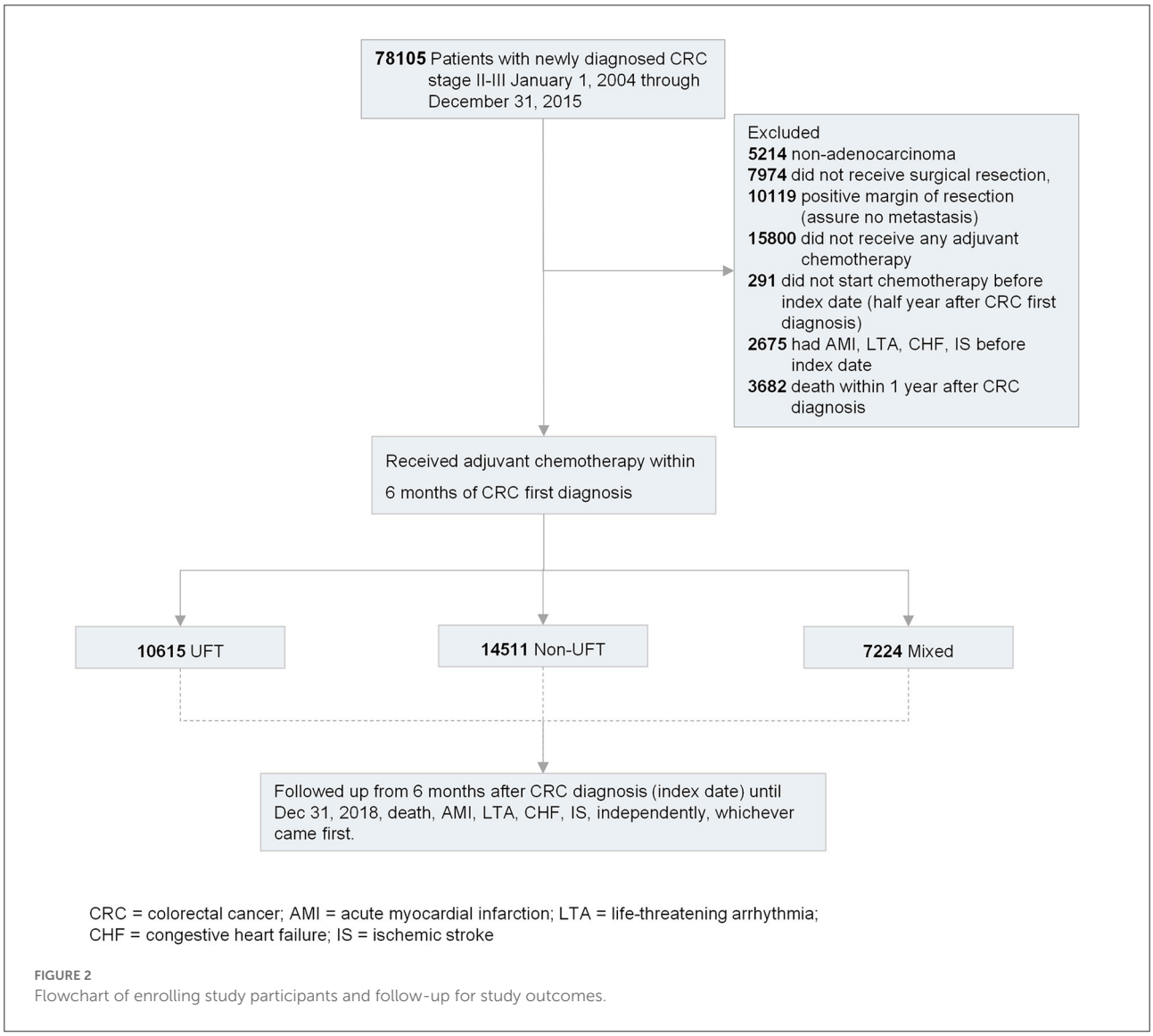

FIGURE 2
Flowchart of enrolling study participants and follow-up for study outcomes.

TABLE 1 Demographic, cancer, comorbidity, and medication characteristics among patients with stage II–III colorectal cancer before SIPTW.

	Before SIPTW			
	UFT ($n = 10,615$)	Non-UFT ($n = 14,511$)	Mixed ($n = 7,224$)	ASMD
Age at diagnosis, years				0.5249
Median (Q1–Q3)	67.72 (12.47)	61.24 (12.24)	62.12 (12.49)	
Mean (SD)	69 (18)	61 (17)	62.5 (18)	
Range	12–99	14–99	17–97	
<50	905 (8.53%)	2,376 (16.37%)	1,134 (15.7%)	0.5075
50–59	1,868 (17.6%)	3,989 (27.49%)	1,824 (25.25%)	
60–69	2,545 (23.98%)	4,182 (28.82%)	2,017 (27.92%)	
≥70	5,297 (49.90%)	3,964 (25.72%)	2,249 (31.13%)	
Gender				0.0127
Men	5,950 (56.05%)	8,225 (56.68%)	4,089 (56.6%)	
Women	4,665 (43.95%)	6,286 (43.32%)	3,135 (43.4%)	
Enrollee category				0.1274
EC1	780 (7.35%)	1,228 (8.46%)	552 (7.64%)	
EC2	2,806 (26.43%)	4,477 (30.85%)	2,105 (29.14%)	
EC3	4,414 (41.58%)	5,686 (39.18%)	3,000 (41.53%)	
EC4	2,615 (24.63%)	3,120 (21.5%)	1,567 (21.69%)	
Income level				0.2410
Dependent (quartile1)	3,771 (35.53%)	4,507 (31.06%)	2,320 (32.12%)	
<15,000 (quartile2)	1,981 (18.66%)	2,415 (16.64%)	1,200 (16.61%)	
15,000–24,999 (quartile3)	3,449 (32.49%)	4,421 (30.47%)	2,327 (32.21%)	
≥25,000 (quartile4)	1,414 (13.32%)	3,168 (21.83%)	1,377 (19.06%)	
Year of diagnosis				0.0870
2004–2006	1,524 (14.36%)	2,472 (17.04%)	1,163 (16.1%)	
2007–2010	3,478 (32.76%)	4,811 (33.15%)	2,396 (33.17%)	
2011–2014	5,613 (52.88%)	7,228 (49.81%)	3,665 (50.73%)	
Primary site				0.1776
Colon	6,442 (60.69%)	9,229 (63.6%)	4,055 (56.13%)	
Rectosigmoid	798 (7.52%)	1,265 (8.72%)	619 (8.57%)	
Rectum	3,375 (31.79%)	4,017 (27.68%)	2,550 (35.3%)	
Stage				0.9657
II	6,980 (65.76%)	2,747 (18.93%)	1,694 (23.45%)	
III	3,606 (33.97%)	11,731 (80.84%)	5,518 (76.38%)	
Unknown	29 (0.27%)	33 (0.23%)	12 (0.17%)	
Grade				0.1589
Well or moderately differentiated	9,564 (90.1%)	12,497 (86.12%)	6,108 (84.55%)	
Poorly differentiated	687 (6.47%)	1,387 (9.56%)	701 (9.7%)	
Unknown	364 (3.43%)	627 (4.32%)	415 (5.74%)	
Primary treatment				0.3264
OP alone	0 (0%)	0 (0%)	0 (0%)	
OP-CCRT	516 (4.86%)	1,010 (6.96%)	576 (7.97%)	
OP-CT	9,230 (86.95%)	11,738 (80.89%)	5,450 (75.44%)	
Neo-CCRT	428 (4.03%)	851 (5.86%)	676 (9.36%)	
Neo-CT	48 (0.45%)	57 (0.39%)	57 (0.79%)	
Unknown + missing	393 (3.7%)	855 (5.89%)	465 (6.44%)	

(Continued)

TABLE 1 Continued

	Before SIPTW			
	UFT ($n = 10,615$)	Non-UFT ($n = 14,511$)	Mixed ($n = 7,224$)	ASMD
Comorbidity				
Hypertension	6,033 (56.83%)	6,747 (46.5%)	3,518 (48.7%)	0.208
Dyslipidemia	3,181 (29.97%)	3,118 (21.49%)	1,688 (23.37%)	0.1949
Coronary artery disease	3,106 (29.26%)	3,571 (24.61%)	1,783 (24.68%)	0.1050
Diabetes mellitus	3,999 (37.67%)	4,904 (33.8%)	2,449 (33.9%)	0.0810
Chronic obstructive pulmonary disease	308 (2.9%)	224 (1.54%)	140 (1.94%)	0.0922
Peripheral arterial disease	810 (7.63%)	718 (4.95%)	397 (5.5%)	0.1107
Chronic kidney disease	2,379 (22.41%)	2,353 (16.22%)	1,246 (17.25%)	0.1575
Atrial fibrillation	529 (4.98%)	400 (2.76%)	193 (2.67%)	0.1207
Moderate or severe liver disease	28 (0.26%)	26 (0.18%)	15 (0.21%)	0.0180
Postdiagnostic medication				
Aspirin	2,107 (19.85%)	2,066 (14.24%)	1,135 (15.71%)	0.1497
Metformin	1,339 (12.61%)	1,562 (10.76%)	777 (10.76%)	0.0579
Statin	1,726 (16.26%)	1,996 (13.76%)	1,023 (14.16%)	0.0702

ASMD, absolute standardized mean difference; EC1, civil servants: full-time or regularly paid personnel with a government or public affiliation; EC2, employees of privately owned institutions; EC3, self-employed individuals, other employees, and members of farmers' or fishermen's associations; EC4, veterans, members of low-income families, and substitute service draftees; CCRT, chemotherapy and radiotherapy; CT, chemotherapy; OP, operation; SIPTW, stabilized inverse probability of treatment weighting using propensity score; UFT, fluoropyrimidine.

fluoropyrimidine derivatives including intravenous 5-FU, capecitabine, and tegafur-uracil (UFT) have a different effect on cardiotoxicity remains unclear. UFT is an oral agent in which uracil competes with dihydropyrimidine dehydrogenase, which reduces the catabolism of 5-FU and its cardiotoxic metabolites. No study has compared UFT with other fluoropyrimidine derivatives concerning their subsequent CVD risk. The Taiwan Cancer Registry (TCR), National Death Registry (NDR), and National Health Insurance Research Database (NHIRD) provide comprehensive and accurate information on the diagnosis, staging, treatment, and survival of cancer patients in Taiwan. Here, we linked the above databases to evaluate the cardiotoxicity of different 5-FU derivatives in the adjuvant setting for patients with CRC.

Methods

Data sources

The data sources for this study included the TCR, NHIRD, and TDR. These three databases are linked with encrypted personal identification numbers and are available at the Health and Welfare Data Center (HWDC). In addition, we obtained approval from the IRB of the Chang Gung Medical Foundation, Taiwan (201901844B0). The need for informed consent was waived because the personal ID had already been encrypted.

Study design

We established a nationwide cohort of patients with newly diagnosed stage II–III CRC in 2004–2015 and received FU-based adjuvant chemotherapy for resection. All eligible patients were followed up from 6 months after the first diagnosis of CRC (index date) until the occurrence of cardiotoxicity (AMI, LTA, CHF, IS, independently), death, and loss to follow-up on December 31st 2018, whichever came first. The index date was set 6 months after CRC first diagnosis because (1) the majority of patients with stage II–III CRC had their tumor removed surgically and started FU-based adjuvant chemotherapy within 6 months after the initial diagnosis of CRC, and (2) all eligible patients were followed equally with the same initial time point to reduce immortal time bias (Figure 2) (12).

The cohort was divided into three adjuvant chemotherapy groups: UFT, non-UFT, and mixed. Patients were excluded if they (1) had non-adenocarcinomatous CRC; (2) did not receive surgical resection; (3) had a positive resection margin; (4) did not receive any adjuvant chemotherapy; (5) did not start chemotherapy before the index date (6 months after initial CRC diagnosis); (6) had AMI, LTA, CHF, or IS before the index date; (7) missing sex and birth year data; and (8) implausible data, such as death before CRC diagnosis or inconsistent initial date of adjuvant chemotherapy in TCR, NHIRD, and TDR (Figure 2).

TABLE 2 Demographic, cancer, comorbidity, and medication characteristics among patients with stage II–III colorectal cancer after SIPTW.

	After sIPTW			
	UFT ($n = 9138.89$)	**Non-UFT ($n = 12773.7$)**	**Mixed ($n = 6367.9$)**	***P*-value**
Age at diagnosis, years				0.0776
Median (Q1–Q3)	64.19 (12.07)	63.24 (12.34)	63.35 (12.43)	
Mean (SD)	65(19)	64(18)	64(18)	
Range	12–99	14–99	17–97	
<50	1,213.11 (12.19%)	1,955.88 (13.9%)	968.85 (13.76%)	0.0972
50–59	2,319.08 (23.3%)	3,378.27 (24.01%)	1,692.20 (24.03%)	
60–69	2,694.03 (27.07%)	3,892.11 (27.66%)	1,929.81 (27.41%)	
≥70	2,912.67 (37.44%)	3,548.44 (34.43%)	1,777.04 (34.80%)	
Gender				0.0084
Men	5,613.07 (56.4%)	7,973.92 (56.67%)	4,000.61 (56.82%)	
Women	4,339.14 (43.6%)	6,097.22 (43.33%)	3,040.73 (43.18%)	
Enrollee category				0.0282
EC1	760.65 (7.64%)	1,091.26 (7.76%)	539.80 (7.67%)	
EC2	2,786.84 (28%)	4,083.52 (29.02%)	2,045.62 (29.05%)	
EC3	4,111.67 (41.31%)	5,758.37 (40.92%)	2,867.40 (40.72%)	
EC4	2,293.05 (23.04%)	3,137.99 (22.3%)	1,588.51 (22.56%)	
Income level				0.0558
Dependent (quartile 1)	3,316.54 (33.32%)	4,578.32 (32.54%)	2,320.54 (32.96%)	
<15,000 (quartile 2)	1,752.40 (17.61%)	2,419.03 (17.19%)	1,212.52 (17.22%)	
15,000–24,999 (quartile 3)	3,139.98 (31.55%)	4,454.99 (31.66%)	2,201.41 (31.26%)	
≥25,000 (quartile 4)	1,743.29 (17.52%)	2,618.80 (18.61%)	1,306.87 (18.56%)	
Year of diagnosis				0.0445
2004–2006	1,634.14 (16.42%)	2,242.34 (15.94%)	1,126.93 (16%)	
2007–2010	3,440.38 (34.57%)	4,661.65 (33.13%)	2,351.83 (33.4%)	
2011–2014	4,877.69 (49.01%)	7,167.14 (50.94%)	3,562.59 (50.6%)	
Primary site				0.0220
Colon	5,986.40 (60.15%)	8,641.89 (61.42%)	4,285.85 (60.87%)	
Rectosigmoid	764.36 (7.68%)	1,160.58 (8.25%)	587.97 (8.35%)	
Rectum	3,201.45 (32.17%)	4,268.67 (30.34%)	2,167.52 (30.78%)	
Stage				0.0627
II	3,678.71 (36.96%)	4,809.89 (34.18%)	2,437.08 (34.61%)	
III	6,250.42 (62.8%)	9,230.41 (65.6%)	4,592.69 (65.22%)	
Unknown	23.08 (0.23%)	30.84 (0.22%)	11.57 (0.16%)	
Grade				0.0583
Well or moderately differentiated	8,702.29 (87.44%)	12,231.23 (86.92%)	6,116.67 (86.87%)	
Poorly differentiated	798.83 (8.03%)	1,232.69 (8.76%)	612.12 (8.69%)	
Unknown	451.09 (4.53%)	607.23 (4.32%)	312.55 (4.44%)	
Primary treatment				0.1472
OP alone	0 (0%)	0 (0%)	0 (0%)	
OP-CCRT	652.58 (6.56%)	925.74 (6.58%)	455.80 (6.47%)	
OP-CT	8,121.55 (81.61%)	11,466.29 (81.49%)	5,742.30 (81.55%)	
Neo-CCRT	612.75 (6.16%)	856.59 (6.09%)	433.28 (6.15%)	
Neo-CT	43.30 (0.44%)	63.41 (0.45%)	34.04 (0.48%)	
Unknown + missing	522.03 (5.25%)	759.11 (5.39%)	375.92 (5.34%)	

(Continued)

TABLE 2 Continued

	After sIPTW			
	UFT ($n = 9138.89$)	Non-UFT ($n = 12773.7$)	Mixed ($n = 6367.9$)	*P*-value
Comorbidity				
Hypertension	5,131.89 (51.57%)	7,078.44 (50.3%)	3,535.89 (50.22%)	0.0270
Dyslipidemia	2,538.28 (25.5%)	3,406.76 (24.21%)	1,734.15 (24.63%)	0.0299
Diabetes mellitus	2,637.37 (26.5%)	3,631.37 (25.81%)	1,821.48 (25.87%)	0.0158
Coronary artery disease	3,461.63 (34.78%)	4,884.72 (34.71%)	2,434.68 (34.58%)	0.0043
Chronic obstructive pulmonary disease	211.47 (2.12%)	264.23 (1.88%)	133.51 (1.9%)	0.0176
Peripheral arterial disease	603.16 (6.06%)	797.19 (5.67%)	413.71 (5.88%)	0.0168
Chronic kidney disease	1,910.97 (19.2%)	2,573.97 (18.29%)	1,290.95 (18.33%)	0.0233
Atrial fibrillation	355.08 (3.57%)	480.38 (3.41%)	218.21 (3.1%)	0.0261
Moderate or severe liver disease	17.50 (0.18%)	21.73 (0.15%)	12.32 (0.17%)	0.0053
Postdiagnostic medication				
Aspirin	1,670.38 (16.78%)	2,263.41 (16.09%)	1,150.93 (16.35%)	0.0189
Metformin	1,117.73 (11.23%)	1,547.76 (11%)	801.37 (11.38%)	0.0121
Statin	1,469.83 (14.77%)	2,038.47 (14.49%)	1,021.51 (14.51%)	0.0080

ASMD, absolute standardized mean difference; EC1, civil servants: full-time or regularly paid personnel with a government or public affiliation; EC2, employees of privately owned institutions; EC3, self-employed individuals, other employees, and members of farmers' or fishermen's associations; EC4, veterans, members of low-income families, and substitute service draftees; CCRT, chemotherapy and radiotherapy; CT, chemotherapy; OP, operation; SIPTW, stabilized inverse probability of treatment weighting using propensity score; UFT, fluoropyrimidine.

Outcomes

The study outcomes were as follows: (1) mortality, all-cause mortality, cancer mortality, CV mortality, and non-CV mortality; and (2) CV events including acute myocardial infarction (AMI), life-threatening arrhythmia (LTA), congestive heart failure (CHF), and ischemic stroke (IS). Furthermore, to reduce misclassification, all CV outcomes had to be the principal diagnosis of hospitalization admission or the first diagnosis through the emergency department based on ICD-9 (until 2015) or ICD-10 (since 2016) (Supplementary Table 1).

