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SYSTEMATIC REVIEW

Ticagrelor or Clopidogrel as Antiplatelet Agents in Patients with Chronic Kidney Disease and Cardiovascular Disease: A Meta-analysis

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Abstract

Introduction The worldwide prevalence of chronic kidney disease (CKD) has significantly increased in the past decades. Scientific reports have shown CKD to be an enhancing risk factor for the development of cardiovascular disease (CVD), which is the leading cause of premature death in patients with CKD. Clinical practice guidelines are ambiguous in view of the use of antiplatelet drugs in patients with CKD because patients with moderate-to-severe CKD were often excluded from clinical trials evaluating the efficacy and safety of anticoagulants and antiplatelet agents. In this analysis, we aimed to systematically assess the adverse cardiovascular and bleeding outcomes that were observed with ticagrelor versus clopidogrel use in patients with CKD and cardiovascular disease.

Methods Electronic databases including Web of Science, Google Scholar, http://www.ClinicalTrials.gov, Cochrane database, EMBASE, and MEDLINE were carefully searched for English-based articles comparing ticagrelor with clopidogrel in patients with CKD. Adverse cardiovascular outcomes and bleeding events were the endpoints in this study. The latest version of the RevMan software (version 5.4) was used to analyze the data. Risk ratios (RR) with 95% confidence intervals (CI) were used to represent the data post analysis.

Results A total of 15,664 participants were included in this analysis, whereby 2456 CKD participants were assigned to ticagrelor and 13,208 CKD participants were assigned to clopidogrel. Our current analysis showed that major adverse cardiac events (MACEs) (RR: 0.85, 95% CI: 0.71–1.03; $P = 0.09$), all-cause mortality (RR: 0.82, 95% CI: 0.57– 1.18; $P = 0.29$), cardiovascular death (RR: 0.83, 95% CI: 0.56–1.23; $P = 0.35$), myocardial infarction (RR: 0.87, 95% CI: 0.70–1.07; $P = 0.19$), ischemic stroke (RR: 0.80, 95% CI: 0.58–1.11; $P = 0.18$), and hemorrhagic stroke (RR: 1.06, 95% CI: 0.38–2.99; $P = 0.91$) were not significantly different in CKD patients who were treated with ticagrelor versus clopidogrel. Thrombolysis in myocardial infarction (TIMI)-defined minor (RR: 0.89, 95% CI: 0.52–1.53; $P = 0.68$) and TIMI major bleeding (RR: 1.10, 95% CI: 0.69–1.76; $P = 0.67$) were also not significantly different. However, bleeding defined according to the academic research consortium (BARC) bleeding type 1 or 2 (RR: 1.95, 95% CI: 1.13–3.37; $P = 0.02$) and BARC bleeding type 3 or 5 (RR: 1.70, 95% CI: 1.17–2.48; $P = 0.006$) were significantly higher with ticagrelor.

Conclusions When compared with clopidogrel, even though ticagrelor was not associated with higher risk of adverse cardiovascular outcomes in these patients with CKD, it was associated with significantly higher BARC bleeding. Therefore, the safety outcomes of ticagrelor still require further evaluation in patients with CKD. Nevertheless, this hypothesis should only be confirmed with more powerful results that could usually only be achieved using large-scale randomized trials.

1 Introduction

The worldwide prevalence of chronic kidney disease (CKD) has significantly increased in the past decades [1]. An estimated 37 million individuals are currently living with CKD in the USA, and a further increase in the number of CKD patients is expected in view of the rise in CKD risk factor prevalence [2–4].

Scientific reports have shown CKD to be an enhancing risk factor for the development of cardiovascular disease (CVD), which is the leading cause of premature death in such patients [5]. Despite optimal medical management, any stage of CKD patients with cardiovascular events fare worse compared with similar patients without CKD [5]. Moreover,

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Key Findings

The worldwide prevalence of chronic kidney disease (CKD) has significantly increased in the past decades.

Scientific reports have shown CKD to be an enhancing risk factor for the development of cardiovascular disease (CVD), and CVD is the leading cause of premature death in patients with CKD.

Clinical practice guidelines are ambiguous in view of the use of antiplatelet drugs in patients with CKD because patients with moderate-to-severe CKD were often excluded from clinical trials evaluating the efficacy and safety of anticoagulants and antiplatelet agents.

Our analysis showed that even though ticagrelor was not associated with significantly higher risk of adverse cardiovascular outcomes in these patients with CKD, it was associated with significantly higher BARC bleeding.

Therefore, even though ticagrelor was as effective as clopidogrel, its safety outcomes still require further evaluation in patients with CKD.

compared with the general population, the prevalence of CVD is increased by twofold in the early stage of CKD [5], but is increased by 10–20 fold in CKD patients on dialysis, thereby increasing the mortality rate in dialysis patients by 50% [6].

CKD patients on medical therapy without any invasive procedure would require anticoagulants as a primary prevention from cardiovascular events. Percutaneous coronary intervention (PCI) is an invasive revascularization procedure in patients with cardiovascular events including acute coronary syndrome (ACS) [7]. Following implantation with drug-eluting stents (DES), patients are required to be on a dual antiplatelet (DAPT) regimen for at least 1 year to prevent adverse cardiovascular outcomes such as stent thrombosis [8].