Covariates

For demographic characteristics, we obtained age, sex, income level, and enrollment category from the NHIRD. In addition, we obtained the calendar year of CRC diagnosis, primary site, stage, tumor grade, and tumor treatment modality from the TCR for cancer-related characteristics. For comorbidities, we obtained data on hypertension, dyslipidemia, diabetes, coronary artery disease, chronic obstructive pulmonary disease (COPD), peripheral arterial disease, chronic kidney disease, atrial fibrillation, and moderate or severe liver disease from the NHIRD. All comorbidities had to occur 1 year before the first diagnosis of CRC. Regarding CV-related medication, we were confined to metformin, aspirin, and statins, which were prescribed 1 year before the first diagnosis of CRC from the NHIRD (Supplementary Table 1).

Statistical analysis

We first balanced all covariates among the three chemotherapy groups by stabilizing the inverse probability of treatment weighting using the propensity score (SIPTW) (13). The advantage of using SIPTW is obtaining an appropriate estimation of the variance of the main effect (average treatment effect for the population, ATE) and maintaining an adequate type I error by preserving the sample size of the original data. In SIPTW, we used a generalized boosted model (GBM) (14) to compute the propensity score because GBM gives the best performance in various scenarios (additivity and linearity, mild non-additivity and non-linearity, and moderate non-additivity and non-linearity in different weight trimming percentiles) (15), and can be extended to more than two treatment groups (14). The covariates in Table 1 were included in the GBM. Next, the absolute standardized mean difference (ASMD) was used to assess the balance of covariates at baseline (index date) among the three chemotherapy groups. A maximum value of ASMD $\leq$0.1 indicated an insignificant difference in covariates among the three chemotherapy groups (16).

Next, we performed survival analysis [log-rank test in univariate analysis, Cox's proportional hazard model (17) and

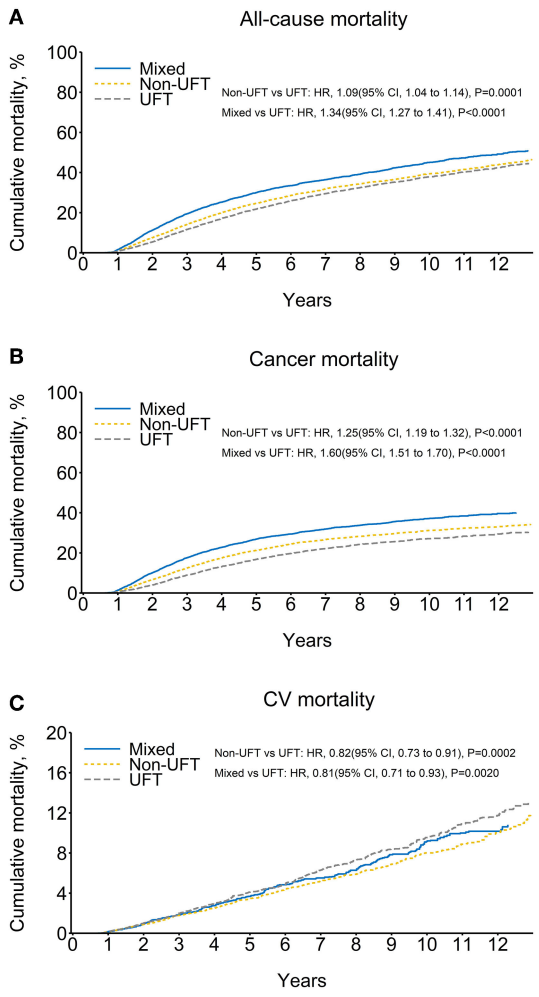

FIGURE 3
Cumulative mortality among patients with stage II–III colorectal cancer, after SIPTW (SIPTW, stabilized inverse probability of treatment weighting using propensity score; UFT, fluoropyrimidine).

cause-specific hazard model (18) in the multivariate analysis] to examine the association between study outcomes and chemotherapy groups. We treated death as a competing risk event in the cause-specific hazard model. In either Cox's or the cause-specific hazard models, chemotherapy (CT) grouping was the only covariate because the three chemotherapy groups were balanced after SIPTW (19). We plotted log {-log[S(t)]} vs. log(t) to check the proportional hazards assumption in the Cox and cause-specific hazard models, where S(t) is the cumulative survival over time t. The lines of the three CT grouping within each plot of log {-log [S(t)]} vs. log(t) were parallel, indicating no violation of proportional hazards (20).

We also performed subgroup analysis to examine whether the differences in study outcomes between the three CT groups were maintained in specific subgroups: stage II and age <70 years, stage II and age ≥70 years, stage III and age <70 years, and stage III and age ≥70 years. For each subgroup analysis, we re-estimated the SIPTW to ensure a balance of covariates across groups.

Results

From 2004 to 2015, 78,105 patients were newly diagnosed with stage II–III CRC. Based on the exclusion criteria, 32,350 patients were eligible for this study. Among these 32,350 patients, 10,615 (32.8%) received UFT alone, 14,511 (44.8%) received non-UFT, and 7,224 (22.3%) received mixed chemotherapy (Figure 2). Before SIPTW, the UFT group was older, had a lower income; had better tumor grade; had a higher proportion of receiving OP-CT; had a higher prevalence of hypertension, coronary artery disease, diabetes, peripheral arterial disease, and COPD; and a higher aspirin prescription rate than those of the other two CT groups (Table 1). After SIPTW, the three CT groups were well-balanced in demographic characteristics, cancer-related characteristics, comorbidities, and CV-related medication (Table 2).

Before SIPTW, there were 3,367, 4,672, and 2,693 all-cause deaths in the UFT, non-UFT, and mixed groups, respectively, equivalent to all-cause mortality of 5.00, 4.95, and 6.14 per 100 person-years. The mixed group had a significantly higher risk of all-cause mortality than the UFT group (HR = 1.24, 95% CI = 1.18–1.30). Cancer was still the leading cause of death, and the cancer death rates per 100 person-years were 3.12, 4.03, 5.11 for the UFT, non-UFT, and mixed groups, respectively. The non-UFT group (HR = 1.36, 95% CI = 1.29–1.43) and the mixed group (HR = 1.70, 95% CI = 1.61–1.81) had significantly more cancer deaths than the UFT group. CV events accounted for 23.5, 12.9, and 12.0% of all-cause deaths, and the CV death rates per 100 person-years were 1.17, 0.64, and 0.74 in the UFT, non-UFT, and mixed groups, respectively. The non-UFT (HR = 0.53, 95% CI = 0.47–0.58) and mixed groups (HR = 0.58, 95% CI = 0.51–0.66) had significantly lower CV death rates than the UFT group (Supplementary Figure 1). After SIPTW, the differences in all-cause mortality, cancer death rate, and CV death rates between the three CT groups were similar to those before SIPTW, except that a significantly higher all-cause mortality was observed in the non-UFT group than in the UFT group (HR = 1.09, 95% CI = 1.04–1.14) (Figure 3; Table 3).

The ischemic stroke had the highest CV outcomes, followed by heart failure, AMI, and life-threatening arrhythmia. The non-UFT and mixed groups had significantly lower ischemic stroke and heart failure rates than those in the UFT group before and after SIPTW. There was no significant difference in life-threatening arrhythmias between the three CT groups before or after SIPTW. The non-UFT group and the mixed group had a significantly lower AMI rate than the UFT group before

TABLE 3 Mortality among patients with stage II–III colorectal cancer before and after SIPTW.

	Before SIPTW			After SIPTW			Before SIPTW		After SIPTW	
	No. of event	Person-years	Incidence rate	No. of event	Person-years	Incidence rate	Hazard ratio	*p*-value	Hazard ratio	*p*-value
All-cause death										
UFT	3,367	67,378.74	5.00 (4.83–5.17)	3,103.3	66,102.60	4.69 (4.53–4.86)	Reference		Reference	
Non-UFT	4,672	94,472.91	4.95 (4.80–5.09)	4,618.13	90,038.84	5.13 (4.98–5.28)	1.00 (0.96–1.04)	0.9505	1.09 (1.04–1.14)	0.0001
Mixed	2,693	43,884.61	6.14 (5.90–6.37)	2,672.06	42,630.69	6.27 (6.03–6.51)	1.24 (1.18–1.30)	<0.0001	1.34 (1.27–1.41)	<0.0001
Cancer death										
UFT	2,099	67,378.74	3.12 (2.98–3.25)	2,134.3	66,102.60	3.23 (3.09–3.37)	Reference		Reference	
Non–UFT	3,804	94,472.91	4.03 (3.90–4.15)	3,608.62	90,038.84	4.01 (3.88–4.14)	1.36 (1.29–1.43)	<0.0001	1.25 (1.19–1.32)	<0.0001
Mixed	2,243	43,884.61	5.11 (4.90–5.32)	2,191.25	42,630.69	5.14 (4.92–5.36)	1.70 (1.61–1.81)	<0.0001	1.60 (1.51–1.70)	<0.0001
CV death										
UFT	790	67,378.74	1.17 (1.09–1.25)	611.78	66,102.60	0.93 (0.85–1.00)	Reference		Reference	
Non-UFT	602	94,472.91	0.64 (0.59–0.69)	700.16	90,038.84	0.78 (0.72–0.84)	0.53 (0.47–0.58)	<0.0001	0.82 (0.73–0.91)	0.0002
Mixed	324	43,884.61	0.74 (0.66–0.82)	348.58	42,630.69	0.82 (0.73–0.90)	0.58 (0.51–0.66)	<0.0001	0.81 (0.71–0.93)	0.0020

CV, cardiovascular; SIPTW, stabilized inverse probability of treatment weighting using propensity score; UFT, fluoropyrimidine; The hazard ratio was obtained using Cox's proportional hazard model and chemotherapy (CT) grouping was the only covariate included because the three CT groups were balanced after SIPTW. () represent then 95% confidence interval.

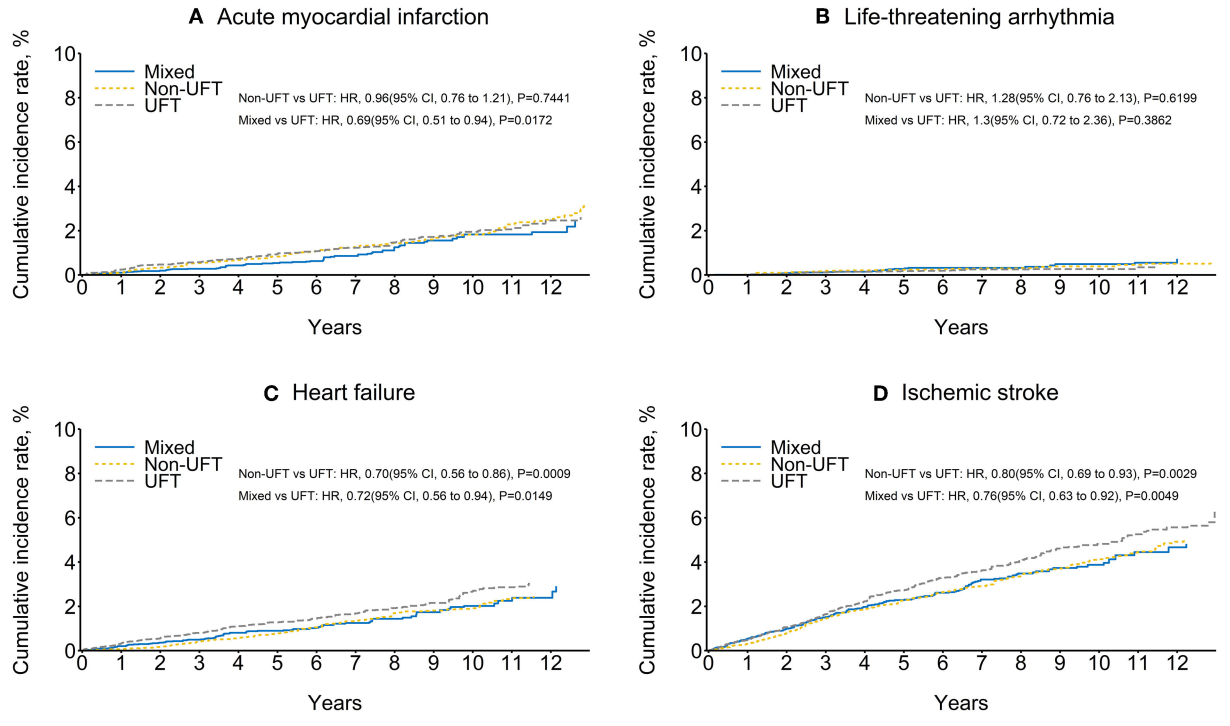

FIGURE 4
Cumulative rate of cardiovascular outcomes among patients with stage II–III colorectal cancer after SIPTW (SIPTW, stabilized inverse probability of treatment weighting using propensity score; UFT, fluoropyrimidine).

TABLE 4 Cardiovascular outcomes among patients with stage II–III colorectal cancer before and after SIPTW.

	Before SIPTW			After SIPTW			Before SIPTW		After SIPTW	
	No. of event	Person years	Incidence rate	No. of event	Person years	Incidence rate	Sub-hazard ratio	*p*-value	Sub-hazard ratio	*p*-value
Acute myocardial infarction										
UFT	155	67,006.37	0.23 (0.19–0.27)	126.42	65,769.99	0.19 (0.16–0.23)	Reference		Reference	
Non-UFT	159	94,001.24	0.17 (0.14–0.20)	170.72	89,569.80	0.19 (0.16–0.22)	0.71 (0.57–0.88)	0.0022	0.96 (0.76–1.21)	0.7441
Mixed	59	43,727.66	0.13 (0.10–0.17)	61.03	42,484.72	0.14 (0.11–0.18)	0.54 (0.40–0.73)	<.0001	0.69 (0.51–0.94)	0.0172
Life–threatening arrhythmia										
UFT	31	67,362.05	0.05 (0.03–0.06)	22.69	66,090.27	0.03 (0.02–0.05)	reference		reference	
Non–UFT	31	94,441.10	0.03 (0.02–0.04)	40.71	89,983.29	0.05 (0.03–0.06)	0.70 (0.42–1.14)	0.1532	1.28 (0.76–2.13)	0.3513
Mixed	21	43,869.56	0.05 (0.03–0.07)	20.71	42,618.10	0.05 (0.03–0.07)	0.97 (0.56–1.68)	0.9026	1.30 (0.72–2.36)	0.3862
Heart failure										
UFT	231	66,884.73	0.35 (0.30–0.39)	167.52	65,759.45	0.25 (0.22–0.29)	Reference		Reference	
Non–UFT	145	94,122.35	0.15 (0.13–0.18)	163.86	89,682.55	0.18 (0.15–0.21)	0.44 (0.35–0.54)	<0.0001	0.70 (0.56–0.86)	0.0009
Mixed	81	43,708.12	0.19 (0.14–0.23)	84.86	42,446.16	0.20 (0.16–0.24)	0.50 (0.39–0.64)	<0.0001	0.72 (0.56–0.94)	0.0149
Ischemic stroke										
UFT	418	65,992.73	0.63 (0.57–0.69)	336.67	64,953.99	0.52 (0.46–0.57)	Reference		Reference	
Non–UFT	330	93,334.74	0.35 (0.32–0.39)	380.88	88,775.08	0.43 (0.39–0.47)	0.55 (0.48–0.64)	<0.0001	0.80 (0.69–0.93)	0.0029
Mixed	164	43,223.62	0.38 (0.32–0.44)	182.89	41,914.30	0.44 (0.37–0.50)	0.56 (0.47–0.67)	<0.0001	0.77 (0.64–0.92)	0.0049

SIPTW, stabilized inverse probability of treatment weighting using propensity score; UFT, fluoropyrimidine; The sub-hazard ratio was obtained using the cause-specific hazard models and chemotherapy (CT) grouping was the only covariate included because the three CT groups were balanced after SIPTW. () represent then 95% confidence interval.

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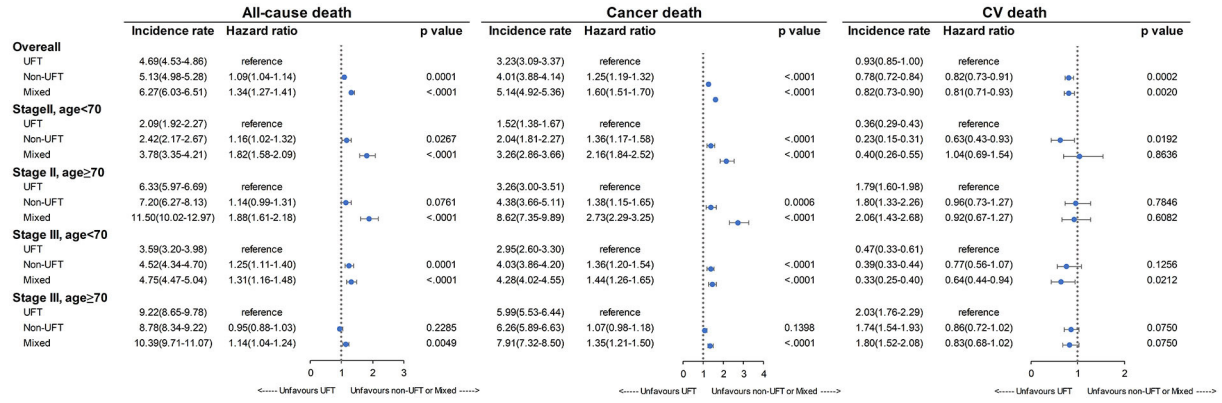

FIGURE 5
Mortality rate among patients with stage II–III colorectal cancer after SIPTW subgroup analysis (SIPTW, stabilized inverse probability of treatment weighting using propensity score; UFT, fluoropyrimidine).

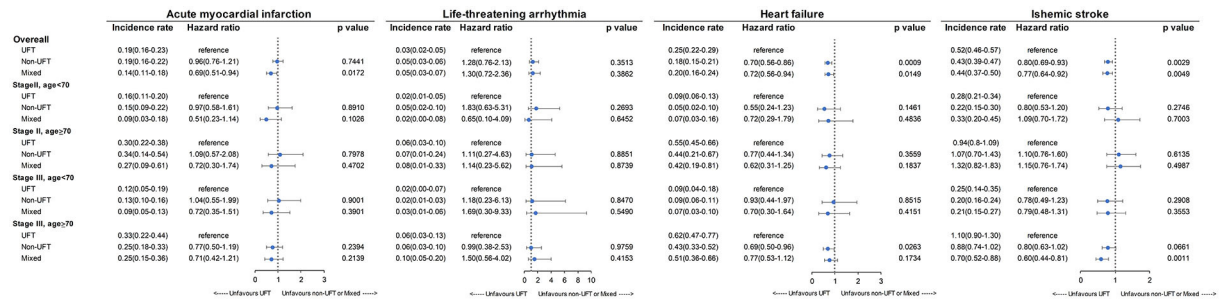

FIGURE 6
Incidence rate of cardiovascular outcomes among patients with stage II–III colorectal cancer after SIPTW subgroup analysis (SIPTW, stabilized inverse probability of treatment weighting using propensity score; UFT, fluoropyrimidine).

SIPTW (Supplementary Figure 2), but the difference was non-significant between the non-UFT and UFT groups after SIPTW (HR = 0.96, 95% CI = 0.76–1.21) (Figure 4; Table 4).

Figure 5 presents the mortality results of subgroup analysis for stage II and age <70 years, stage II and age ≥70 years, stage III and age <70 years, and stage III and age ≥70 years. Again, the UFT group had significantly lower all-cause and cancer mortality rates than the other two CT groups, except for stage III and age ≥70 years and the non-UFT users in the group of stage II and age ≥70 years ($p = 0.0761$). In contrast, the UFT group had higher CV mortality than the non-UFT group and reached significance in the stage II and age <70 years subgroup.

Figure 6 presents the CV outcomes of subgroup analysis for stage II and age <70 years, stage II and age ≥70 years, stage III and age <70 years, and stage III and age ≥70 years. There was no significant difference among the three CT groups for the four subgroup analyses for AMI, LTA, heart failure, and ischemic stroke, except for the following: the UFT group had a significantly higher heart failure rate than the non-UFT groups in those with stage III and age ≥70 years ($p = 0.0263$). However, for ischemic stroke, a marginally higher rate in the UFT group than in the non-UFT group was seen only in those with stage III disease and aged ≥70 years ($p = 0.0661$).

Discussion

Although the survival benefit of adjuvant chemotherapy in patients with high-risk stage II or III CRC is generally accepted (21–23), cardiotoxicity from 5-FU derivatives may compromise the quality of life and overall survival. Therefore, this study explored the association between cardiotoxicity and fluoropyrimidine-based adjuvant chemotherapy in CRC patients. Mechanistically, two hypotheses of 5-FU-related cardiotoxicity included (1) dihydropyrimidine dehydrogenase (DPD) downstream metabolites and (2) 5-FU direct injury to endothelial cells (24).

First, oral fluoropyrimidines, including TS-1 and UFT, may affect the risk of cardiotoxicity by regulating DPD enzymes.

DPD enzyme activity related to cardiotoxicity has been reported previously (25). The downstream metabolites are fluoroacetate and F-citrate, which have been related to potent cardiotoxicity in previous studies (26, 27). Second, according to our hypothesis, UFT, an adjuvant chemotherapeutic agent, inhibits DPD with uracil and may decrease CV events. However, our results did not support this hypothesis.

Second, 5-FU can directly damage endothelial cells, causing vasoconstriction and thromboembolism. Previous studies have reported that continuous intravenous injection (2–18%) is more likely to induce cardiotoxicity than a bolus regimen (1.6–3.0%) (28, 29). Another oral prodrug, capecitabine, is 5.9% in cardiotoxicity (30). Therefore, prodrug or continuous intravenous injection may prolong 5-FU toxic exposure, inducing more endothelial cell damage. UFT was a prodrug that increased 5-FU toxicity exposure time in our study. Our results revealed a continuing need for a mechanism of cardiotoxicity induced by metabolites in this pathway. Much more also needs to be known about the role of uracil and DPD in cardiotoxicity. Future work will hopefully clarify the mechanism of 5-FU-induced cardiotoxicity.

Several studies have examined the association between 5-FU-based adjuvant chemotherapy and cardiotoxicity. However, there are no retrospective studies on a large number of patients with CRC comparing different 5-FU-based adjuvant chemotherapy regimens. Our study took steps to compare different regimens in a nationwide cohort. UFT did not decrease the possibility of induced cardiotoxicity. Oral UFT, the most common and clinically prescribed drug in outpatients, may be associated with a higher likelihood of CV events. Further surveys of heart function should be considered before UFT use, especially in older adults and advanced-stage disease.

The first limitation of our study is selection bias. Oncologists may consider performance status and, therefore, prescribe different 5-FU derivatives. In addition, higher comorbidities were noted in the UFT group. Patients in poor condition may prefer oral UFT. Another limitation is that potential confounders were not recorded in the Taiwan's National Health Insurance Research Database. Individual demographic and lifestyle factors, including performance status, BMI, smoking, and exercise activity, may be associated with the development of CV events. Lastly, we did not have data of UFT or other FU dose for further analysis of dose-event relationship.

Conclusion

In conclusion, UFT use was associated with a higher CV events and deaths rate than adjuvant chemotherapy-induced cardiotoxicity. Specifically, the subgroup analysis revealed higher CV events in the UFT group, older patients, and stage III patients. The present study provides the first comparative analysis of cardiotoxicity between UFT and other 5-FU derivatives. Our results suggest that caregivers should be alert to UFT use in older patients with multiple comorbidities. Further research is needed to develop a risk prediction tool to stratify patients and guide the choice of 5-FU regimens accordingly.

Data availability statement

We used the Taiwan Cancer Registry, National Health Insurance Research Database Taiwan, Taiwan Death Registry, which are only available in the Health and Welfare Data Science Center, Taiwan. We cannot make our research data available, accessible, discoverable, and usable.

Ethics statement

The study was approved by the Institutional Review Board of the Chang Gung Medical Foundation (201901844B0). Informed consent was waived because all personal identification information was encrypted.

Author contributions

W-KH, W-PH, and L-CS contributed to the conceptualization and drafted the manuscript. W-KH, W-PH, H-CH, and L-CS designed this study. S-HC and L-CS performed data curation. S-HC, W-KH, and L-CS performed formal analyses. W-KH, H-CH, W-CC, and S-HC are involved in the resources and software development. D-YC, W-CC, P-HC, T-SY, and J-SC contributed to project administration. L-CS was responsible for the funding acquisition. W-KH, W-PH, H-CH, S-HC, D-YC, W-CC, P-HC, J-SC, T-SY, and L-CS contributed to the review and editing of this manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.880956/full#supplementary-material

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Electrocardiographic changes associated with SGLT2 inhibitors and non-SGLT2 inhibitors: A multi-center retrospective study

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Background: Sodium-glucose co-transporter 2 (SGLT2) inhibitors has been shown with cardiovascular benefit in type 2 diabetes mellitus (T2DM) patients. However, its osmotic diuresis still concern physicians who may look for possible electrolyte imbalance. We therefore aimed to investigate electrocardiographic (ECG) changes associated with SGLT2 inhibitors.

Methods: Electronic medical records from Chang Gung Research Database between January 1, 2001 and January 31, 2019 were searched for patients with ECG reports and patients on an oral hypoglycemic agent (OHA). We then separate these T2DM patients with EKG into those taking either SGLT2 inhibitors or non-SGLT2 inhibitors. We excluded patients with OHA use < 28 days, age < 18 years, baseline ECG QTc > 500 ms, and ECG showing atrial fibrillation or atrial flutter. Propensity score matching (PSM) was performed between groups by age, sex, comorbidities, and medications (including QT prolonging medications). Conditional logistic regression and Firth's logistic regression for rare events were employed to compare the difference between SGLT2 and non-SGLT2 inhibitor patients.

Results: After exclusion criteria and PSM, there remained 1,056 patients with ECG on SGLT2 inhibitors and 2,119 patients with ECG on non-SGLT2 inhibitors in the study. There were no differences in PR intervals, QT prolongations by Bazett's or Fridericia's formulas, new onset ST-T changes, new onset CRBBB or CLBBB, and ventricular arrhythmia between the group of patients on SGLT2 inhibitors and the group of patients on non-SGLT2 inhibitors. There were no differences between the two groups in terms of cardiovascular death and

sudden cardiac death. In addition, there were no differences between the two groups in terms of electrolytes.

Conclusions: Compared with T2DM patients on non-SGLT2 inhibitors, there were no differences in PR interval, QT interval, ST-T changes, bundle-branch block, or ventricular arrhythmia in the patients on SGLT2 inhibitors. There were no differences in cardiovascular mortality between these two groups. In addition, there were no electrolyte differences between groups. SGLT2 inhibitors appeared to be well-tolerated in terms of cardiovascular safety.

KEYWORDS

type 2 diabetes mellitus, sodium-glucose co-transporter 2 (SGLT 2) inhibitors, electrocardiogram, QT prolongation, outcome

Introduction

Patients with type 2 diabetes mellitus (T2DM) have increased risks of atherosclerosis and are predisposed to cardiovascular events. Appropriate treatment of diabetes, therefore, does not only hinge on lowering serum glucose level but also drugs that can effectively decrease cardiovascular morbidity and mortality in diabetic patients.

The introduction of sodium-glucose co-transporter-2 (SGLT2) inhibitors as the latest category of antidiabetic agents was evidenced by successful clinical trials of EMPAG-REG, DECLARE-TIMI 58, CANVAS, showing a reduction of major cardiovascular events in patients with T2DM (1–3). The DAPA-Heart Failure (HF) trial published shortly after, showed that the use of dapagliflozin also resulted in decreased hospitalization for HF in patients with reduced ejection fraction, regardless of the presence or absence of diabetes (4).

The versatility of SGLT2 inhibitors, derived their benefits from inhibition of glucose reabsorption from proximal convoluted tubules in kidney and the additional diuresis effect. Within extracellular fluid, the SGLT2 inhibitor causes a 200% interstitial fluid volume reduction compared to plasma volume, while traditional diuretics such as furosemide results in a 78% reduction (5). Therefore, the pharmacologic action of osmotic diuresis by SGLT2 inhibition leads to greater electrolyte-free water clearance from interstitial fluid space than from the circulation, causing relief in congestion, with minimal impact on plasma volume. By reducing interstitial fluid volume greater than plasma volume, the SGLT2 inhibitor provides better control of congestion with minimal impact on arterial filling and perfusion. The natriuresis by SGLT2 inhibition also increases 30% to 60% urinary sodium excretion and 300 mL urine volume per day: equivalent to an approximately 7% reduction in plasma volume after 3 months of treatment (6). SGLT2 inhibitor's osmotic diuresis and natriuresis uniformly reduce body fluid volume to relieve congestion, with minimal impact on blood volume and diminished ECF reduction effect in patients without extracellular fluid retention.

The beneficial effects and increased use of SGLT2 inhibitors are not without concerns, including the rare but serious complication of diabetic ketoacidosis, bone fracture, amputation, and electrolyte imbalance (7). Previously investigators have raised concerns over SGLT2 inhibitors with its sodium inhibition, diuresis, and consequent disturbance of electrolyte balance (8). Through small studies in healthy volunteers, use of dapagliflozin and empagliflozin were reported to not be associated with QT interval prolongations (9, 10). However, whether the same findings may hold true for patients with T2DM using SGLT2 inhibitors are not known. Therefore, in this study we aimed to investigate the QT prolongations in patients using SGLT2 inhibitors.

Abbreviations: AVB, atrioventricular block; CLBBB, complete left bundle branch block; CRBBB, complete right bundle branch block; ECG, electrocardiogram; HF, heart failure; OHA, oral hypoglycemic agent; SGLT2, sodium-glucose co-transporter-2; T2DM, type 2 diabetes mellitus.

Methods

Data source

In this retrospective cohort study, patient data were obtained from the largest health-care provider in Taiwan, Chang Gung Memorial Hospital System, comprising three tertiary-care medical centers and four major teaching hospitals (11–14). The health care provider has more than 10,000 beds and admits more than 280,000 patients servicing approximately one-tenth of the Taiwanese population each year. The hospital identification number of each patient was encrypted and de-identified to protect their privacy. Therefore, informed consent was waived for this study. The diagnosis and laboratory data could be linked and continuously monitored using consistent data encryption. The institutional review board of Chang Gung Memorial Hospital approved the study protocol (IRB No. 202001017B0).

Study patients

By searching electronic medical records from the Chang Gung Research Database (CGRD) between January 1, 2001 and January 31, 2019, we retrieved patient records with electrocardiogram (ECG). We excluded patients with repeated ECG on the same date, had ECG only once, ECG linked to no or multiple hospital identification, and patients not on oral hypoglycemic agent (OHA) or on insulin. We then separate these patients with T2DM and records of ECG into either the group on SGLT2 inhibitors or the group on non-SGLT2 inhibitors. Within each group, we excluded patients that had OHA use $<$ 28 days, age $<$ 18 years, no ECG prior, during, after OHA use, baseline ECG QTc $>$500 ms, and ECG showing atrial fibrillation or atrial flutter. Propensity score matching was performed between groups by age, sex, comorbidities, and medications (including QT prolonging medications) (Figure 1). The patients with T2DM enrolled, therefore, had at least 28 days of use of OHA, and we compared the ECGs prior to the use and after the use of OHA such that the first ECG was performed within 1 year prior to the use of OHA and second ECG was performed during the use of OHA (Figure 2).

Covariate and study outcomes

Disease was detected using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) and 10th Revision (ICD-10-CM) codes. Covariates included age, sex, diabetes duration, comorbidity, medications, laboratory data, and follow-up years (Table 1). The comorbidity was defined as having two outpatient diagnoses or one inpatient diagnosis in the previous year. Most diagnostic codes of these comorbidities have been validated in previous national database studies. Usage of medication was retrieved based on claim data in the previous year.

Outcomes of primary interest included PR interval, atrioventricular block (AVB), QT prolongation (Bazett), QT prolongation (Fridericia), new onset ST-T changes, new onset complete right bundle branch block (CRBBB) or complete left bundle branch block (CLBBB), ventricular arrhythmia, and cardiovascular mortality. There are four formulae to correct the QT interval, namely Bazett, Fridericia, Framingham, and Hodges, of which Bazett is the most commonly used and Fridericia is the recommended one in the context of the introduction of new drugs:

$$\textit{Bazett formula: } \mathrm{QTc} = \frac{QT}{\sqrt{RR}}$$

$$\textit{Fridericia formula: } \mathrm{QTc} = \frac{QT}{\sqrt[3]{RR}}$$

Each patient was followed until the day of outcome occurrence, date of death or December 31, 2021, whichever came first.

Statistical analysis

To reduce the potential confounding when comparing outcomes between the study groups (patients on SGLT2 inhibitors vs patients on non-SGLT2 inhibitors), propensity score matching was performed to reduce bias between groups, and the covariates are listed in Table 1. The conditional logistic regression was employed to compare the difference of outcome events between SGLT2 and non-SGLT2 inhibitor group. Moreover, because some outcomes were rare events, the Firth's bias reduction method (sub-type of logistic regression) (15) were used for rare events outcomes. A P value $<$ 0.05 was considered to be statistically significant. No adjustment of multiple testing (multiplicity) was made in this study. All statistical analyses were performed using commercial software (SAS 9.4, SAS Institute, Cary, NC).

Results

Study population

There were 2,336,972 patient records retrieved with hospital records of ECG between January 1, 2001 and January 31, 2019. After excluding patients with repeated ECG on the same date, had ECG only once, ECG linked to no or multiple hospital identification, and patients not on OHA or on insulin, there were 159,453 patients with ECG on OHA. Since SGLT2 inhibitors became available in Taiwan on May 1, 2016, we identified 21,523 patients with ECG on SGLT inhibitors and 137,930 patients with ECG on non-SGLT2 inhibitors between May 1, 2016 and January 31, 2019. We further excluded patients that had OHA use $<$ 28 days, no follow-up ECG, age $<$ 18 years, no ECG prior, during, after OHA use, baseline ECG QTc $>$ 500 ms, atrial fibrillation or atrial flutter within each group, and there were 1,170 patients with ECG on SGLT2 inhibitors and 6,236 patients with non-SGLT2 inhibitors. Using 1:2 propensity score matching by age, sex, comorbidities, and medications (including QT prolonging medications), there remained 1,075 patients with ECG on SGLT2 inhibitors and 2,150 patients with ECG on non-SLGT2 inhibitors in the study (Figure 1). Mean diabetes duration of patients on SGLT2 inhibitors was 7.98 $\pm$ 5.26 years, and mean diabetes duration of patients on non-SGLT2 inhibitor was 6.75 $\pm$ 5.26 years. Mean follow-up of patients on SGLT2 inhibitor was 1.62 $\pm$ 0.78 years and mean follow-up of patients on non-SLGT2 inhibitor was 2.11 $\pm$ 0.79 years (Table 1).

TABLE 1 Clinical characteristics of study population.