However, renal impairment is a major predictor of thrombosis and bleeding complications for such patients [9]. Clinical practice guidelines are ambiguous in view of the use of antiplatelet drugs in patients with CKD because patients with moderate-to-severe CKD were often excluded from clinical trials evaluating the efficacy and safety of anticoagulants and antiplatelet agents [10].

Patients with CKD are at higher risk for thrombotic events [11]. Several studies have shown CKD patients to have a poor response with anticoagulants [12]. In view of the lack of data to guide antiplatelet therapy in patients with CKD in national as well as international guidelines, which only provide level C recommendations, the correct choice of antiplatelet agents for cardiovascular protection in patients with CKD is often challenging [10].

Recently, newer potent antiplatelet agents have been approved for use [13]. Ticagrelor and prasugrel, when included in the DAPT regimen instead of clopidogrel, have shown potential benefits in terms of cardiovascular outcomes [14].

In this analysis, we aimed to systematically assess the adverse cardiovascular and bleeding outcomes that were observed with ticagrelor versus clopidogrel use in patients with CKD and cardiovascular disease.

2 Methods

2.1 Search Databases and Search Strategies

Electronic databases including Web of Science, Google Scholar, http://www.ClinicalTrials.gov, Cochrane database, EMBASE, and MEDLINE (subset PubMed) were carefully searched for English-based articles comparing ticagrelor with clopidogrel in patients with CKD/end stage renal disease/on dialysis.

The search terms "ticagrelor, clopidogrel and chronic kidney disease," "ticagrelor and clopidogrel and end stage renal disease," "ticagrelor and clopidogrel and dialysis," "ticagrelor and clopidogrel and renal impairment," "antiplatelet and chronic kidney disease," "antiplatelet and end stage renal disease," and "chronic kidney disease and ticagrelor" were used to identify relevant publications.

2.2 Inclusion and Exclusion Criteria

The inclusion criteria were as follows:

- Publications in English;
- Randomized or nonrandomized studies comparing ticagrelor versus clopidogrel in patients with CKD;
- Studies that reported adverse cardiovascular outcomes and bleeding events as their endpoints;
- Studies with a follow up time of 12 months.

The exclusion criteria were as follows:

- Non-English-language publications;
- Systematic reviews and meta-analyses, literature reviews, case studies, editorials;
- Studies that did not report cardiovascular outcomes but instead reported only platelet reactivity;
- Studies involving patients with acute kidney injury;
- Studies with a follow-up of less than 12 months;

- Studies that consisted of data that could not be used in the meta-analysis. That is, studies that reported data in hazard ratios or consisted of data not compatible with data in this analysis;
- Duplicated studies or studies that were based on the same trial or cohort study.

2.3 Definitions, Outcomes, and Follow-Up

The outcomes reported in the original studies have been listed in Table 1. The duration of follow-up was 12 months.

The endpoints that were assessed in this analysis included:

- Major adverse cardiac events (MACEs), which were defined as a total of several cardiovascular adverse events including all-cause mortality/cardiac death, any myocardial infarction, and stroke/repeated revascularization;
- All-cause mortality;
- Myocardial infarction (MI);
- Cardiovascular mortality;
- Ischemic stroke;
- Hemorrhagic stroke;
- Any bleeding event;
- Any minor bleeding event;
- Any major bleeding event;
- Bleeding defined by the academic research consortium (BARC) [22] bleeding type 1 or 2;
- BARC bleeding type 3 or 5;
- Thrombolysis in myocardial infarction (TIMI) [22] major bleeding;
- TIMI minor bleeding.

2.4 Data Extraction and Quality Assessment

Data were independently extracted by all the five authors. The abstracts, methods, and results, as well as all the data given in the respective tables were carefully assessed and relevant data including the type of participants, type of study, year of participants' enrollment, methodological features, assignment of participants to each antiplatelet group, the outcomes that were reported, the follow-up time, the number of events reported within each outcome, the country of origin where participants were enrolled, and the baseline features of the participants were extracted.

During this data extraction process, if any disagreement occurred among the authors, it was carefully discussed among all of them and then a consensus was reached.

This analysis included both randomized and nonrandomized studies. The methodological quality of the nonrandomized studies was assessed by the Newcastle Ottawa Scale (NOS) [23] while the methodological quality of the randomized trial was assessed based on the recommendations suggested by the Cochrane collaboration tool [24].

To establish transparency of systematic review results and findings, a risk of bias assessment was performed for each included randomized study. The recommendations suggested by the Cochrane collaboration included:

Table 1 Outcomes and follow-up duration reported in the original studies

Studies	Outcomes reported	Duration of follow-up
Chen 2022 et al. [15]	MACEs, all-cause mortality, cardiovascular death, MI, ischemic stroke, total BARC bleedings, BARC 1 or 2, BARC 3 or 5 bleedings	12 months
Jain 2021 et al. [16]	MACEs, all-cause mortality, cardiovascular death, coronary revascularization, gastrointestinal hemorrhage	12 months
James 2010 et al. [17]	MACEs, all-cause mortality, major bleeding, major or minor bleeding, non-CABG major bleeding, fatal major bleeding, TIMI major or minor bleeding, non-CABG major TIMI bleeding, intracranial bleeding, dyspnea, ventricular pauses	12 months
Lee 2019 et al. [18]	MACEs, all-cause mortality, cardiovascular death, MI, cerebrovascular attack, any bleeding event, gastrointestinal bleeding, intracranial hemorrhage, TIMI major, TIMI minor, TIMI major + minor	12 months
Li 2020 et al. [19]	MACEs, MI, all-cause mortality, stroke, any bleeding event, any major bleeding	12 months
Mavrakanas 2021 et al. [20]	MACEs, cardiovascular death, MI, stroke, revascularization, all-cause mortality, clinically relevant bleeding	12 months
Roh 2022 et al. [21]	MACCEs, BARC type 3–5, all-cause mortality, cardiac death, MI, stent thrombosis, cerebrovascular attack (ischemic and hemorrhagic), BARC type 2, BARC type 2–5	12 months

BARC bleeding defined according to the academic research consortium, *CABG* coronary artery bypass grafting, *MACEs* major adverse cardiac events, *MACCEs* major adverse cardiovascular and cerebrovascular events, *MI* myocardial infarction, *TIMI* Thrombolysis in Myocardial Infarction

*Study Lee 2019 and study Li 2020 are from the same retrospective cohort. Since both have few endpoints which are reported in one of the studies and not in the other and vice versa, we have decided to retain both studies in our analysis; however, the number of participants will be counted only once. There will not be any repetition during data analysis.

- Random sequence generation (selection bias);
- Allocation concealment (selection bias);
- Blinding of participants and personnel (performance bias);
- Blinding of outcome assessment (detection bias);
- Incomplete outcome data (attrition bias);
- Selective reporting (reporting bias);
- Other bias.

For the nonrandomized studies, the NOS was used to assess bias risk. This tool was developed to assess the quality of nonrandomized studies based on its design, content, and ease of use directed to the task of incorporating the quality assessments in the interpretation of meta-analytic results. A "star system" has been developed in which a study is judged on three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively:

(a) Selection:

- Representative of the exposed cohort;
- Selection of the external control;
- Ascertainment of exposure;
- Outcome of interest not present at the start of the study.

(b) Comparability:

- Main factor and additional factor based on comparability of cohorts.

(c) Outcome:

- Assessment of outcomes;
- Sufficient follow-up time;
- Adequacy of follow-up.

For the data extraction, it should be noted that the studies by Lee et al. [20] and Li et al. [21] were based on the same retrospective study. Even though we have included both studies in this paper (due to different outcomes reported), the count for the number of participants was not repeated.

2.5 Statistical Analysis

The latest version of the RevMan software (version 5.4) was used to analyze the data in this study. Risk ratios (RR) with 95% confidence intervals (CI) were used to represent the data post analysis.

The studies included in this analysis show variation and, in a meta-analysis, this variability is termed heterogeneity. Heterogeneity during this statistical analysis was assessed first of all by the Q statistic test, based on a P-value. Interpretation is as follows: a P-value less than or equal to 0.05 was considered statistically significant whereas a P-value above 0.05 was not considered significant statistically. A second method was used to assess heterogeneity based on the I^2 value, which was reported as a percentage. During the data analysis, a higher I^2 value denoted higher heterogeneity whereas a lower I^2 value indicated lower heterogeneity.

A quality-effect meta-analysis has a strong aspect in that it allows available methodological evidence to be used over subjective random effects, thereby helping to close the damaging gap that occurs between methodology and statistics in clinical research. For example, if study A is of good quality, and the other studies are of poor qualities, a proportion of their quality-adjusted weights is mathematically redistributed to study A to give it more weight toward the overall effect size.

A random-effect model was used during the statistical analysis. A meta-regression was not applicable since the number of studies is less than ten.

A sensitivity analysis was also carried out and publication bias was visually assessed through funnel plots by observing the symmetrical feature of the funnel.

2.6 Compliance with ethical guidelines

This meta-analysis was based on previously published studies and did not contain any studies with human participants or animals performed by any of the authors.

3 Results

3.1 Search Outcomes

Online databases were carefully searched with reference to the Preferred Reporting Items in Systematic Reviews and Meta-Analyses (PRISMA) study guideline [25]. A total number of 109 publications were obtained. The titles and abstracts were carefully assessed, and irrelevant publications were directly eliminated (59). Fifty full-text articles were assessed for eligibility.

Further eliminations were carried out based on the following:

- Systematic reviews and meta-analysis (1);
- Case studies/editorials (5);
- Reporting only platelet reactivity as endpoints (4);
- Included data that could not be used in this meta-analysis (1);
- A follow up time period of less than 12 months (3);
- Duplicated studies or studies based on similar trials or observational studies (29).

Finally, only seven studies [15–21] were selected for this analysis. The study selection is shown in Fig. 1.

3.2 General and Baseline Features of the Studies and Participants

All the patients included in this analysis were patients with CKD, including mostly patients with end-stage renal diseases (ESRD) on dialysis. All the patients suffered from ACS or coronary artery disease. The estimated glomerular filtration rate (eGFR) or creatinine clearance (CrCl) of the patients have been listed in Table 2.