Variable	Before propensity score matching		After propensity score matching		
	SGLT2 inhibitors (n = 1,170) n, %	Non-SGLT2 inhibitors (n = 6,236) n, %	SGLT2 inhibitors (n = 1,056) n, %	Non-SGLT2 inhibitors (n = 2,119) n, %	*p*-value
Age, years	62.54 ± 10.37	66.79 ± 12.24	63.40 ± 10.11	63.69 ± 11.71	0.4589
Male	776 (66.32)	3362 (53.91)	673 (63.73)	1332 (62.86)	0.6316
Diabetes duration, year	7.74 ± 5.3	7.38 ± 5.4	7.98 ± 5.25	6.75 ± 5.25	<0.0001
Comorbidity (n, %)					
Hypertension	875 (74.79)	4619 (74.07)	787 (74.53)	1611 (76.03)	875 (74.79)
Hyperlipidemia	781 (66.75)	3575 (57.33)	704 (66.67)	1413 (66.68)	781 (66.75)
Coronary artery disease	517 (44.19)	1819 (29.17)	423 (40.06)	816 (38.51)	517 (44.19)
Myocardial infarction	391 (33.42)	1247 (20)	310 (29.36)	576 (27.18)	391 (33.42)
Ischemic stroke	50 (4.27)	488 (7.83)	47 (4.45)	90 (4.25)	50 (4.27)
Peripheral artery disease	11 (0.94)	167 (2.68)	11 (1.04)	18 (0.85)	11 (0.94)
Heart Failure	156 (13.33)	702 (11.26)	127 (12.03)	228 (10.76)	156 (13.33)
Atrial fibrillation	26 (2.22)	195 (3.13)	25 (2.37)	48 (2.27)	26 (2.22)
Chronic kidney disease	33 (2.82)	756 (12.12)	31 (2.94)	56 (2.64)	33 (2.82)
Malignancy	124 (10.6)	1213 (19.45)	118 (11.17)	229 (10.81)	124 (10.6)
Medication (n, %)					
QT prolonging agents	428 (36.58)	3650 (58.53)	406 (38.45)	826 (38.98)	0.7712
Alprazolam	116 (9.91)	934 (14.98)	112 (10.61)	227 (10.71)	0.9270
Amiodarone	41 (3.5)	266 (4.27)	40 (3.79)	66 (3.11)	0.3198
Amitriptyline	22 (1.88)	220 (3.53)	21 (1.99)	54 (2.55)	0.3278
Aripiprazole	4 (0.34)	36 (0.58)	4 (0.38)	10 (0.47)	1.0000[a]
Chlorpromazine	5 (0.43)	76 (1.22)	4 (0.38)	15 (0.71)	0.2573
Ciprofloxacin	21 (1.79)	559 (8.96)	21 (1.99)	108 (5.1)	<0.0001
Clozapine	0 (0)	7 (0.11)	0 (0)	3 (0.14)	05553[a]
Dexmedetomidine	3 (0.26)	26 (0.42)	3 (0.28)	5 (0.24)	0.7261[a]
Donepezil	7 (0.6)	92 (1.48)	6 (0.57)	21 (0.99)	0.2215
Dronedarone	5 (0.43)	40 (0.64)	5 (0.47)	7 (0.33)	0.5483[a]
Escitalopram	11 (0.94)	135 (2.16)	11 (1.04)	34 (1.6)	0.2062
Flecainide	13 (1.11)	57 (0.91)	13 (1.23)	13 (0.61)	0.0689
Furosemide	181 (15.47)	1856 (29.76)	164 (15.53)	380 (17.93)	0.0905
Fluconazole	9 (0.77)	141 (2.26)	9 (100)	26 (1.23)	<0.0001[a]
Levetiracetam	9 (0.77)	117 (1.88)	9 (0.85)	11 (0.52)	0.2636
Levofloxacin	2 (0.17)	781 (12.52)	2 (0.19)	130 (6.13)	<0.0001
Lithium	43 (3.68)	9 (0.14)	42 (3.98)	4 (0.19)	<0.0001
Metoclopramide	2 (0.17)	1568 (25.14)	2 (0.19)	315 (14.87)	<0.0001
Mirtazapine	101 (8.63)	84 (1.35)	94 (8.9)	19 (0.9)	<0.0001
Olanzapine	0 (0)	35 (0.56)	0 (0)	6 (0.28)	0.1874[a]
Ondansetron	4 (0.34)	250 (4.01)	4 (0.38)	49 (2.31)	<0.0001
Phenobarbital	26 (2.22)	0 (0)	26 (2.46)	0 (0)	<0.0001
Risperidone	0 (0)	65 (1.04)	0 (0)	11 (0.52)	0.0202[a]
Venlafaxine	1 (0.09)	41 (0.66)	1 (0.09)	10 (0.47)	0.1134[a]
Ziprasidone	2 (0.17)	3 (0.05)	2 (0.19)	1 (0.05)	0.2582[a]
ACEI or ARB	753 (64.36)	3699 (59.32)	667 (63.16)	1351 (63.76)	0.7433
ARNI	35 (2.99)	59 (0.95)	14 (1.33)	37 (1.75)	0.3747

(Continued)

TABLE 1 (Continued)

Variable	Before propensity score matching		After propensity score matching		
	SGLT2 inhibitors (n = 1,170) n, %	Non-SGLT2 inhibitors (n = 6,236) n, %	SGLT2 inhibitors (n = 1,056) n, %	Non-SGLT2 inhibitors (n = 2,119) n, %	*p*-value
Beta-blockers	725 (61.97)	3579 (57.39)	632 (59.85)	1272 (60.03)	0.9224
Dihydropyridine CCB	71 (6.07)	496 (7.95)	69 (6.53)	126 (5.95)	0.5157
Non-dihydropyridine CCB	73 (6.24)	522 (8.37)	71 (6.72)	130 (6.13)	0.5211
Digoxin	25 (2.14)	128 (2.05)	23 (2.18)	39 (1.84)	0.5172
Ivabradine	23 (1.97)	49 (0.79)	10 (0.95)	23 (1.09)	0.7170
Nitrates	111 (9.49)	707 (11.34)	97 (9.19)	202 (9.53)	0.7523
Diuretics	291 (24.87)	2285 (36.64)	265 (25.09)	517 (24.4)	0.6679
Antiplatelet	673 (57.52)	3126 (50.13)	579 (54.83)	1133 (53.47)	0.4686
Anticoagulant	20 (1.71)	111 (1.78)	19 (1.8)	35 (1.65)	0.7620
Statin	924 (78.97)	3897 (62.49)	818 (77.46)	1656 (78.15)	0.6597
Laboratory (mean ± SD)					
HbA1c, %	8.53 ± 1.65	7.73 ± 1.67	8.51 ± 1.65	7.76 ± 1.66	<0.0001
Hemoglobin	13.57 ± 1.92	12.18 ± 2.21	13.51 ± 1.91	12.95 ± 2.1	<0.0001
Na	139.55 ± 3.31	138.33 ± 5.97	139.57 ± 3.36	138.9 ± 5.42	0.0019
K	4.26 ± 0.58	4.23 ± 0.68	4.26 ± 0.59	4.21 ± 0.5	0.0646
Ca	8.99 ± 0.57	8.88 ± 0.77	9 ± 0.58	8.91 ± 0.8	0.0552
Mg	1.77 ± 0.19	1.77 ± 0.33	1.76 ± 0.19	1.76 ± 0.41	0.9749
Creatinine	0.92 ± 0.36	1.66 ± 2.15	0.92 ± 0.36	1.23 ± 1.41	<0.0001
eGFR	90.71 ± 35.19	75.57 ± 41.41	90.15 ± 35.87	83.76 ± 36.5	<0.0001
AST	31.93 ± 17.8	30.93 ± 22.46	31.93 ± 18.04	30.93 ± 20.49	0.3088
ALT	31.3 ± 21.64	26.58 ± 25.84	30.72 ± 20.04	28.09 ± 23.72	0.0020
Follow-up (years)	1.63 ± 0.77	2.02 ± 0.84	1.64 ± 0.76	2.13 ± 0.77	<0.0001

ACEi, angiotensin converting enzyme inhibitor; ALT, alanine transaminase; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; ASCVD, atherosclerotic cardiovascular disease; AST, aspartate transaminase; BNP, brain natriuretic peptide; CCB, calcium channel blockers; DM, diabetes mellitus; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP1-RA, glucagon-like peptide 1 receptor agonist; HbA1c, hemoglobin A1c; LVEF, left ventricular ejection fraction; NT-proBNP, N terminal pro B type natriuretic peptide; OHA, other hypoglycemic agent; SGLT2i, sodium glucose co-transporters 2 inhibitor; TZD, thiazolidinedione.
*All statistical tests were 2 tailed, and type I error rate of 0.05 (p) is used.

Characteristics of ECG of study population

As shown in Table 2, between baseline and follow-up, there were significant differences (but not clinically relevant) of PR interval (1.37 ± 18.38 ms, $p = 0.00169$), QT prolongation by Bazett's formula (2.58 ± 32.17 ms, $p = 0.0093$), and QT prolongation by Fridericia's formula (4.12 ± 30.81 ms, $p < 0.0001$) in patients on SGL2 inhibitors. In addition, between baseline and follow-up, there were significant differences (but not clinically relevant) of PR interval (1.64 ± 18.31 ms, $p < 0.0001$), QT prolongation by Bazett's formula (2.78 ± 31.06 ms, $p < 0.0001$), and QT prolongation by Fridericia's formula (2.10 ± 25.85 ms, $p = 0.0002$) in patients on non-SGL2 inhibitors. However, there were no differences in PR interval, QT prolongation by Bazett's formula, and QT prolongation by Fridericia's formula between groups of patients on SGLT2 inhibitors and patients on non-SGLT2 inhibitors.

ECG outcomes of study population

PR interval

As shown in Table 3, in terms of PR interval, there was no difference between group of patients on SGLT2 inhibitors and group of patients on non-SGLT2 inhibitors in terms of first degree AVB. In addition, there was no difference between the two groups in terms of type II second degree AVB or complete AVB.

QT interval

In terms of QT prolongation by Bazett's formula, including men with QTc > 440 ms, women with QTc > 460 ms, QTc > 500 ms, QTc < 350 ms, or increase in QTc > 60 ms, there were no differences between the two groups. In terms of QT prolongation by Fridericia's formula, including men with QTc

> 440 ms, women with QTc > 460 ms, QTc > 500 ms, QTc < 350 ms, or increase in QTc > 60 ms, there were no differences between the two groups.

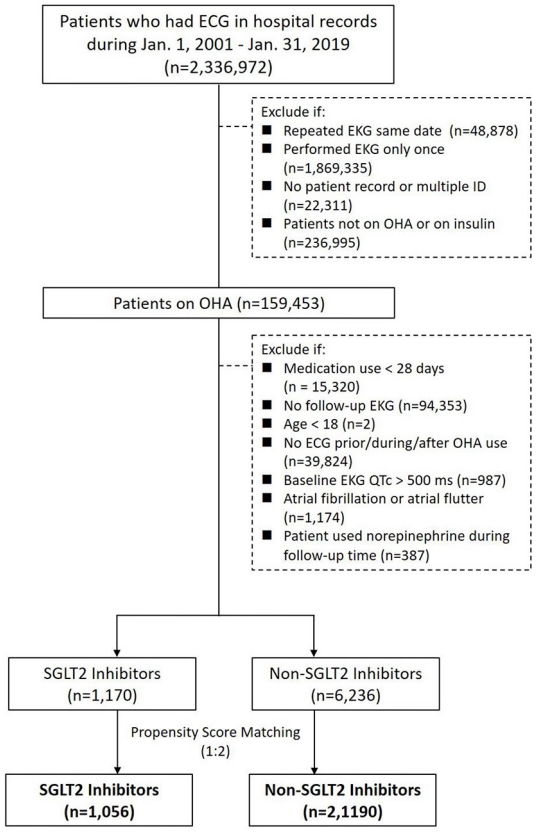

FIGURE 1
Study design and screening criteria flow chart for the inclusion of patients with T2DM using SGLT2 inhibitors and non-SGLT2 inhibitors with EKG.

ST-T changes

In terms of new onset ST-T changes, there was no difference between the two groups.

Bundle-branch block

In terms of new onset complete right bundle branch block (CRBBB) or complete left bundle branch block (CLBBB), there was no difference between the two groups.

Ventricular arrhythmia

In terms of ventricular arrhythmia, including ventricular tachycardia, ventricular fibrillation, or Torsades de Pointes, there were no differences between the two groups.

Mortality outcome of study population

In terms of cardiovascular mortality, including cardiovascular death and sudden cardiac death, there were also no differences between the two groups (Table 4).

Electrolyte outcomes of study population

As shown in Table 5, between baseline and follow-up electrolyte levels, the group of patients on SGLT2 inhibitors had a significant increase (but not clinically relevant) in sodium (0.66 ± 4.06 mEq/L, $p = 0.0009$), but no difference in potassium (0.04 ± 1.17 mEq/L, $p = 0.3771$), calcium (0.002 ± 0.98 mg/dL, $p = 0.9836$), and magnesium (0.06 ± 0.25 mEq/L, $p = 0.3306$). On the other hand, between baseline and follow-up electrolyte levels, the group of patients on non-SGLT2 inhibitors had no difference in sodium (0.32 ± 7.77 mEq/L, $p = 0.2083$), but a significant increase (but not clinically relevant)

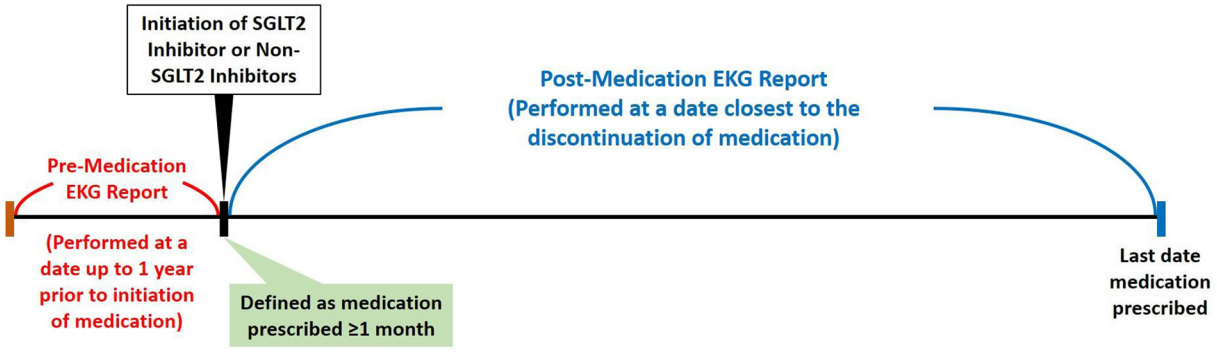

FIGURE 2
Enrollment criteria for patients with ECG.

TABLE 2 ECG characteristics of study population.

EKG characteristics	SGLT2 Inhibitors Mean ± SD	*p*-value[a]	Non-SGLT2 Inhibitors Mean ± SD	*p*-value[a]	*p*-value[b]
PR Interval		0.0169		<0.0001	0.6954
Baseline PR interval, ms	170.28 ± 28.76		167.23 ± 28.05		
Follow-up PR interval, ms	171.39 ± 29.57		168.81 ± 29.66		
PR interval difference, ms	1.37 ± 18.38	–	1.64 ± 18.31	–	
QT prolongation, Bazett's formula		0.0093		<0.0001	0.8680
Baseline QTc, ms	435.03 ± 33.10		434.28 ± 29.99		
Follow-up QTc, ms	437.61 ± 27.75		437.05 ± 29.34		
QTc difference, ms	2.58 ± 32.17	–	2.78 ± 31.06	–	
QT prolongation, Fridericia's formula		<0.0001		<0.0002	0.0687
Baseline QTc, ms	417.51 ± 30.57		418.25 ± 24.91		
Follow-up QTc, ms	421.57 ± 25.18		420.26 ± 26.55		
QTc difference, ms	4.12 ± 30.81	–	2.10 ± 25.84	–	

*Difference: between follow-up and baseline.
[a]Paired *t* test.
[b]Independent *t* test.

TABLE 3 ECG outcomes of study population.

Outcome	SGLT2 Inhibitors n, %	Non-SGLT2 Inhibitors n, %	OR (95% CI)	*p*-value
PR Interval				
First degree AVB	96 (9.09)	179 (8.45)	1.086 (0.838 to 1.408)	0.5323
Type II second degree AVB or complete AVB	1 (0.09)	4 (0.19)	0.668 (0.105 to 4.249)	0.6692
QT prolongation, Bazett's formula				
QTc > 440 ms in men	245 (23.20)	489 (23.08)	1.008 (0.846 to 1.200)	0.9314
QTc > 460 ms in women	95 (9.00)	169 (7.98)	1.143 (0.879 to 1.486)	0.3184
QTc > 500 ms	16 (1.52)	55 (2.60)	0.590 (0.339 to 1.027)	0.0622
QTc < 350 ms	2 (0.19)	0 (0)	10.049 (0.482 to 209.663)	0.1366
Increase in QTc >60	19 (1.80)	53 (2.50)	0.726 (0.430 to 1.226)	0.2313
QT prolongation, Fridericia's formula				
QTc > 440 ms in men	112 (10.61)	220 (10.38)	1.026 (0.807 to 1.305)	0.8329
QTc > 460 ms in women	32 (3.03)	72 (3.40)	0.896 (0.588 to 1.364)	0.6085
QTc > 500 ms	6 (0.57)	16 (0.76)	0.789 (0.317 to 1.962)	0.6099
QTc < 350 ms	2 (0.19)	2 (0.09)	2.008 (0.347 to 11.616)	0.4363
Increase in QTc >60	21 (1.99)	43 (2.03)	0.991 (0.588 to 1.671)	0.9733
New onset ST-T changes	0 (0)	3 (0.14)	0.286 (0.015 to 5.553)	0.4083
New onset CRBBB or CLBBB	5 (0.47)	22 (1.04)	0.488 (0.191 to 1.243)	0.1324
Ventricular Arrhythmia	13 (1.23)	14 (0.66)	1.879 (0.892 to 3.958)	0.0973
Ventricular Tachycardia	13 (1.23)	14 (0.66)	1.879 (0.892 to 3.958)	0.0973
Ventricular Fibrillation	0 (0)	0 (0)	–	–
Torsades de Pointes	0 (0)	0 (0)	–	–

AVB, atrioventricular block; CRBBB, complete right bundle branch block; CLBBB, complete left bundle branch block; OR, odds ratio; CI, confidence interval.

in potassium (0.05 ± 0.67 mEq/L, $p = 0.0096$), calcium (0.12 ± 1.08 mg/dL, $p = 0.0404$), and magnesium (0.08 ± 0.24, $p = 0.0456$). There was overall no difference of electrolyte levels between groups.

Discussion

This is the first study to compare the changes of ECG of patients on SGLT2 inhibitors and patients on non-SGLT2

inhibitors in a large T2DM patient cohort. There were no differences in PR interval, AV conduction block, QT prolongation (by Bazett's or Fridericia's formulas), new onset ST-T changes, new onset CRBBB or CLBBB, ventricular arrhythmia, and cardiovascular mortality between the groups.

Diabetes is a chronic metabolic disease and causes a complex myocardial dysfunction, referred to as diabetic cardiomyopathy, which even in the absence of other cardiac risk factors results in abnormal diastolic and systolic function (16). Altered electrical function is a major feature of the diabetic myocardium alongside mechanical abnormalities (16). Diabetic patients often exhibit cardiac electrical remodeling, primarily a prolonged ventricular repolarization visible in the electrocardiogram as a lengthening of the QT interval duration secondary to alterations on the expression and activity of several cardiac ion channels and their associated regulatory proteins (16). The changes in sodium, calcium, and potassium currents can together lead to a delay in repolarization that increase the risk of developing life-threatening ventricular tachycardia, Torsades de Pointes, and ventricular fibrillation (16). Since QT prolongation is a qualitative marker of proarrhythmic risk, a thorough QT/QTc (TQT) analysis evaluating QT interval prolongation is often performed to assess potential proarrhythmic effects during new drug administration. In light of diabetic patients often have a higher risk of cardiovascular events, cardiovascular safety of the new antidiabetic drugs must be carefully assessed in these T2DM patients.

In a randomized, placebo-controlled, double-blind, four-period crossover study at a single-center inpatient clinical pharmacology unit, 50 healthy men were to receive doses of dapagliflozin 150 mg, dapagliflozin 20 mg, moxifloxacin 400 mg, and placebo (9). Digital 12-lead electrocardiograms were recorded and QT intervals were corrected for heart rate using a study-specific correction factor (QTcX) and Fridericia's formula (9). For dapagliflozin, the upper bound of the one-sided 95% confidence interval (CI) for time-matched, placebo-subtracted, baseline adjusted QTc intervals ($\Delta\Delta$QTc) was $<$ 10 ms of dapagliflozin had little effect on heart rate (9). The results showing that dapagliflozin, at supratherapeutic doses,

TABLE 4 Mortality outcomes of study population.

Outcome	SGLT2 Inhibitors n, %	Non-SGLT2 Inhibitors n, %	OR (95% CI)	*p*-value
Cardiovascular mortality	4 (0.37)	13 (0.58)	0.665 (0.228 to 1.938)	0.4547
Cardiovascular Death	1 (0.09)	3 (0.13)	0.857 (0.126 to 5.813)	0.8741
Sudden cardiac death	3 (0.28)	8 (0.36)	0.823 (0.236 to 2.864)	0.759

OR, odds ratio; CI, confidence interval.

TABLE 5 Electrolyte outcomes of study population.

Laboratory	SGLT2 Inhibitors Mean ± SD	*p*-value[a]	Non-SGLT2 Inhibitors Mean ± SD	*p*-value[a]	*p*-value[b]
Na		0.0009		0.2083	0.3017
Baseline	139.56 ± 3.36		138.91 ± 5.4		
Follow-up	140.26 ± 3.47		139.15 ± 5.48		
Na difference	0.66 ± 4.06	–	0.32 ± 7.77	–	
K		0.3771		0.0096	0.8452
Baseline	4.26 ± 0.59		4.21 ± 0.5		
Follow-up	4.3 ± 0.94		4.26 ± 0.54		
K difference	0.04 ± 1.17	–	0.05 ± 0.67	–	
Ca		0.9836		0.0404	0.3456
Baseline	9.01 ± 0.58		8.91 ± 0.8		
Follow-up	9.04 ± 0.72		8.99 ± 0.75		
Ca difference	0.002 ± 0.98		0.12 ± 1.08		
Mg		0.3306		0.0456	0.7498
Baseline	1.77 ± 0.19		1.76 ± 0.4		
Follow-up	1.82 ± 0.29		1.79 ± 0.32		
Mg difference	0.06 ± 0.25	–	0.08 ± 0.24	–	

*Difference: between follow-up and baseline.
[a]Paired *t* test.
[b]Independent *t* test.

does not have a clinically significant effect on the QT interval in healthy subjects (9).

In another randomized, placebo-controlled, single-dose, double-blind, five-period crossover study, 30 volunteers were randomized to receive single empagliflozin doses of 25 mg (therapeutic) and 200 mg (supratherapeutic), matching placebo, and open-label moxifloxacin 400 mg (positive control) (10). Triplicate 12-lead ECGs of 10 second duration were recorded at baseline and during the first 24 h after dosing (10). The findings showed that single doses of empagliflozin 25 mg and 200 mg were not associated with QTc prolongation and were well tolerated (10).

In a recent study, the risk of new-onset arrhythmias (NOA) and all-cause mortality with the use of SGLT2 inhibitors were investigated using the national health insurance database (17). Patients with T2DM taking SGLT2 inhibitors were compared to patients with T2DM without taking SGLT2 inhibitors using 1:1 propensity score matching (17). The results showed that compared to 79,150 T2DM patients not taking SGLT2 inhibitors, 79,150 T2DM patients on SGLT2 inhibitors were associated with a lower risk of all-cause mortality (adjusted hazard ratio [aHR] 0.547; 95% confidence interval [CI] 0.482–0.621; $P = 0.0001$) and NOA (aHR 0.830; 95% CI 0.751–0.916; $P = 0.0002$) (17).

A group of researchers recently investigated the effects of SGLT2 inhibitors as an add-on therapy to metformin on electrocardiographic indices of ventricular repolarization in 141 consecutive patients (18). After the six-month follow-up, there was a significant decrease in the QT interval in patients who were using SGLT2 inhibitors as an add-on therapy to metformin compared to other glucose-lowering agents (SGLT2 inhibitors: 373.4 ± 9.9 ms vs. dipeptidyl peptidase-4 inhibitors: 385.4 ± 12.5 ms, sulfonylureas: 382.9 ± 11.2 ms; $p < 0.001$ respectively) (18). The authors concluded that using SGLT2 inhibitors as an add-on therapy to metformin favorably alters ventricular repolarization indices in patients with T2DM (18). In another study the researchers studied the class effects of SGLT2 inhibitors in mouse cardiomyocytes and found that SGLT2 inhibitors directly inhibit cardiac Na^+/H^+ exchanger flux and reduce cardiac cytosolic [Na^+], possibly by binding with the Na^+-binding site of Na^+/H^+ exchanger (19). SGLT2 inhibitors also affect the healthy heart by inducing vasodilation (19). The cardiac cytosolic [Na^+]-lowering class effect of SGLT2i is a potential approach to combat elevated cardiac cytosolic [Na^+] known to occur in heart failure and diabetes (19).

In a recent review of mineral and electrolyte disorders with SGLT2 inhibitor therapy, there were the postulated effects of SGLT2 inhibitors on serum electrolytes (sodium, potassium, and magnesium) that inhibition of SGLT2 receptors promotes glycosuria, natriuresis, and osmotic diuresis, which in turn causes an elevation of aldosterone activity with increased kaliuresis and magnesuria (20). These effects are counterbalanced by an improvement in glycemic control with an elevation of serum glucagon and reduction of insulin, which favors redistribution of potassium and magnesium in cells from the intracellular space with a net effect of a potential low increase of serum potassium and magnesium concentrations (20).

In this study, our enrolled patients were propensity score matched between patients on SGLT2 inhibitor and patients on non-SGLT2 inhibitors, including age, sex, comorbidities, medications, especially those QT prolonging agents. For ECG characteristics, between baseline and follow-up, there were minute increases in PR interval, QT prolongation by Bazett's formula, and QT prolongation by Fridericia's formula in both SGLT2 inhibitor group and non-SGLT2 inhibitors group that may be related to diabetic cardiomyopathy, albeit not clinically relevant. Between groups of patients, there were also no differences in PR interval and QT prolongation by Bazett's formula or Fridericia's formula.

In brief, for ECG outcomes, there was no difference between group of patients on SGLT2 inhibitors and group of patients on non-SGLT2 inhibitors in terms of PR intervals, QT prolongations, new onset ST-T changes, new onset CRBBB or CLBBB, or ventricular arrhythmia. For mortality outcomes, there were no differences between the two groups in terms of cardiovascular death and sudden cardiac death. And for electrolyte outcomes, there were also no difference between the two groups in sodium, potassium, calcium, and magnesium levels at follow-up lab tests, which may be associated with no increased morality associated with SGLT2 inhibitors compared to non-SGLT2 inhibitors. These results are in line with previous literature, that SGLT2 inhibitors are relatively safe, do not cause sodium, potassium, calcium, nor magnesium level imbalance, and may have mortality benefits (19, 21–23). To summarize, our study showed stable ECG changes in these patients and offered clinical evidence to the electrocardiographic and cardiovascular safety of SGLT2 inhibitors for treatment of patients with T2DM.

Limitations

There are several limitations in epidemiologic data from CGRD. First, using ICD-9-CM and ICD-10-CM codes for patient screening and enrollment may have missed some cases for which conditions were coded incorrectly. A second limitation occurs when ECG measurements are performed automatically by the ECG machine as there is no manual validation of the results from automatic measurements. Third, due to a limited number of patients where SGLT2i was prescribed as monotherapy, there may be not enough patient data to decrease the range of days the ECG was acquired to the use of OHA. Due to small number of patients on SGLT2 inhibitors, we did not discern each SGLT2 inhibitor for the individual outcomes against non-SGLT2 inhibitors. Last, since our study consisted of nearly homogenous racial background, application of the results to other populations requires further studies.

Conclusion

Compared with T2DM patients on non-SGLT2 inhibitors, there was no difference in PR interval, QT interval, ST-T changes, bundle-branch block, or ventricular arrhythmia in the patients on SGLT2 inhibitors. There was no difference in cardiovascular mortality between these two groups. In addition, there were no electrolyte difference between groups. SGLT2 inhibitors appeared to be well-tolerated in terms of cardiovascular safety.

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 Institutional Review Board of Chang Gung Memorial Hospital approved the study protocol (IRB No. 202001017B0). The Ethics Committee waived the requirement of written informed consent for participation.

Author contributions

Study conception and design: VC-CW, K-PC, C-LW, and S-HC. Acquisition of data: C-YH, H-TT, and Y-TH. Analysis and interpretation of data: C-HC, C-HH, C-FK, and S-WC. Drafting of manuscript: VC-CW and K-PC. Critical revision: C-LW, P-HC, and S-HC.

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Conflict of interest

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

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Education level may modify the association between cardiac index and cognitive function among elders with normal ejection function

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Background: Lower cardiac index (CI) in elders has been associated with incident dementia, and higher CI has protectively effect with brain aging. In the present study, we investigated the modulating effects of education level and arterial stiffness on the association between CI and cognitive function among older adults.

Methods: A total of 723 elders (≥60 years, 50.1% women) with normal left ventricular ejection fraction (≥50%) were identified from the Cardiovascular Diseases Risk Factor Two-Township Study. CI was calculated from the Doppler-derived stroke volume. We evaluated arterial stiffness by measuring carotid-femoral pulse wave velocity (CFPWV) and global cognitive function by using the Mini-Mental Short Examination (MMSE). Education level was determined by years of formal education.

Results: In linear regression analysis adjusting for age, sex, formal years of education, and CFPWV, CI was significantly positively associated with MMSE (BETA=0.344±0.130, $P = 0.0082$). In logistic regression analysis adjusting for age, sex, formal years of education, and CFPWV, subjects with a CI≥75 percentile had a significantly lower risk of low MMSE (<26) (OR = 0.495, 95% CI = 0.274–0.896, $P = 0.02$). In subgroup analysis, higher CI was significantly associated with higher MMSE and lower risk of low MMSE only in elders with ≤9 years of formal education. Causal mediation analysis suggests that higher CI maintains higher MMSE in elders with lower education levels whereas higher CFPWV causes lower MMSE in all the elders.

Conclusion: In elders with normal ejection fraction, a higher CI was associated with a lower risk of cognitive function impairment, independent of arterial stiffness, mainly in subjects with a lower education level and possibly a smaller cognitive reserve.

KEYWORDS

education, cognitive function, cardiac index, elderly population, cohort

Background

Reduced systemic blood flow may reduce cerebral perfusion and cause subclinical brain injury, and thereby compromise cognitive function (1, 2). In the extreme, patients with systolic heart failure have a higher prevalence of cognitive impairment than those with normal cardiac function (3–5). In the community-based participants free from clinical stroke, transient ischemic attack, dementia, or heart disease, a subtle reduction in cardiac index (CI) may be associated with reduced brain volumes (1, 6), furthermore, the higher CI (top tertile) had a higher mean total brain volume equivalent to nearly brain aging compared with those participants in either the middle or bottom teriles of CI. Therefore, a higher CI, implying better systemic blood flow, may help ensure adequate cerebral blood flow (7) to prevent cognitive function decline due to aging.

In addition to aging, low education is a recognized risk factor for dementia (8). A higher level education in early life is usually associated with a significant reduction in prevalence and incidence of dementia (8). Education may influence the course and outcome of cognitive decline and protect against the onset of dementia, the so-called cognitive reserve hypothesis (8–11). The interaction between the effect of education on cognitive reserve and the joint effect of cardiac and arterial aging on cognitive decline remains poorly understood (12).

We hypothesized that the potential protective effect of relatively higher CI and the well-documented detrimental effect from arterial aging on cognitive decline may differ in elders with different education levels, because of the difference in cognitive reserve. Therefore, the present study aimed to elucidate the interrelationship of CI, arterial aging and education level with cognitive function among the elders with normal left ventricular ejection fraction in the community. Specifically, we investigated the modulating effects of education level and arterial stiffness on the association between CI and cognitive function among older adults.

Methods

Study population

The Cardiovascular Disease Risk Factors Two-Township Study (CVDFACTS) is an ongoing longitudinal study of the risk factors for and pathogenesis of cardiovascular disease in two Taiwanese townships, Chu-Dung (a Hakka community) and Pu-Tzu (a Fukienese community) (13). The CVDFACTS study was instituted in 1989–1991 (baseline) and had 4 waves of surveys (1991–1993, 1993–1997, 1997–1999, and 1999–2002). Due to carotid hemodynamic parameters were measured in the 4th wave, we invited those (n = 2,014) with carotid hemodynamic measures and aged more than 60 years old after January 2014, by letter or by telephone to attend the present study project entitled "The Impact of Pulsatile Hemodynamics on Elderly Cognitive Function: the Cardio-cerebral Interactions" conducted between 2014 and 2016. Those none participants had higher age (77 vs. 69 years old, $p < 0.05$), lower male proportion (43 vs. 50%, $p < 0.05$) and shorter schooling education (7 vs. 10 years, $p < 0.05$), compared to the participants. The study protocol was approved by the Institutional Review Board of National Yang-Ming University. Each participant was well informed, and a written consent was obtained before entering the study.

In total, two visits of data collection within 3 months were arranged for each participant. In the first visit, personal characteristics, anthropometric measurements, cognitive function assessment, and fasting blood samples were collected. The histories of stroke and heart disease were collected by the structured questionnaires such as: "Did you have heart disease diagnosed by a physician at a clinic or hospital?". The second visit involved the measurements of cardiovascular hemodynamics.

A total of 819 elders aged 60 years or more participated in the project and completed the cognitive function assessment. For the purpose of the present analysis, we excluded 89 subjects with a left-ventricular ejection fraction <50% or missing ejection fraction data, and 7 additional subjects with missing CI data. The cognitive function had no difference between elders with and without ejection fraction <50%. Finally, 723 subjects aged ≥ 60 years and with normal left ventricular ejection fraction (>50%) were eligible and included in the present analysis (Figure 1).

Measurements

Cognitive function

The global cognitive function was assessed using the Mini-Mental Short Examination (MMSE), (14). Chinese version for Taiwan, *via* face-to-face interview with the well-trained study nurses at the study sites. The MMSE consists of 20 items clustered into 11 subscores to assess different aspects of cognitive function, namely, orientation, memory, attention, calculation and following a three-stage command, and has a total score of 30 points (14). A cut-off point of 26 was used to define cognitive impairment.

Education level

The usual formal education in Taiwan is elementary school (6 years), junior high school (3 years), senior high

Abbreviations: CI, Cardiac Index; CFPWV, Carotid-Femoral Pulse Wave Velocity; MMSE, Mini-Mental Short Examination; CVDFACTS, The Cardiovascular Disease Risk Factors Two-Township Study.

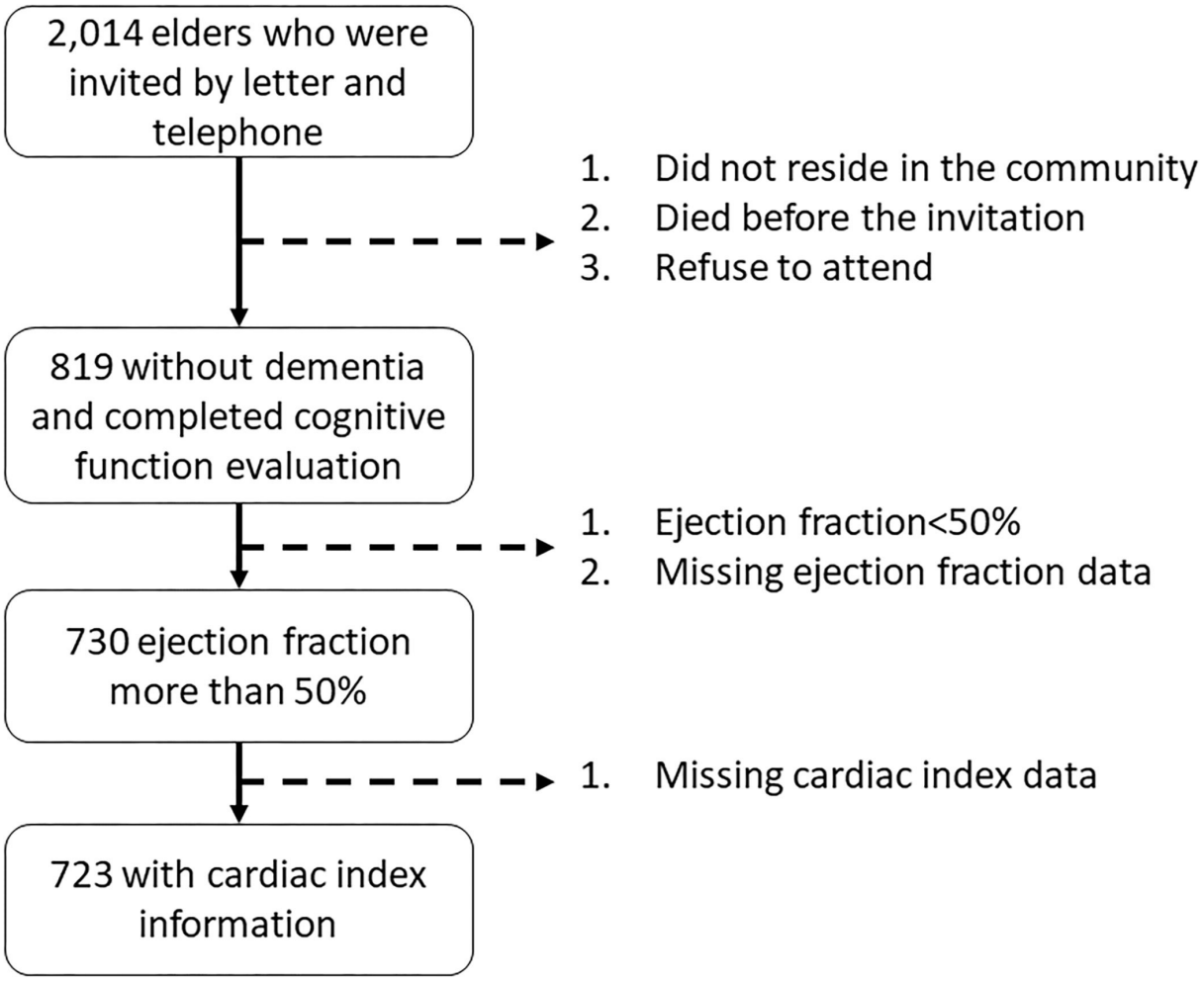

FIGURE 1
Study population flowchart.

school (3 years), college (4 years), and graduate school (2–4 years). Total years of formal education were registered for each participant and a cut-off point 9 years was used to define lower education level (≤9 years), since 9-year education was cumulated school years of elementary and junior high school.

Cardiac index

All the subjects received a transthoracic echocardiography performed by the same experienced sonographer using a commercially available machine (HD11 XE Ultrasound system, Koninklijke Philips N.V.). Therefore, there was no intra-measurers errors in this study. All the images were digitized for off-line analysis by the sonographer, using the TomTec Image-Arena^{TM} Software 4.0 (TomTec Imaging Systems GmbH, Munich, Germany). Left ventricular volume was measured from the summation of a stack of elliptical disks by tracing the endocardial border of the left ventricle at end-diastole and end-systole in apical 4 chamber view. Left ventricular ejection fraction was calculated from the M-mode measurements. Doppler-derived stroke volume was the product of the cross-sectional area of the left ventricular outflow tract and the flow across the left ventricular outflow tract, which is determined by the velocity time integral of the Doppler signal during systole (15). Doppler-derived cardiac output was calculated as stroke volume times heart rate and CI was cardiac output divided by body surface area (15).