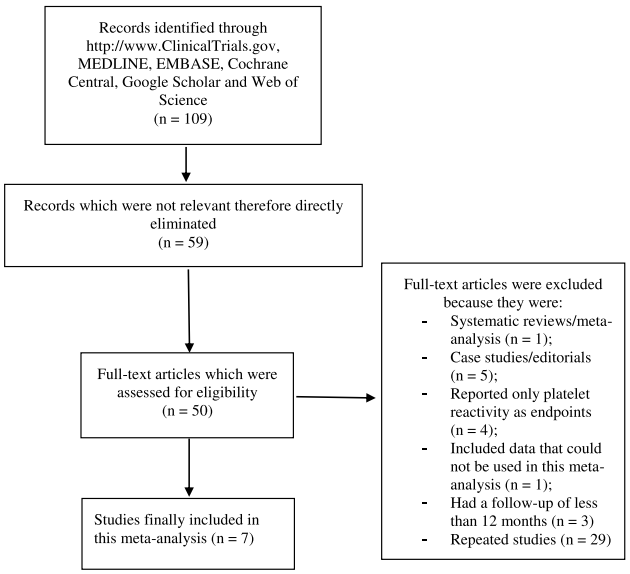

Fig. 1 Flow diagram showing the study selection

A total number of 15,664 participants were included in this analysis, whereby 2456 CKD participants were assigned to ticagrelor and 13,208 CKD participants were assigned to clopidogrel, as presented in Table 2.

The general features of the studies are listed in Table 3. Most of the studies were prospective and retrospective studies. The patients' enrollment period varied from 2006 to 2019 and the participants were from countries including the USA, China, Korea, and Taiwan.

The antiplatelet drugs used and the dosage are listed in Table 3. According to Table 3, most of the patients were on DAPT with aspirin 100 mg and clopidogrel 75 mg once daily, or aspirin 100 mg once daily and ticagrelor 90 mg twice daily. As stated in Table 3, in two studies, no detail was provided about aspirin use in these patients with CKD. However, aspirin use is often not recorded in most US claims databases, and it is comprehensible that most patients are on DAPT.

The methodological quality of the studies were assessed based on the recommendations of the Cochrane collaboration for the randomized trials and the NOS for the nonrandomized trials. Details of this assessment are detailed in Table 4.

Table 5 lists the baseline features of the participants. The CKD participants had a mean age ranging from 64.0 to 74.0 years. The majority of the patients were males with a mean percentage varying from 50.0 to 77.0%. Table 4 also lists the mean percentage of CKD participants with co-morbid conditions including hypertension, diabetes mellitus, dyslipidemia, and those who were smokers in both the experimental (ticagrelor) and the control (clopidogrel) groups.

Table 2 Types of participants and their assignment to antiplatelet agents

Studies	Type of participants	Renal function (eGFR or creatinine clearance)	No. of patients assigned to ticagrelor (*n*)	No. of patients assigned to clopidogrel (*n*)
Chen 2022 et al.	Severe renal insufficiency undergoing PCI for ACS	≤ 30 ml/min/1.73 m^2 or on dialysis	108	168
Jain 2021 et al.	ESRD receiving long-term dialysis and CAD	≤ 15 ml/min/1.73 m^2 on dialysis	880	3520
James 2010 et al.	CKD and ACS	≤ 60 ml/min	300	339
Lee 2019 et al.	ESRD with AMI	≤ 15 ml/min/1.73 m^2 on dialysis	74	116
Li 2020 et al.	ACS and receiving dialysis	≤ 15 ml/min/1.73 m^2 on dialysis	270	1915
Mavrakanas 2021 et al.	CKD and CAD	≤ 15 ml/min/1.73 m^2 on dialysis	449	6648
Roh 2022 et al.	CKD and ACS	< 60 ml/min/1.73 m^2 or on dialysis	449	618
Total no of participants (*n*)			2456	13,208

ACS acute coronary syndrome, *AMI* acute myocardial infarction, *CAD* coronary artery disease, *CKD* chronic kidney disease, *ESRD* end-stage renal disease, *eGFR* estimated glomerular filtration rate, *PCI* percutaneous coronary intervention

Table 3 General features of the studies included in this analysis

Studies	Type of study	Participant enrollment	Country of participants enrollment	Antiplatelet drugs
Chen 2022 et al.	Retrospective	2015–2020	China	DAPT with ASA 100 mg once daily, and either clopidogrel 75 mg once daily or ticagrelor 90 mg twice daily
Jain 2021 et al.	National cohort	2011–2015	USA	Clopidogrel 75 mg once daily or ticagrelor 90 mg twice daily. There was no mention about the use of ASA
James 2010 et al.	Randomized trial	2006–2008	USA	DAPT with ASA 100 mg once daily, and either clopidogrel 75 mg once daily or ticagrelor 90 mg twice daily
Lee 2019 et al.	Retrospective cohort	2013–2016	Taiwan	DAPT with ASA 100 mg once daily, and either clopidogrel 75 mg once daily or ticagrelor 90 mg twice daily
Li 2020 et al.	Retrospective cohort	2013–2016	Taiwan	DAPT with ASA 100 mg once daily, and either clopidogrel 75 mg once daily or ticagrelor 90 mg twice daily
Mavrakanas 2021 et al.	Retrospective cohort	2012–2015	USA	Clopidogrel 75 mg once daily or ticagrelor 90 mg twice daily. Data on ASA use is not available
Roh 2022 et al.	Prospective cohort	2013–2019	Korea	DAPT with ASA 100 mg once daily, and either clopidogrel 75 mg once daily or ticagrelor 90 mg twice daily