Arterial stiffness

Applanation tonometry was performed with a pencil-type tonometer incorporating a high-fidelity strain-gauge transducer in a 7-mm-diameter flat tip (SPC-350, Millar Instruments Inc,

Texas) to record the pulse waveforms at the right common carotid artery and right femoral artery sequentially (16). CFPWV was estimated by the distance between the right carotid and right femoral artery measured by a measuring tape divided by the pulse transit time. The pulse transit time between the right carotid artery and the right femoral artery was calculated by a simultaneously recorded ECG signal using a custom-designed software on a commercial software package (Matlab, version 4.2, The MathWorks, Inc.) (16).

Others

Supine brachial systolic and diastolic blood pressure were measured at the right arm using automated analyzer, VP-1000 (Colin Co., Komaki, Japan) with an appropriate-sized cuff at heart level. Body surface area was calculated by the product of body height (cm) and body weight (kg) divided by 3,600. Body mass index was estimated by the body weight in kg divided by body height in meter.

Statistical analysis

Characteristics of study population and subgroups of higher and lower education levels > and ≤9 years of formal education) were presented as mean and SD for interval variables, and number with proportion for categorical variables. The Students *t*-test was used to compare the mean difference between two groups and appropriate *p*-value with fitting assumptions or not was presented.

Association of MMSE with CI and CFPWV was evaluated by univariable and multivariable linear regression analyses for the total study population and subgroups of education levels. Association between low MMSE (total score < 26) and quartile analyses of CI and CFPWV was evaluated by multivariable logistic regression analyses for the total population and subgroups of education levels. We also evaluated the modulating effect of education on the association between cardiac index and cognitive function by stratified analysis and interaction evaluation. The estimated minima sample size for the study hypothesis that cardiac index associated with MMSE score ($r = 0.30$) was 195 for 0.05 alpha value with two-tail, power with 99%.

We further constructed causal models to elucidate the significance of CI and CFPWV as mediators on the causal pathway between advancing age and declining MMSE, with years of formal education as a confounder. The path analysis was frequently used to explore the potential cause relationship among a set of observed variables. The process CALIS in the statistic software SAS was usually conducted for path analysis. The direct effect of each pathway in the causal models was estimated by a Path coefficient and its *P*-value and the goodness-of-fitness index of each model was presented. All the statistical analysis were conducted in SAS 9.4. Significance level was set at 0.05.

Results

Characteristics of study population

Among the 723 eligible elders with normal left ventricular ejection fraction (mean age 69.2 ± 7.2 years, 49.93% women, average left ventricular ejection fraction 71.3 ± 6.7%), the average MMSE score was 27.9 ± 2.7 (28.3 ± 2.07 for men, 27.6 ± 3.08 for women, P = 0.0008), and 97 subjects had an MMSE<26 (13.4%; 10.8% for men vs. 16.0% for women, $P = 0.0395$) (Table 1).

Subjects with a lower education level (≤9 years of formal education, average 5.2 years) were significantly older, had a significantly lower MMSE score and higher prevalence of cognitive impairment (MMSE<26), and had a significantly higher CI and CFPWV than those with a higher education level (>9 years of formal education and average 12.6 years) (Table 1).

Subjects with a lower education level had a higher proportion of women, greater body mass index, higher brachial systolic blood pressure and fasting glucose, and a higher prevalence of heart disease, compared to those elders with a higher education level (Table 1).

Association of MMSE with CI and CFPWV

In the multivariable analysis for the study population, CFPWV was significantly negatively, and CI was significantly positively associated with MMSE, when age, gender, and years of formal education were included in the model (Table 2). In subjects with a lower education level, CFPWV was significantly negatively, and CI was significantly positively associated with MMSE (Table 2). In contract, in subjects with a higher education level, CFPWV remained significantly negatively associated with MMSE, but CI was no longer associated with MMSE (Table 2).

Association between cognitive impairment and quartile analyses of CI and CFPWV

In subjects with a lower education level, subjects in the upper quartile of CI, whereas subjects in the upper quartile of CFPWV were not significantly associated with a higher risk for cognitive impairment ($P = 0.0592$). In contrast, in subjects with a higher education level, subjects in the upper quartile of CFPWV were significantly associated with a higher risk, whereas subjects in the upper quartile of CI were not associated with a lower risk of cognitive impairment (Table 3, separate upper quartile analysis).

TABLE 1 Characteristics of the study population with lower and higher levels of education ($n = 723$).

Variable	Total ($n = 723$)	Lower education level (≤9 years) ($n = 231$)	Higher education level (>9 years) ($n = 492$)	P value
Age, years	69.2 ± 7.2	72.3 ± 7.6	67.8 ± 6.5	<0.0001
Male gender, n (%)	361 (49.9)	86 (36.9)	275 (55.9)	<0.0001
Formal education, years	10.3 ± 4.2	5.2 ± 1.9	12.6 ± 2.7	<0.0001
Body mass index, kg/m^2	24.7 ± 3.4	25.3 ± 3.3	24.4 ± 3.4	0.0013
Brachial systolic BP	133.4 ± 17.7	136.3 ± 17.3	132.0 ± 17.8	0.0024
Brachial diastolic BP	77.1 ± 10.3	77.2 ± 9.3	77.0 ± 10.7	0.8188
Triglycerides, mg/dL	127.4 ± 77.5	134.1 ± 77.1	124.1 ± 77.4	0.1066
HDL-cholesterol, mg/dL	54.3 ± 15.6	53.3 ± 14.1	54.8 ± 16.3	0.2293
LDL-cholesterol, mg/dL	116.3 ± 34.6	116.7 ± 34.2	116.4 ± 35.0	0.9114
Total cholesterol, mg/dL	195.8 ± 39.5	196.5 ± 38.5	195.6 ± 40.0	0.7766
Fasting glucose, mg/dL	104.3 ± 26.3	107.6 ± 31.3	102.7 ± 23.4	0.0192
Cardiac index, L/min/m^2	2.8 ± 0.7	2.92 ± 0.75	2.75 ± 0.65	0.0022
CFPWV, m/sec	13.7 ± 4.6	14.6 ± 5.2	13.3 ± 4.3	0.0007
Ejection fraction, %	71.3 ± 6.7	71.3 ± 6.8	71.3 ± 6.7	0.9677
MMSE	27.9 ± 2.7	26.3 ± 4.3	28.6 ± 1.8	<0.0001
MMSE<26, n (%)	97 (13.4)	68 (29.2)	31 (6.3)	<0.0001
Heart disease, n (%)	151 (20.9)	59 (25.3)	92 (18.7)	0.0403
Stroke history, n (%)	24 (3.3)	12 (5.2)	12 (2.4)	0.0567

BP, blood pressure; CFPWV, carotid-femoral pulse wave velocity; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MMSE, Mini-Mental State Examination.

TABLE 2 Association of MMSE with CI and CFPWV, adjusted for age, sex and education whole population and stratified by levels of education.

Variable	Total ($n = 723$)		Lower education level (≤9 years) ($n = 231$)		Higher education level (>9 years) ($n = 492$)	
Multivariable analysis	BETA (SE)	*P* value	BETA (SE)	*P* value	BETA (SE)	*P* value
Age, years	−0.071 (0.014)	<0.0001	−0.052 (0.030)	0.089	−0.068 (0.013)	<0.0001
Gender, male vs. female	0.490 (0.186)	0.0086	0.737 (0.436)	0.0928	0.346 (0.165)	0.0362
Formal education, years	0.197 (0.023)	<0.0001	0.701 (0.110)	<.0001	0.013 (0.030)	0.6507
CFPWV, m/sec	−0.070 (0.021)	0.0008	−0.090 (0.042)	0.0341	−0.045 (0.020)	0.0250
CI, L/min/m^2	0.344 (0.130)	0.0082	0.649 (0.274)	0.0187	0.093 (0.112)	0.4467

BETA, standardized regression coefficient; CFPWV, carotid-femoral pulse wave velocity; CI, cardiac index; SE, standard error of BETA.

In the logistic regression model, upper quartile CI and upper quartile CFPWV were negatively and positively significantly associated with cognitive impairment, respectively (Table 3, bivariate upper quartile analysis). In subjects with a lower education level, upper quartile CI was significantly associated with a lower risk, and upper quartile CFPWV was not significantly associated with a higher risk for cognitive impairment ($P = 0.0732$). In contrast, in subjects with a higher education level, upper quartile CFPWV was significantly associated with a higher risk, whereas upper quartile CI was not associated with a lower risk for cognitive impairment (Table 3, bivariate upper quartile analysis).

In total, four subgroups were generated according to higher and lower CI and CFPWV. The subjects in the subgroups of higher CI and lower CFPWV, higher CI and higher CFPWV, and lower CI and lower CFPWV had significantly lower risks of cognitive impairment as compared with the referent subgroup of lower CI and higher CFPWV when age, sex, and years of formal education were accounted for (Table 3, combined upper quartile analysis). Similar significant results were observed in subjects with

TABLE 3 Association between low MMSE and cardiac index, carotid-femoral pulse wave velocity and education years, multivariable logistic analyses stratified by levels of education.

Variable	Total ($n = 723$)		Lower education level (<9 years) ($n = 231$)		Higher education level (≥9 years) ($n = 492$)	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Bivariate upper quartile analysis						
Cardiac index, ≥ vs. <75th percentile	0.495 (0.274–0.896)	0.0202	0.357 (0.158–0.808)	0.0134	0.788 (0.314–1.977)	0.6116
CFPWV, ≥ vs. <75th percentile	2.187 (1.287–3.716)	0.0038	1.947 (0.939–4.037)	0.0732	2.553 (1.100–5.925)	0.0292
Combined upper quartile analysis						
Higher CI (≥75th percentile) and lower CFPWV(<75th percentile) ($N = 133$)	0.246 (0.112–0.542)	0.0005	0.211 (0.073–0.609)	0.0040	0.297 (0.077–1.149)	0.0786
Lower CI (<75th percentile) and lower CFPWV(<75th percentile) ($N = 409$)	0.403 (0.221–0.737)	0.0031	0.385 (0.167–0.889)	0.0040	0.406 (0.156–1.057)	0.0649
Higher CI (≥75th percentile) and higher CFPWV(≥75th percentile) ($N = 49$)	0.364 (0.143–0.929)	0.0345	0.171 (0.043–0.671)	0.0254	0.845 (0.238–3.001)	0.7940
Lower CI (<75th percentile) and higher CFPWV (≥75th percentile) ($N = 132$)	1.0 (referent)		1.0 (referent)		1.0 (referent)	

All the models were adjusted for age, sex, and years of formal education.
CI, cardiac index; CFPWV, carotid-femoral pulse wave velocity. All the subjects were then divided into 4 subgroups according to higher and lower CI and CFPWV using the sex-specific 75th percentile as the cut-points.

a lower education level but not in those with a higher education level.

Modulating effects of education on the relationship between cardiac index and MMSE

We conducted a modulate analysis to evaluate the modulating effect of education on the association between CI and MMSE. The interaction variable of education and CI for MMSE was borderline significant with $p = 0.07$. This result indicates that the association between cardiac index and cognitive function was slightly modulated by education, but not reach statistic significant.

We further conducted path analysis to describe the potential causal interrelationships of age, cardiac index, carotid-femoral pulse wave velocity, education, and cognitive function. According to the Path analysis with years of formal education as a confounder, advancing age might directly decrease MMSE, and indirectly affect MMSE favorably and unfavorable by increasing CI and CFPWV for the total study population (Figure 2A, and in subjects with a lower education level (Figure 2B). In contrast, in subjects with a higher education level, advancing age might directly decrease MMSE and indirectly decrease MMSE through increased CFPWV. However, the favorable effect of increased CI on MMSE was no longer observed (Figure 2C).

Discussion

Main findings

Our study found that education level could modify the association between CI and cognitive function among elders with normal left ventricular ejection. The association between cardiac index and MMSE score was significant only in elders with a lower education level but was not significant in those with a higher education level. Furthermore, causal inference by the Path analysis also supports that higher CI maintains higher MMSE in elders with the lower education levels. Thus, elders with a lower education level may have a lower cognitive reserve and may be more vulnerable to the adverse effect of a subtle reduction of systemic blood flow on cognitive function.

Our study also found that CI and CFPWV simultaneously and independently contribute to the pathogenesis of cognitive function decline in the elders, especially in those with a lower education level, strategies to preserve systemic blood flow and prevent arterial stiffening may be considered for maintaining or restoring brain health. Enrichment of cognitive reserve through early life education and life

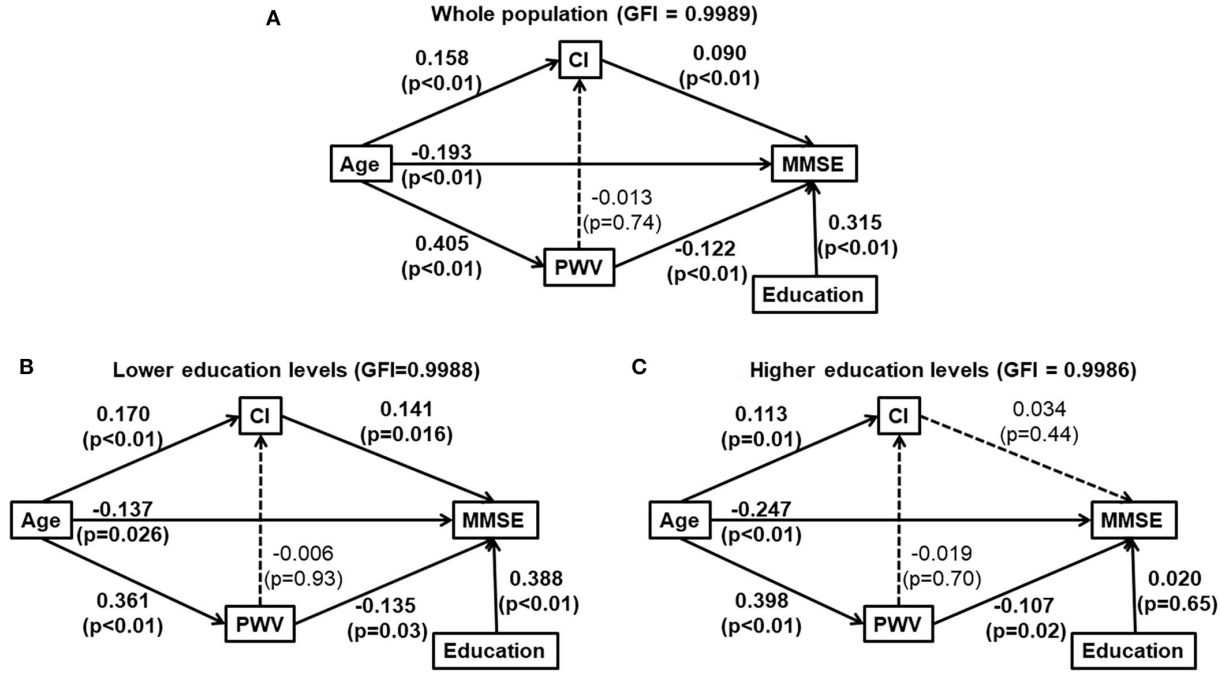

FIGURE 2
Path analysis diagrams for the whole study population **(A)**, subjects with lower education levels [≤9 years of formal education, **(B)**] and those with higher education levels [>9 years of formal education, **(C)**]. Solid line indicates significant association. Dotted line indicates none-significant association. Path coefficient and its *P*-value are presented for the evaluation of direct effect between two adjacent variables. **(A)** was for whole population and **(B,C)** were for those elders with and without lower education, respectively. CI, cardiac index; education, years of formal education; GFI, the goodness of fitness index; MMSE, Mini-Mental State Examination; PWV, carotid-femoral pulse wave velocity; The interrelationship of cardiac index (CI), carotid-formal pulse wave velocity (PWV), education and cognitive function (Mini-Mental State Examination).

time learning may help preserve cognitive function during late life.

Cardiac index and cognitive function in other studies

Few studies investigated the relationship between cardiac function and cognitive function among general population with normal cardiac function (1, 17, 18). The Framingham Offspring Cohort participants free of clinical stroke, transient ischemic attack, dementia, and clinically prevalent cardiovascular disease, CI was significantly positively related to total brain volume, and low CI was related to poorer performances on information processing/executive function with borderline significance (1). Follow-up of the same cohort excluding clinically prevalent cardiovascular disease and atrial fibrillation revealed that individuals with clinically low CI (<2.5 L/min/m^2) had a higher relative risk of both dementia and Alzheimer's disease compared with individuals with normal CI (19).

However, the underlying mechanisms of the association between cardiac function and cognitive function among subjects with normal cardiac function were unclear, and the mechanisms underlying clinically low CI in about one-third of the ambulatory older adults were unknown (19).

Our study results may compliment the Framingham Offspring Cohort study, which showed the harmful effect of a clinically significant low CI, by clearly demonstrating the protective effect of a higher CI (upper quartile) in preventing the age-related cognitive function decline, independent of age-related arterial stiffening. Overall, our results may suggest that a normal systemic blood flow is important in maintaining adequate cerebral blood flow and normal cognitive function, especially in elders with a lower cognitive reserve.

The association between cardiac index and cognitive function decline maybe inked by cerebral blood flow. Cerebral hypoperfusion resulting from the reduced systemic perfusion has been considered as the major cause of cognitive function impairment in heart failure patients (3–5). Cerebral blood flow is substantially reduced in patients with severe heart failure and it may be reversible after heart transplantation (5). Moreover, it has been shown that decreased CI was associated with smaller subcortical gray matter volume in patients with heart failure. Furthermore, cardiac resynchronization

therapy in the moderate-to-severe heart failure patients may improve left ventricular ejection fraction and enhance cognitive outcome, namely, global cognition, executive function, and visuospatial function (20).

Modulating effect of cognitive reserve on cognitive function decline

Cognitive reserve refers to the ability of the brain to optimize or maximize performance through differential recruitment of brain networks or use of alternative strategies against brain damage (11). Subjects with a higher education level usually experience less cognitive changes in the presence of age-related or Alzheimer's disease, probably because of a higher cognitive reserve (21). High education in early life may help to postpone cognitive and brain reserve decline in normal aging (22). Cognitive reserve can be measured by proxy indicators, such as years of full-time education and occupational complexity (23). The Cognitive Function and Aging Study Wales cohort reported cognitive reserve was an important mediator of the association between lifestyle factors and cognitive function, with indirect effects *via* cognitive reserve contributing 21% of the overall effect on cognition (23). In our study, education level measured by years of formal education was significantly associated with MMSE in both univariable and multivariable linear regression analyses (Table 2). In Path analysis, a formal education year was significantly associated with a higher MMSE score in subjects with a lower education level, but not in those with a higher education level (Figures 2B,C). Moreover, the protective effect of higher CI on preserving MMSE was also significant only in subjects with a lower education level. These results may support that cognitive reserve plays an important role in the development of cognitive dysfunction in later life. Elders with a higher education level, implying the presence of a higher cognitive reserve, may rely less on the protective effect from a higher CI.

Artery stiffness and cognitive function decline

It has been shown that marked stiffening of the aorta may augment the transmission of excessive flow pulsatility into the brain, causing microvascular structural brain damage and various cognitive function impairments (24). Our study also found that a higher CFPWV was significantly and independently associated with a lower MMSE. Moreover, we found that the effects of CFPWV and CI on MMSE were additive in elders with a lower education level but not in those with a higher education level. In Path analysis, age had a significant direct effect and two separate and independent significant indirect effects *via* CI and CFPWV, respectively, on MMSE. The indirect effect *via* CFPWV was significant in elders regardless of their education levels. In contrast, the indirect effect *via* CI was significant only in elders with a lower education level. These results may suggest that higher cognitive reserve does not prevent the age-related arterial stiffness, or arterial aging, from damaging the brain (3). Strategies to slow down or reverse arterial aging may be needed to maintain brain health.

Limitations and strength

Several limitations in this study are addressed as follows. First, this study was a cross-sectional design and therefore the results do not prove the causal inference. In the current design, we did not avoid the possible reverse causality which a small brain requires a small Cardiac index. This issue needs further investigation. Second, the modulating effect of education levels on the association between CI and cognitive function observed in our study may not be extrapolated to other populations that have a higher homogeneity in education levels. Third, we did not have the reliability information of hemodynamic parameters, however, all hemodynamic parameters were performed by a well-trained technician to avoid the intra measurer error.

Conclusion/Implication

In elders with normal ejection fraction, a higher CI was associated with a lower risk of cognitive function impairment, independent of arterial stiffness, mainly in subjects with a lower education level and possibly a smaller cognitive reserve. A higher education level may imply a higher cognitive reserve that may not require the protective effect of high CI on cognitive function.

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.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of National Yang-Ming University. The patients/participants provided their written informed consent to participate in this study. 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

Manuscript drafting and study design: H-MC, S-YC, C-HC, and W-HP. Data-analysis: S-YC and W-LL. Data collection and bio-information capture: Y-TK, C-YH, and C-FL. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Use of fibrates is not associated with reduced risks of mortality or cardiovascular events among ESRD patients: A national cohort study

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Background: Although a recent study reported that fibrates are associated with a low risk of cardiovascular (CV) death and can postpone the need for long-term hemodialysis in patients with advanced chronic kidney disease (CKD), little is known regarding whether the CV protective effects of fibrates extend to patients with end-stage renal disease (ESRD). The present study compared CV outcomes and mortality among patients with ESRD treated with fibrates, statins, neither, or their combination.

Methods: This cohort study extracted data from Taiwan's National Health Insurance Research Database (NHIRD). Adult patients with ESRD and hyperlipidemia were identified and categorized into four groups (fibrate, statin, combination, and non-user groups) according to their use of different lipid-lowering therapies within 3 months prior to the commencement of permanent dialysis. Inverse probability of treatment weighting was used to balance the baseline characteristics of the groups. The follow-up outcomes were all-cause mortality, CV death, and major adverse cardiac and cerebrovascular events (MACCEs).

Results: Compared with the non-user and statin groups, the fibrate group did not exhibit significantly lower risks of all-cause mortality [fibrate vs. non-user: hazard ratio (HR), 0.97; 95% confidence interval (CI), 0.92–1.03; statin vs. fibrate: HR, 0.95; 95% CI, 0.90–1.01], CV death (fibrate vs. non-user: HR, 0.97; 95% CI, 0.90–1.05; statin vs. fibrate: HR, 0.97; 95% CI, 0.90–1.06), and MACCEs (fibrate vs. non-user: HR, 1.03; 95% CI, 0.96–1.10; statin vs. fibrate: HR, 0.94; 95% CI, 0.87–1.004). The combination of fibrates and statins (specifically moderate- to high-potency statins) did not result in lower risks of all-cause mortality, CV death, or MACCEs compared with statins alone.

Conclusion: In patients with ESRD, the use of fibrates might be not associated with reduced mortality or CV risks, regardless of whether they are used alone or in combination with statins.

KEYWORDS

fibrates, hypertriglyceridemia, end-stage renal disease, cardiovascular, mortality

Introduction

Cardiovascular disease (CVD) is the leading cause of death in patients with end-stage renal disease (ESRD) and accounts for 40–50% of mortality among such patients (1). The risk of CVD increases with the decline of kidney function (2). In the general population, atherosclerosis is the primary cause of CVD. Common risk factors for atherosclerotic cardiovascular disease (ASCVD) have been identified, and several preventive strategies have been demonstrated to effectively reduce the risk of ASCVD. One of the most effective preventive measures is lipid-lowering therapy, which mainly consists of two categories of medications: statins and fibrates. Although statins are considered the most powerful lipid-lower agents reducing ASCVD risk, they seem to be less effective for patients with chronic kidney disease (CKD) and ESRD than for the general population (3). This discrepancy may be attributed to alterations in the lipid metabolism pathway that accompany CKD progression. Compared with statins, the reduction of triglyceride (TG) levels by fibrates is thought to play a minor role in cardiovascular protection in the general population; however, studies have revealed that TG-rich lipoproteins are causal risk factors for ASCVD (4–7). Medications that decrease TG or TG-rich lipoproteins reduce the risk of CVD in patients with hypertriglyceridemia, especially in those with low levels of high-density lipoprotein (HDL) (8, 9). Hypertriglyceridemia is a hallmark lipid abnormality in patients with CKD (10, 11) and mainly results from the dysfunction of lipoprotein lipase (LPL) and hepatic lipase that are responsible for the degradation of TG-rich chylomicron and low-density lipoprotein (VLDL) (11, 12). Decreased levels and functional disturbance of HDL, which are caused by low levels of apoprotein (Apo) A-I, ApoA-II, and lecithin-cholesterol acyltransferase (LCAT) (12, 13), are other lipid abnormalities commonly observed in patients with CKD. Because they can simultaneously decrease TG and elevate HDL levels (14), fibrates might be more beneficial for patients with CKD than for the general population.

Fibrates are activators of the nuclear transcription receptor peroxisome proliferator–activated receptor (PPAR)-α, which modulates the synthesis of multiple proteins involved in lipid metabolism. Fibrates upregulate the expression of LPL and downregulate the expression of ApoC-III, an LPL inhibitor, thus reduce the levels of TG and TG-rich lipoproteins in the blood. Meanwhile, fibrates upregulate ApoA-I and ApoA-II, thereby increasing HDL levels (15). Fibrates are primarily eliminated through urine and have prolonged half-lives and elevated concentrations in patients with renal insufficiency. This holds true for patients undergoing dialysis because fibrate metabolites are non-dialyzable from the serum (16). Because of such concerns, the use of fibrates for the treatment of dyslipidemia in CKD population remains limited. Studies have evaluated the effectiveness of fibrates in reducing CV risk in populations with mild to moderate (14, 17, 18) and advanced (19) CKD. However, few studies have evaluated the effectiveness of fibrates in reducing CV risk in patients with ESRD. A randomized controlled single-center study demonstrated that fibrates could effectively reduce lipid levels and oxidative stress in patients with ESRD (20). However, whether fibrates effectively reduce CV risk in patients with ESRD, as they do in patients with CKD, remains unknown. We conducted a well-designed, high-quality, large-scale, population-based cohort study to investigate this question. We used data from Taiwan's National Health Institute Research Database (NHIRD) to compare the effects of fibrates and statins, used separately and concurrently, on CV outcomes and mortality among patients with ESRD.

Materials and methods

Data source

This retrospective cohort study collected data from Taiwan's NHIRD. In 1995, the Taiwanese government established the National Health Insurance (NHI) program, a single-payer, mandatory insurance system in which most health-care facilities are enrolled. By the end of 2014, more than 99.9% of Taiwan's population was covered by the NHI program. Physicians are required to upload claims data from each outpatient or inpatient visit. The NHIRD was established by Taiwan's National Health Research Institutes in 2002 for public research purposes, and the cohort of this database is one of the largest health-care cohorts in the world. The NHIRD provides detailed health-care information, including basic demographic information, disease diagnoses, medicine prescriptions, procedural interventions, inpatient management information, and registrations of special conditions, but laboratory data and examination reports are not included in this database. Disease diagnoses in the NHIRD

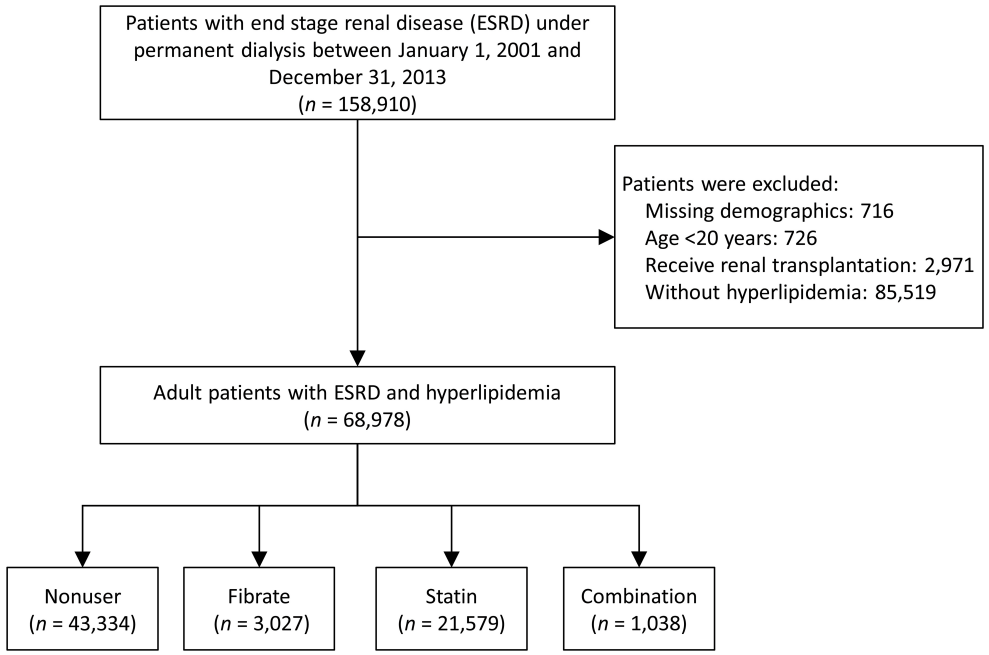

FIGURE 1
Flowchart for illustrating the inclusion and exclusion of the patients.

records are made according to the *International Classification of Diseases, Ninth Edition, Clinical Modification* (*ICD-9-CM*). More details on the NHIRD and methodologic approaches for data validation are provided in previous studies (21, 22). This study was approved with a waiver of consent by the Institutional Review Board of Chang Gung Medical Foundation (Approval Number: 201900840B0).

Study design

We collected data from the NHIRD to determine the effects of fibrates and statins on patients with ESRD and compare the study outcomes of patients using fibrates, statins, neither, or their combination. As shown in Figure 1, we identified patients with ESRD and concurrent hyperlipidemia who underwent permanent dialysis between January 1, 2001, and December 31, 2013. A patient was identified as having ESRD if they had a catastrophic illness certificate for long-term hemodialysis or peritoneal dialysis. The strict review process of the catastrophic illness certificate in Taiwan made the diagnosis of ESRD reliable; the index date was defined as the date on which they obtained the certification.

Patients without previous diagnosis of any kind of hyperlipidemia, with incomplete demographics, who were younger than 20 years, or who had undergone renal transplantation prior to the index date were excluded. The remaining patients were divided into four groups (fibrate, statin, combination, and non-user groups) according to their use of lipid-lowering medications within 3 months prior to the index date (19). In Taiwan, cholestyramine is not available, and, according to NHI's regulations, ezetimibe and niacin could only be prescribed with statin for patients who are difficult to achieve treatment target under statin alone. Thus, about the lipid-lowering medications, we only considered the use of fibrate and statin in this study. Besides, the drug exposure period (within 3 months prior to the index date) was according to the definition of "current use of medication" in a previous study (23). The follow-up period started on the index date and ended on the date of occurrence of any study outcomes, the date of withdrawal from the Taiwan NHI system (usually death), or the end of the study period (December 31, 2013), whichever occurred first. The Taiwan NHI is a single insurance system and data are centralized, therefore the lost to follow up of the insured individuals is rare and the threat of attrition bias is low.

Covariates

The covariates in the study were age, gender, CKD duration, number of outpatient department visits in the year prior to the index date, comorbidities (hypertension, diabetes mellitus, atrial

fibrillation, liver cirrhosis, peripheral artery disease, dementia and immune disease), history of events (hospitalization for heart failure, stroke, and myocardial infarction), and twenty kinds of medication. The CKD duration was defined as the time between the date of CKD diagnosis (first record of CKD codes) and the index date. Comorbidities were defined as diseases that were reported within 1 year of the index date and required hospitalization or more than two outpatient follow-ups. The history of events (heart failure, stroke, and myocardial infarction) was defined by the occurrence of event-associated hospitalizations prior to the index date. Medications were determined using both outpatient and inpatient prescription records from the 3 months prior to the index date. The definition of comorbidities and identification of medications in this study were adopted by many previous high-quality NHIRD-based studies (19, 24, 25). The moderate-to-high-potency statins indicated the statins could reduce LDL-C levels by more than 30% (26).

Outcomes

The study outcomes of interest were all-cause mortality, CV death, and major adverse cardiac and cerebrovascular events (MACCEs). All-cause mortality was detected based on a withdrawal from the Taiwan NHI program (27). In Taiwan, the main reason for withdrawal from the NHI program is death. The other less common reasons are permanent emigration, missing >6 months or being jailed for more than 6 months. CV deaths were defined as deaths resulting from acute myocardial infarction, sudden cardiac death, heart failure, stroke, CV procedures, CV hemorrhage, or other CV causes (28). MACCEs, namely cardiovascular death, ischemic stroke, and acute myocardial infarction, were determined according to the main discharge diagnoses of hospitalizations or ER visits. The diagnostic codes of acute myocardial infarction (29) and ischemic stroke (30, 31) have been validated in previous NHIRD studies.

Statistical analysis

The baseline characteristics of patients with different lipid lowering therapies (fibrate, statin, combination, and non-user groups) were balanced using inverse probability of treatment weighting (IPTW) based on the generalized propensity score of multiple treatments (32). The propensity scores were generated using the generalized boosted model (GBM) based on 50,000 regression trees. Compared to the conventional methods (i.e., multinomial logistic regression model), the GBM method has shown superior performance in most of the scenarios (33). Covariates used to calculate the propensity scores were all of the variables listed in Table 1, where the follow up duration was replaced with the index date. The balance among the multiple treatment groups before and after IPTW was assessed using the maximum absolute standardized difference (MASD) between any two of the groups, where a value <0.1 (34) indicated negligible difference between groups.

The risk of the study outcomes in patients with different lipid lowering therapies was compared using the Cox proportional hazard model. The study group (fibrate, statin, combination, and non-user) was the only explanatory variable in the Cox model. All comparisons between any two groups were made and a total of six pairwise comparisons were obtained for each outcome. Furthermore, the usage of statins was restricted on moderate to high potency statins and the propensity scores as well as GBM-IPTW were re-calculated. A two-sided P-value < 0.05 was considered to be statistically significant. All the statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Patient characteristics

As shown in Figure 1, the data of 68,978 patients with ESRD and hyperlipidemia diagnosed between January 1, 2001, and December 31, 2013, were extracted from the entire Taiwanese population. Of these patients, 3,027 used fibrates (fibrate group), 21,579 used statins (statin group), 1,038 used a combination of fibrates and statins (combination group), and the remaining 43,334 had not used any type of lipid-lowing agent (non-user group) within the 3 months prior to the index date.

The baseline characteristics, namely demographics, comorbidities, history of certain events, and prescribed medications, of the groups are presented in Table 1. Before inverse probability of treatment weighting (IPTW) was applied, the statin and combination groups—compared with the fibrate and non-user groups—were generally younger and had more OPD visits; a higher prevalence of hypertension and diabetes mellitus; and higher proportions of patients using certain medications, namely angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, dihydropyridine calcium channel blockers, loop diuretics, oral hypoglycemic agents, insulin, and antiplatelets. After IPTW, all the MASD values were ≤0.1, which indicated that the baseline characteristics and follow-up durations of all the groups were well-balanced (Supplementary Table 1).

Follow-up outcomes

The follow-up outcomes of the study groups after IPTW are listed in Table 2. The statin and combination groups exhibited a significantly lower risk of all-cause mortality compared with

TABLE 1 Baseline characteristics of dialytic patients according to the use of fibrate and statin before IPTW adjustment.