ASA aspirin, *DAPT* dual antiplatelet therapy

3.3 Main Results of this Analysis

Our current analysis showed that MACEs (RR: 0.85, 95% CI: 0.71–1.03; $P = 0.09$), all-cause mortality (RR: 0.82, 95% CI: 0.57–1.18; $P = 0.29$), cardiovascular death (RR: 0.83, 95% CI: 0.56–1.23; $P = 0.35$), MI (RR: 0.87, 95% CI: 0.70–1.07; $P = 0.19$), ischemic stroke (RR: 0.80, 95% CI: 0.58–1.11; $P = 0.18$), and hemorrhagic stroke (RR: 1.06, 95% CI: 0.38–2.99; $P = 0.91$) were not significantly different in CKD patients who were treated with ticagrelor versus clopidogrel, as shown in Fig. 2.

When bleeding outcomes were assessed in CKD patients who were treated with ticagrelor versus clopidogrel, the former was associated with significantly higher risk of BARC bleeding type 1 or 2 (RR: 1.95, 95% CI: 1.13–3.37; $P = 0.02$) and BARC bleeding type 3 or 5 (RR: 1.70, 95% CI: 1.17–2.48; $P = 0.006$), as shown in Fig. 3. However, TIMI-defined minor (RR: 0.89, 95% CI: 0.52–1.53; $P = 0.68$) and TIMI major bleeding (RR: 1.10, 95% CI: 0.69–1.76; $P = 0.67$) were not significantly different (Fig. 3). Moreover, gastrointestinal bleeding (RR: 0.91, 95% CI: 0.65–1.28; $P = 0.59$), "any bleeding event" (RR: 2.10, 95% CI: 0.87–5.03; $P = 0.10$), "any minor bleeding" (RR: 1.47, 95% CI: 0.90–2.40; $P = 0.13$), and "any major bleeding events" (RR: 1.22, 95% CI: 0.87–1.73; $P = 0.25$) were also not significantly different, as shown in Fig. 3.

This analysis involved studies from both randomized and nonrandomized trials. The analysis consisted of only one study that was a randomized trial. We excluded this trial and carried out an analysis with only the nonrandomized trials. However, there was no significant difference in the results with or without inclusion of the randomized trials. The analysis involving only nonrandomized trials has been provided as Supplementary Figs. 1 and 2.

Consistent results were observed throughout when the sensitivity analysis was carried out. Visual assessment of the funnel plots showed little evidence of publication bias among the studies that were involved when assessing the cardiovascular and bleeding outcomes among these patients with CKD. The funnel plots are shown in Figs. 4 and 5.

4 Discussion

In view of the lack of data to guide antiplatelet therapy in patients with CKD in national as well as international guidelines, the correct choice of antiplatelet agents for cardiovascular protection in patients with CKD is often challenging. Therefore, through this analysis, we aimed to show the impact of ticagrelor, a potent antiplatelet agent, on adverse cardiovascular outcomes and bleeding events in patients with CKD in comparison with clopidogrel.

It should be noted that patients with CKD are at higher risk of thrombotic events and the pathogenic mechanisms associated with thrombosis include platelet activation, increased formation of platelet–leukocyte conjugates and

Table 4 The methodological quality assessment of the studies

For the randomized trial	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
James 2010 et al.	√	√	√	√	x	√	x
For the nonrandomized trials	Chen 2022 et al.	Jain 2021 et al.	Lee 2019 et al.	Li 2020 et al.	Mavrakanas 2021 et al.	Roh 2022 et al.	
Selection							
Representative of the exposed cohort	*	*	*	*	*	*	
Selection of the external control	*	*	*	*	*	*	
Ascertainment of exposure	x	x	x	x	x	x	
Outcome of interest not present at the start of the study	*	*	*	*	*	*	
Comparability							
Main factor and additional factor based on comparability of cohorts	*	*	*	*	*	*	
Outcome							
Assessment of outcomes	*	*	*	*	*	*	
Sufficient follow up time	*	*	*	*	*	*	
Adequacy of follow up	*	*	*	*	*	*	

√ (present); x (absent or not reported)

Table 5 Baseline characteristics of the CKD participants included in this analysis

Studies	Mean age (years) Tica/Clo	Males (%) Tica/Clo	HBP (%) Tica/Clo	DL (%) Tica/Clo	DM (%) Tica/Clo	Smoker (%) Tica/Clo
Chen 2022	66.3/68.2	73.1/67.4	72.2/78.6	–	33.3/43.5	29.6/22.6
Jain 2021	64.0/64.0	55.0/54.9	89.7/89.8	–	81.5/81.6	–
James 2010	74.0/74.0	60.2/60.2	77.8/77.8	47.8/47.8	33.0/33.0	–
Lee 2019	65.2/67.9	64.9/60.3	83.8/89.7	37.8/30.2	68.9/69.0	21.6/12.1
Li 2020	64.2/67.2	64.1/56.5	70.0/75.4	24.1/25.1	69.3/62.9	–
Mavrakanas 2021	64.0/64.0	50.0/55.0	100/99.0	95.0/94.0	88.0/89.0	–
Roh 2022	68.3/70.4	79.1/69.6	74.2/80.7	58.8/57.9	56.1/62.3	47.4/40.6

Clo Clopidogrel, *DL* dyslipidemia, *DM* diabetes mellitus, *HBP* high blood pressure, *Tica* ticagrelor

platelet-derived microparticles, inflammatory reactions, and the effect of uremic toxins on platelets [26]. Further, the risk of bleeding events is also high in CKD patients due to platelet hyporeactivity mediated by uremic toxins and chronic anemia [26].

The current results showed that in patients with CKD, ticagrelor did not significantly reduce the risk of MACEs and other cardiovascular outcomes when compared with clopidogrel. However, BARC bleeding types 1 and 2 and types 3–5 were significantly increased with ticagrelor.

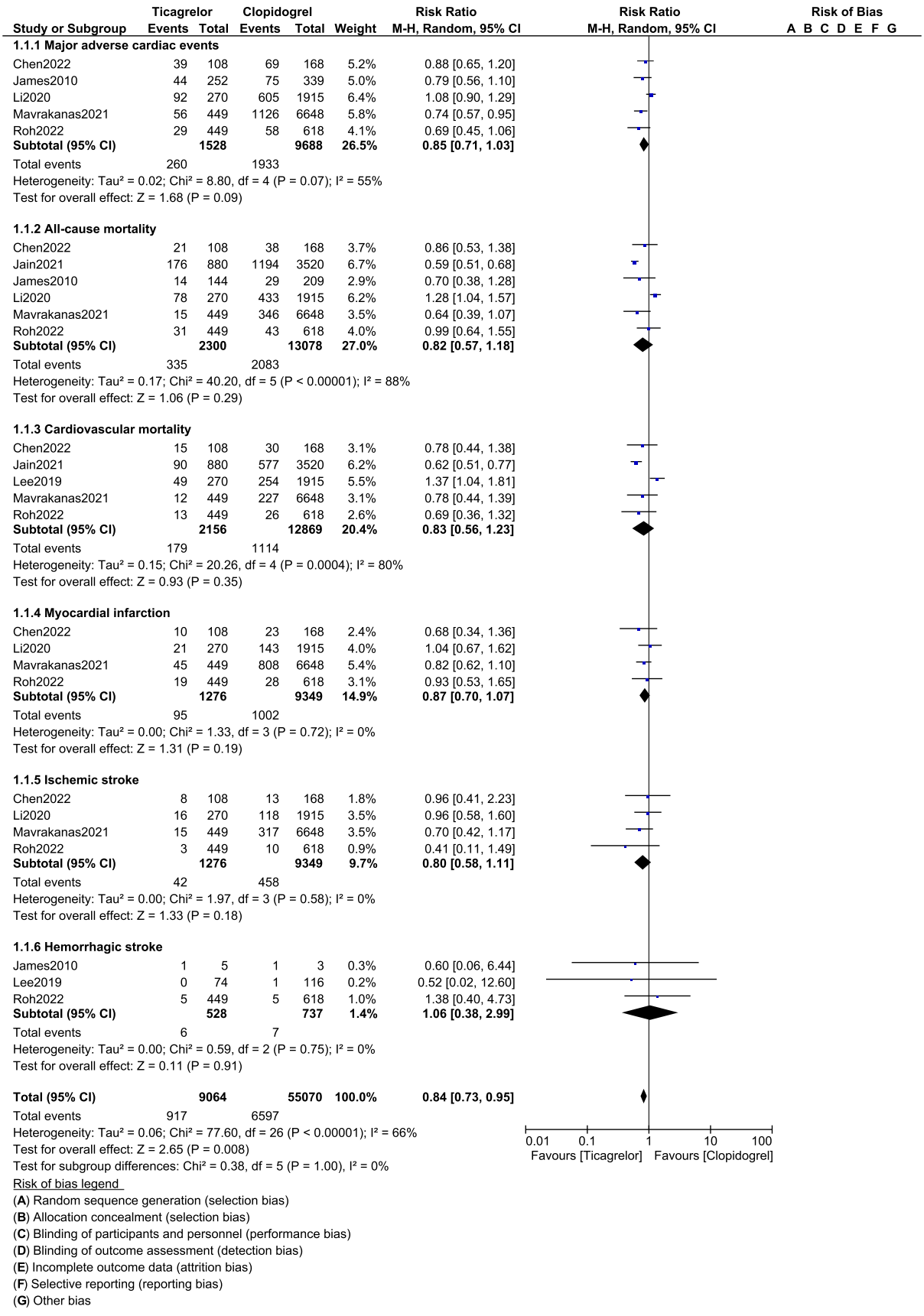

Fig. 2 Adverse cardiovascular outcomes in patients with CKD treated with ticagrelor versus clopidogrel