Variable	Non-user ($n = 43,334$)	Fibrate ($n = 3,027$)	Statin ($n = 21,579$)	Combination ($n = 1,038$)	MASD
Age, year	65.7 ± 12.7	61.1 ± 12.3	62.6 ± 12.4	59.7 ± 11.1	0.47
Age group					0.50
20–64 years	19,387 (44.7)	1,824 (60.3)	12,054 (55.9)	709 (68.3)	
65–74 years	12,742 (29.4)	785 (25.9)	5,918 (27.4)	229 (22.1)	
≥75 years	11,205 (25.9)	418 (13.8)	3,607 (16.7)	100 (9.6)	
Male	21,171 (48.9)	1,461 (48.3)	10,155 (47.1)	445 (42.9)	0.12
CKD duration, year	5 [3, 8]	4 [3, 7]	4 [2, 8]	4 [3, 7]	0.13
No. of outpatient visit in the previous year	8 [1, 17]	7 [1, 15]	10 [3, 17]	8 [1, 15]	0.21
Comorbid conditions					
Hypertension	38,856 (89.7)	2,514 (83.1)	19,995 (92.7)	906 (87.3)	0.32
Diabetes mellitus	30,744 (70.9)	2,187 (72.2)	17,401 (80.6)	824 (79.4)	0.22
Atrial fibrillation	1,697 (3.9)	86 (2.8)	632 (2.9)	15 (1.4)	0.13
Liver cirrhosis	1,562 (3.6)	61 (2.0)	528 (2.4)	14 (1.3)	0.13
Peripheral artery disease	2,066 (4.8)	136 (4.5)	1,005 (4.7)	51 (4.9)	0.02
Dementia	1,892 (4.4)	78 (2.6)	574 (2.7)	24 (2.3)	0.11
Immune disease	1,010 (2.3)	59 (1.9)	448 (2.1)	21 (2.0)	0.03
History of event					
Heart failure	13,667 (31.5)	724 (23.9)	6,651 (30.8)	269 (25.9)	0.17
Stroke	10,813 (25.0)	642 (21.2)	5,023 (23.3)	221 (21.3)	0.09
Myocardial infarction	3,949 (9.1)	227 (7.5)	2,653 (12.3)	119 (11.5)	0.16
Medication					
ACEi/ARB	19,573 (45.2)	1,457 (48.1)	12,588 (58.3)	588 (56.6)	0.26
Beta blocker	20,680 (47.7)	1,602 (52.9)	12,961 (60.1)	639 (61.6)	0.28
DCCB	28,856 (66.6)	1,955 (64.6)	16,732 (77.5)	712 (68.6)	0.28
Loops diuretics	24,119 (55.7)	1,511 (49.9)	15,087 (69.9)	627 (60.4)	0.41
Spironolactone	1,048 (2.4)	50 (1.7)	681 (3.2)	30 (2.9)	0.09
NDCCB	3,330 (7.7)	255 (8.4)	2,145 (9.9)	105 (10.1)	0.09
Oral hypoglycemic agents	16,209 (37.4)	1,304 (43.1)	10,791 (50.0)	486 (46.8)	0.26
Insulin	10,967 (25.3)	1,121 (37.0)	8,300 (38.5)	508 (48.9)	0.51
Antiplatelet	13,324 (30.7)	1,109 (36.6)	9,797 (45.4)	470 (45.3)	0.31
Oral anticoagulants	1,114 (2.6)	90 (3.0)	569 (2.6)	35 (3.4)	0.05
NSAIDs	6,456 (14.9)	604 (20.0)	2,985 (13.8)	204 (19.7)	0.17
Steroid	3,540 (8.2)	222 (7.3)	1,819 (8.4)	70 (6.7)	0.06
Proton pump inhibitor	7,240 (16.7)	526 (17.4)	3,735 (17.3)	177 (17.1)	0.02
Ketosteril	1,419 (3.3)	50 (1.7)	787 (3.6)	22 (2.1)	0.11
Pentoxifylline	5,190 (12.0)	389 (12.9)	3,788 (17.6)	153 (14.7)	0.16
Sodium bicarbonate	3,465 (8.0)	157 (5.2)	1,918 (8.9)	64 (6.2)	0.14
Immunosuppressants	600 (1.4)	31 (1.0)	350 (1.6)	20 (1.9)	0.08
Vitamin D	3,480 (8.0)	241 (8.0)	1,914 (8.9)	95 (9.2)	0.04
Iron supplement	6,352 (14.7)	396 (13.1)	3,739 (17.3)	147 (14.2)	0.12
Calcium	12,447 (28.7)	961 (31.7)	6,877 (31.9)	342 (32.9)	0.09
Follow-up year	3.2 ± 3.0	4.2 ± 3.5	3.3 ± 2.9	4.1 ± 3.5	0.51

IPTW, inverse probability of treatment weighting; CKD, chronic kidney disease; MASD, maximum absolute standardized difference; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; DCCB, dihydropyrinde calcium channel blocker; NDCCB, non-dihydropyrinde calcium channel blocker; NSAIDs, non-steroidal anti-inflammatory drugs; Data were presented as frequency (percentage), median [25th, 75th percentile] or mean ± standard deviation.

the non-user group; however, compared with the non-user and statin groups, the fibrate group did not exhibit significantly lower risks of all-cause mortality [fibrate vs. non-user: hazard ratio (HR), 0.97; 95% confidence interval (CI), 0.92–1.03; statin vs. fibrate: HR, 0.95; 95% CI, 0.90–1.01], CV death (fibrate vs. non-user: HR, 0.97; 95% CI, 0.90–1.05; statin vs. fibrate: HR,

TABLE 2 Follow up outcome for the dialytic patients according to the use of fibrate and statin in the IPTW-adjusted cohort.

Outcome/group	Incidence[$] (95% CI)	HR (95% CI) (Column vs. row)		
		Fibrate	Statin	Combination
All-cause mortality				
Non-user	16.6 (16.4–16.7)	0.97 (0.92–1.03)	**0.93 (0.90–0.95)***	**0.90 (0.82–0.99)***
Fibrate	16.0 (15.8–16.2)	–	0.95 (0.90–1.01)	0.93 (0.83–1.03)
Statin	15.3 (15.1–15.4)	–	–	0.97 (0.89–1.07)
Combination	14.9 (14.7–15.0)	–	–	–
Cardiovascular death				
Non-user	8.7 (8.6–8.8)	0.97 (0.90–1.05)	**0.94 (0.91–0.98)***	0.96 (0.84–1.10)
Fibrate	8.4 (8.3–8.5)	–	0.97 (0.90–1.06)	0.99 (0.85–1.15)
Statin	8.2 (8.0–8.3)	–	–	1.02 (0.89–1.17)
Combination	8.3 (8.2–8.4)	–	–	–
MACCE[#]				
Non-user	12.3 (12.2–12.5)	1.03 (0.96–1.10)	**0.96 (0.94–0.99)***	1.00 (0.89–1.13)
Fibrate	12.7 (12.5–12.8)	–	0.94 (0.87–1.004)	0.97 (0.85–1.11)
Statin	11.8 (11.7–12.0)	–	–	1.04 (0.93–1.17)
Combination	12.3 (12.1–12.4)	–	–	–

IPTW, inverse probability of treatment weighting; HR, hazard ratio; CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular events; [$]Incidence density was presented as event numbers per 100 person-years; [#]Composite of cardiovascular death, ischemic stroke, or acute myocardial infarction; [*]$P < 0.05$. Bold values denote statistical significance at the $P < 0.05$.

0.97; 95% CI: 0.90–1.06), and MACCEs (fibrate vs. non-user: HR, 1.03; 95% CI, 0.96–1.10; statin vs. fibrate: HR, 0.94; 95% CI, 0.87–1.004). Similarly, between the combination and statin groups, no significant differences were identified in all-cause mortality (HR, 0.97; 95% CI, 0.89–1.07), CV death (HR, 1.02; 95% CI, 0.89–1.17), or MACCEs (HR, 1.04; 95% CI, 0.93–1.17). The one-minus-Kaplan–Meier survival rates of the four groups are presented in Figure 2.

Because the duration of the use of lipid-lowering agents may affect the results. We selected patients who initiated statin, fibrate, or combination treatment since 3 months before index date and were still under treatment within 3 months prior to index date for analysis. The main results across long-term fibrate group, long-term statin group, long-term combination group were still consistent (Supplementary Table 4).

Follow-up outcomes for fibrates and moderate- to high-potency statins

A previous study reported that the combination of high-potency statins and fibrates has potential benefits for patients with advanced CKD (19). In this study, we determined whether this combination might benefit patients with ESRD. We excluded patients using low-potency statins and reperformed IPTW to rebalance the groups (Supplementary Tables 2, 3 present the baseline information of the modified groups); the follow-up outcomes are presented in Table 3. The moderate- to high-potency statin group exhibited modest declines in all-cause mortality, CV death, and MACCEs relative to the non-user group, and modest declines in MACCEs relative to the fibrate group; however, no significant differences were identified between the combination group and the moderate- to high-potency statin or fibrate groups.

Discussion

The role of fibrates in the reduction of mortality or CV risk among patients with CKD or ESRD have yet to be thoroughly studied. Although hypertriglyceridemia is commonly observed among patients undergoing permanent dialysis, nephrologists have difficulty in deciding whether to treat it with fibrates because of the lack of relevant researches. We designed this nationwide cohort study to compare all-cause mortality, CV deaths, and MACCEs among patients with ESRD using fibrates, statins, neither, or both to determine whether fibrates can reduce the risks of mortality and CV events in these patients.

Fibrates, a second-line lipid-lowering therapy, are not commonly used in patients with kidney impairment because they are mostly eliminated through urine and their metabolites might accumulate in patients with advanced kidney disease (16). A randomized controlled study reported that long-term fenofibrate (200 mg per day) use was associated with a reduced risk of CV events in patients with moderate kidney impairment (eGFR: 30–59 mL/min/1.73 m^2) (17). Our research team conducted a population-based cohort study, revealing that

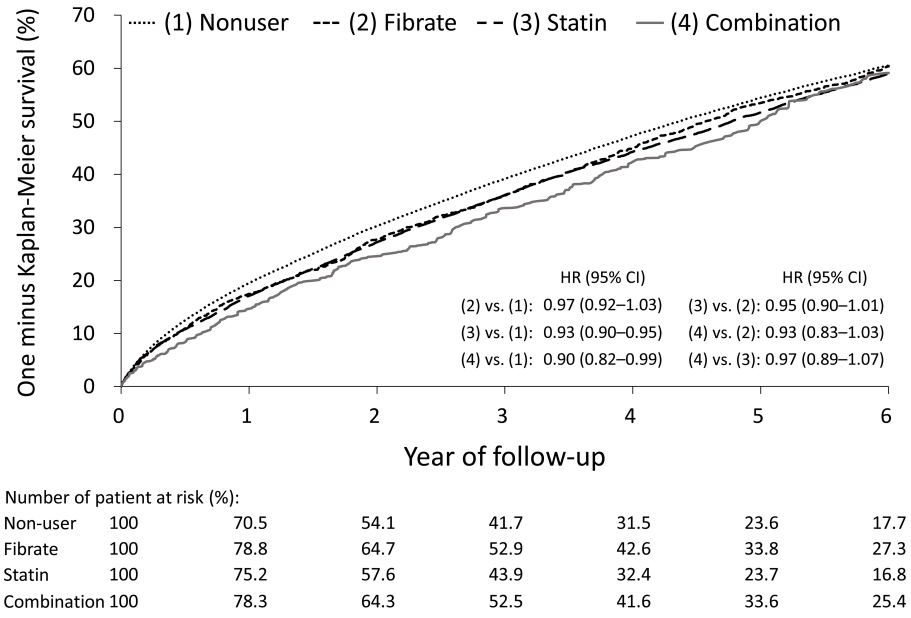

FIGURE 2
One minus Kaplan-Meier survival curves of the patients with concomitant end stage renal disease and hyperlipidemia under different lipid lowering therapies in the IPTW-adjusted cohort. IPTW, inverse probability of treatment weighting.

TABLE 3 Follow up outcomes for the dialytic patients according to the use of fibrate and moderate- to high-potency statins in the IPTW-adjusted cohort.

Outcome/group	Incidence[$] (95% CI)	HR (95% CI) (Column vs. row)		
		Fibrate	Moderate- to high-potency statins	Combination
All-cause mortality				
Non-user	16.7 (16.5–16.9)	0.97 (0.91–1.02)	**0.91 (0.89–0.94)***	**0.88 (0.79–0.98)***
Fibrate	16.0 (15.9–16.2)	–	0.95 (0.89–1.004)	0.91 (0.81–1.03)
Moderate- to high-potency statins	15.2 (15.0–15.4)	–	–	0.96 (0.86–1.08)
Combination	14.6 (14.5–14.8)	–	–	–
Cardiovascular death				
Non-user	8.8 (8.6–8.9)	0.97 (0.89–1.05)	**0.93 (0.90–0.97)***	0.97 (0.83–1.13)
Fibrate	8.4 (8.3–8.6)	–	0.96 (0.89–1.05)	1.00 (0.85–1.19)
Moderate- to high-potency statins	8.1 (8.0–8.2)	–	–	1.04 (0.89–1.21)
Combination	8.4 (8.3–8.6)	–	–	–
MACCE[#]				
Non-user	12.4 (12.3–12.6)	1.03 (0.96–1.10)	**0.96 (0.92–0.99)***	1.01 (0.89–1.15)
Fibrate	12.7 (12.6–12.9)	–	**0.93 (0.87–0.997)***	0.98 (0.85–1.13)
Moderate- to high-potency statins	11.8 (11.7–12.0)	–	–	1.06 (0.93–1.21)
Combination	12.4 (12.3–12.6)	–	–	–

IPTW, inverse probability of treatment weighting; HR, hazard ratio; CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular events; [$]Incidence density was presented as event numbers per 100 person-years; [#]Composite of cardiovascular death, ischemic stroke, or acute myocardial infarction; [*] $P < 0.05$. Bold values denote statistical significance at the $P < 0.05$.

fibrates can postpone the necessity of permanent dialysis and can reduce the risk of CV death in patients with advanced CKD. In subgroup analysis, the previous study also reported that the combination of fibrates and high-intensity statins exerted a stronger protective effect against CV events, though this relationship was less evident because of the fewer patients in the subgroup analyses. Furthermore, reduced-dose, alternate-day administration of fibrates can be safely used to treat patients undergoing hemodialysis, and fibrates exert antioxidative effects in addition to lipid-lowering effects, with the only side effect

being a non-significant elevation of muscle enzymes (20, 35). However, in the present study, patients who used fibrates did not exhibit outcomes (i.e., all-cause mortality, CV death, or MACCEs) superior to those of patients who used statins or who did not use lipid-lowering agents. Furthermore, the combination of statins and fibrates exhibited no additional benefits beyond those exhibited by statins or fibrates alone, regardless of whether the statins used had moderate-to-high potency. By comparison, this study exhibited the modest reduction in the study outcomes in the statin group. Although previous 4D and AURORA trials indicated that, compared with the impressive CV protection of statin treatment in non-ESRD population, statins have much less benefits for patients with ESRD (36, 37). However, this study demonstrated that statins, especially the moderate-to-high potency statins, still have better performances in reducing CV events than fibrates do among new-onset ESRD patients.

The possible explanations of why the TG-lowering and antioxidative properties of fibrates did not translate into reductions in the rates of the study outcomes are discussed as follows. First, the most common cause of mortality among patients with ESRD is sudden cardiac death, which accounts for ∼50% of such mortalities, followed by non-sudden CV disease and non-cardiac causes; these causes differ considerably from in the main causes of mortality among patients with CKD not undergoing dialysis (38), of which the most common cause is ASCVD. Therefore, reductions in traditional risk factors for ASCVD may not strongly affect overall mortality among patients with ESRD. Second, hemodialysis is associated with additional CV risks (39), namely sudden changes in blood pressure, use of anticoagulants, arteriosclerosis induced by calcium–phosphate imbalance, and frequent blood loss during hemodialysis. Therefore, hemodialysis considerably affects CV outcomes. Third, the chronic inflammation among patients with ESRD, including decreased clearance of pro-inflammatory cytokines, recurrent infections, and intestinal dysbiosis, have been proved to increase the CV risks (40), which is less influenced by TG-lowering agents. In patients with ESRD, factors not affected by TG-lowering therapies might dominate the causal pathway of adverse CV outcomes and thus obscure the effect of these drugs.

Actually, to evaluate the role of TG-lowering therapies among ESRD patients is very difficult through an observational study. The analyses would be biased with the confounding by indication. For example, those patients with hyperlipidemia required treatment of fibrate may originally have higher risks of CV events compared to those who do not need treatment, which must bias the results. Thus, this study was designed to compare not only the outcomes of patients using and not using fibrates but also those of patients using fibrates, statins, neither, and both. Studies have reported that among patients with ESRD, very low lipid profiles without requirements of statins or fibrates were conversely associated with higher risks of CV events, infections, and deaths (41, 42), which implies that these patients exhibited protein energy wasting (PEW), a complex of malnutrition and chronic inflammation, and had poor outcomes. If we simply compared the outcomes of fibrate users and non-users, patients with PEW would bias the results. On the other hand, although the direct effect of statins and fibrates are different (LDL-lowering vs.TG-lowering), physicians mostly prescribed these lipid-lowering agents in hopes of reducing risks of CV events. By comparing outcomes between fibrates-users and statins-users, we might, in some degree, reduce the confounding by indication. In this study, patients under treatment of fibrates not only had similar CV outcomes with those who did not receive lipid-lowering agents, but even exhibited slightly higher CV risks compared with patients under treatment of statins, which have been proved to exert less cardioprotective effect among ESRD patients (36, 37). Although an observational study is impossible to directly prove the cause and effect. These indirect evidences of this study implied that the treatment of fibrates may have no significant role in reducing CV events among patients with ESRD.

This study has main strength in being the only large-scale study focusing on the effects of fibrates on patients with ESRD, which enrolled more than 4,000 patients who used fibrates and employed a sufficient observation period. However, this study has some limitations should be acknowledged. First, although IPTW was used to adjust for possible confounding factors, some residual bias may have occurred due to the observational nature of the study. Second, some laboratory data, namely lipid profiles, blood sugar, glycosylated hemoglobin, and albumin, are not available in the NHIRD database, which made it difficult to balance the metabolic and nutritional profiles of the groups. Especially, a previous meta-analysis study enrolled patients with normal renal function has indicated that the fibrate effect on CV risks is greater in patients with higher TG levels (43). The lack of lipid profiles made it impossible to perform further subgroup analysis across different TG or cholesterol levels. Third, the dose of the lipid-lowering agents used by each patient was not available; thus, some heterogeneity in treatment may be inherent. Fourth, not all patients enrolled were new users of lipid-lowering medications. Therefore, the evaluation of possible side effects, which develop most commonly during the period soon after initiation, was out of the scope of this study.

Conclusion

In contrast to our previous study involving patients with advanced CKD, which demonstrated that fibrates might delay the requirement of dialysis and reduce the risk of CV death among such patients, the present study focused on patients with ESRD and determined that the use of fibrates, even when combined with high-potency statins, is not associated with reduced all-cause mortality, CV deaths, and MACCEs among such patients. These results may inform the decisions of nephrologists regarding the treatment of hypertriglyceridemia in patients with ESRD and imply that prescribing fibrates for

reducing CV risk in this population is unnecessary. This study was limited by its retrospective design and the lack of detailed lipid profiles. Additional randomized control trials and large-scale cohort studies with comprehensive laboratory data are warranted to verify our findings.

Data availability statement

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

Ethics statement

This study was approved with a waiver of consent by the Institutional Review Board of Chang Gung Medical Foundation (Approval Number: 201900840B0).

Author contributions

C-HC, C-LY, and H-HH contributed to conception and design of the study. C-YC, C-CL, Y-RT, W-YH, P-HC, and Y-CT collected and interpreted the data. C-CH and Y-RT analyzed the data. W-YH and C-LY wrote the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.907539/full#supplementary-material

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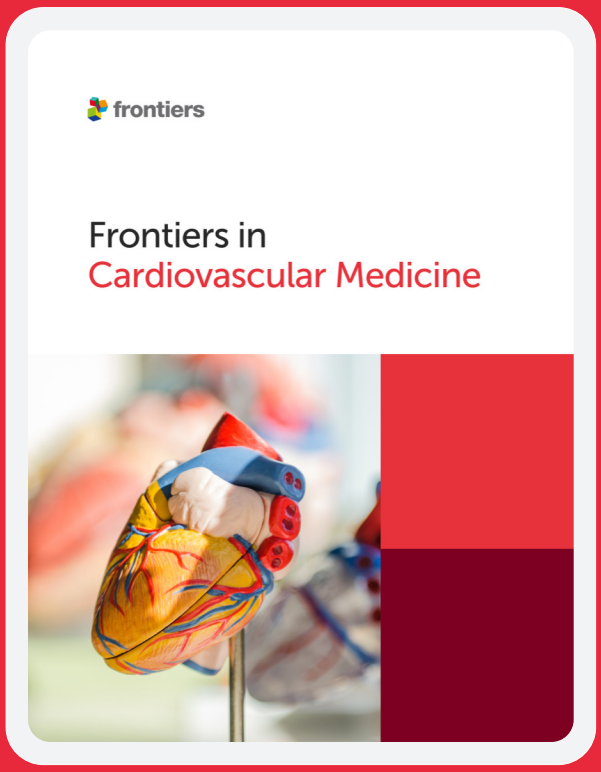

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