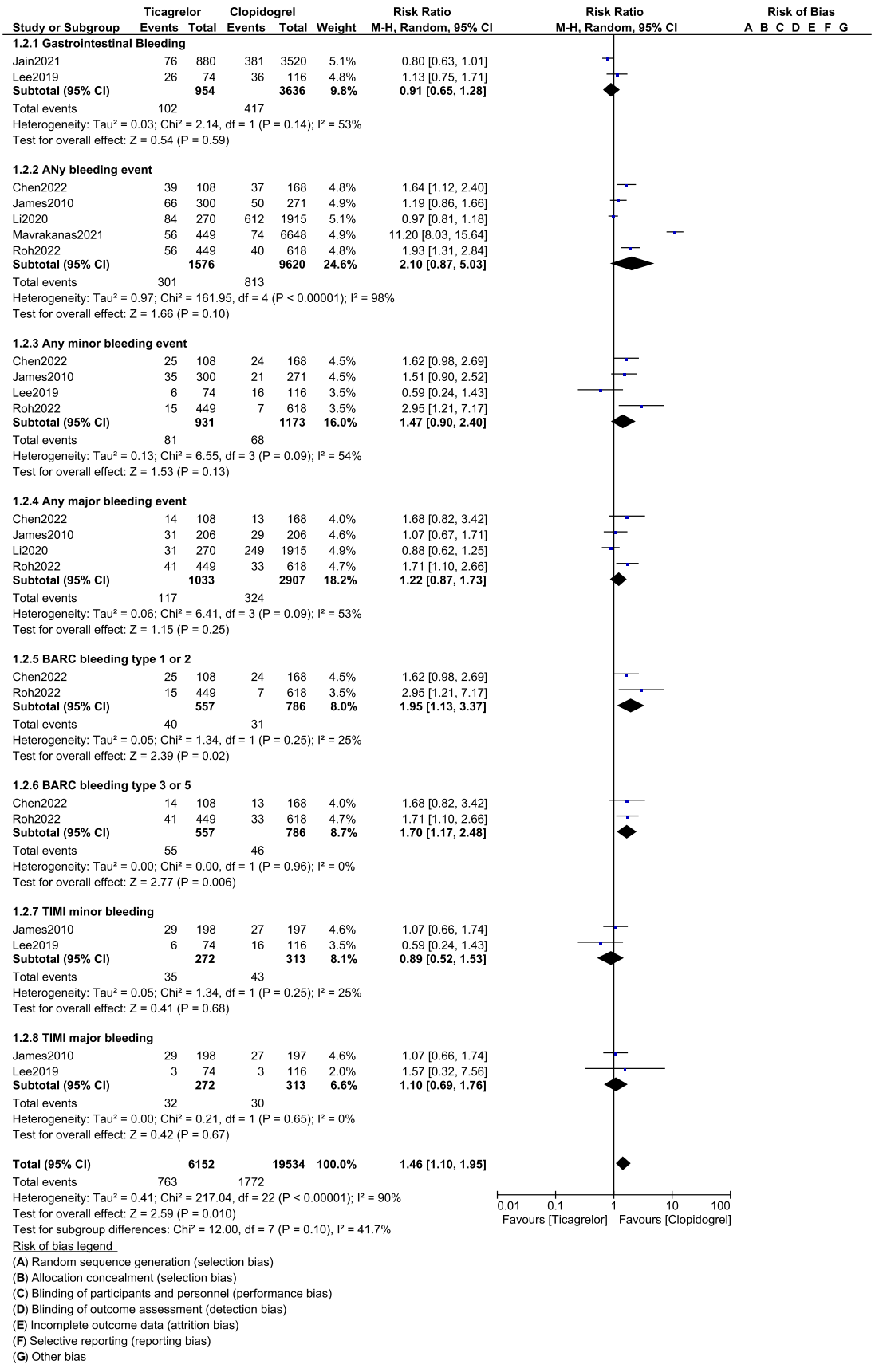

Fig. 3 Bleeding events observed in patients with CKD treated with ticagrelor versus clopidogrel

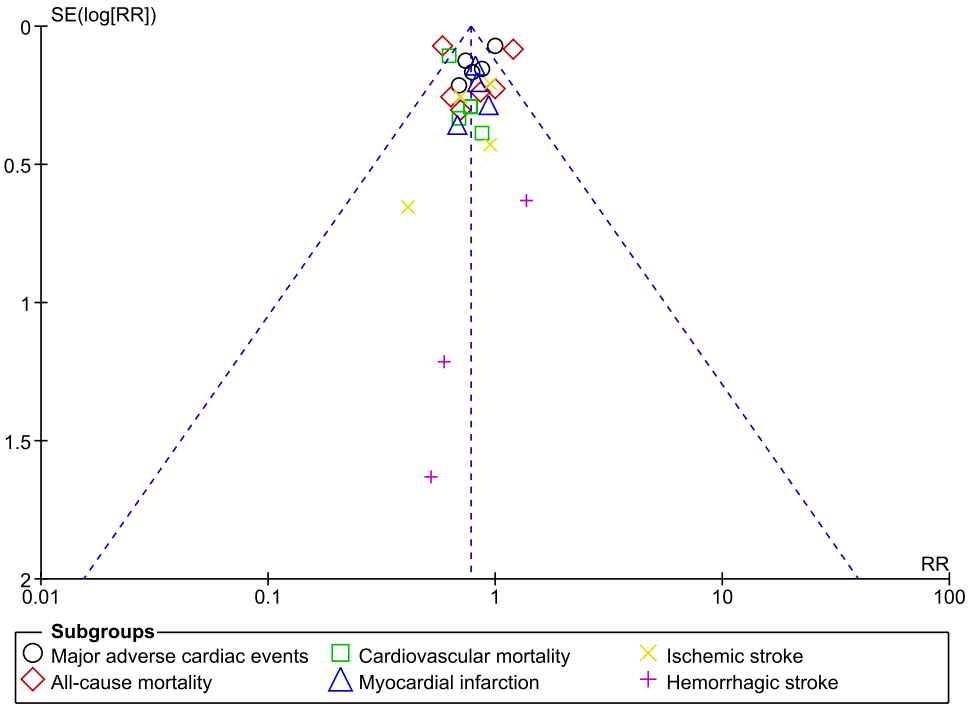

Fig. 4 Funnel plot showing publication bias (A)

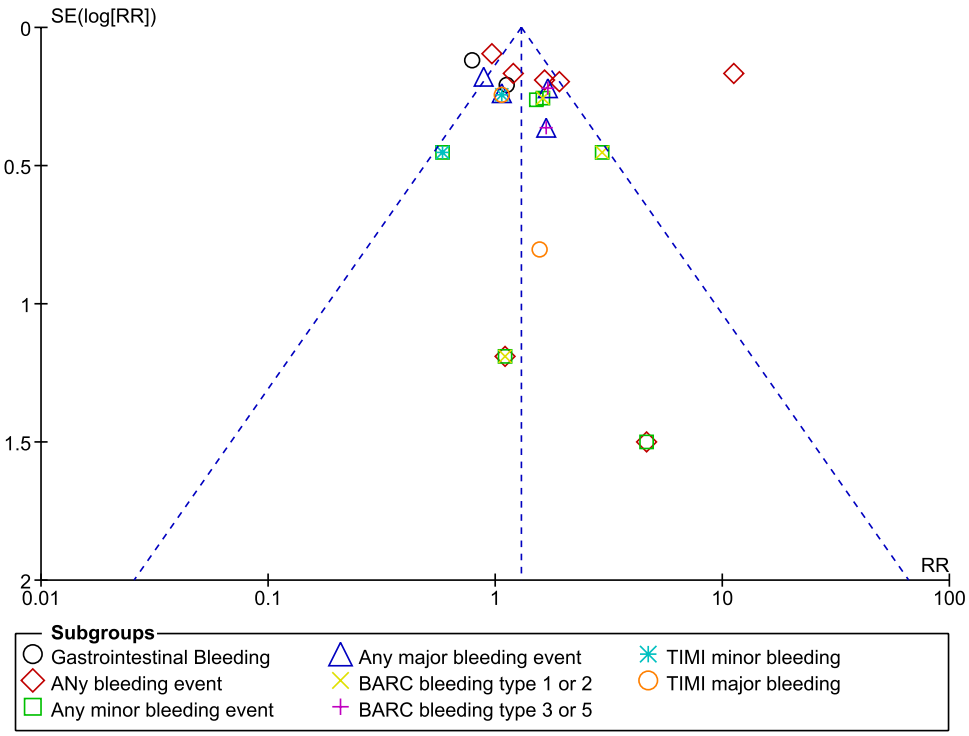

Fig. 5 Funnel plot showing publication bias (B)

This analysis consisted of studies from randomized and nonrandomized trials. A new analysis was carried out based only on nonrandomized trials; however, there was no significant difference in the results compared with the main results of this analysis. A study from the PLATO trial compared ticagrelor versus clopidogrel in ACS patients with impaired renal function [17]. The results from the PLATO trial varied significantly from the results of our current analysis. In the PLATO trial, among ACS patients with CKD, ticagrelor significantly reduced ischemic endpoints and mortality (hazard ratio: 0.71, 95% CI: 0.59–0.86; $P = 0.03$) without any significant increase in major bleeding, but with more

nonprocedure-related bleeding. Our current analysis showed a significant increase in bleeding, as defined by the academic research consortium. However, TIMI-defined major and minor bleedings were not increased with ticagrelor.

A recent systematic review and meta-analysis [27] based on the effect of antiplatelet therapy on cardiovascular and kidney outcomes in patients with CKD involving 27,773 patients showed that antiplatelet therapy reduced the odds of major cardiovascular events by 15% and had no significant effect on all-cause mortality or kidney failure events; however, antiplatelet agents increased the odds of major and minor bleedings. The authors specified that among every 1000 patients with CKD treated with antiplatelet therapy for 12 months, 23 major cardiovascular events could be prevented while 9 major bleeding events would occur, and since prevention of cardiovascular events outweighed the risk of bleeding events, an overall net benefit was observed with antiplatelet use in CKD patients. The authors thus concluded that individual evaluation and careful monitoring of patients with CKD on antiplatelet therapy would be required.

A double-blind randomized trial [28] comparing the effect of ticagrelor versus clopidogrel in 48 patients with nondialysis CKD stage 4–5 showed significant differences in platelet aggregation and anti-inflammatory properties between ticagrelor- and clopidogrel-based DAPT and therefore suggested that ticagrelor-based DAPT might lower inflammatory burden of asymptomatic patients with CKD stage 4 or 5.

In contrast, in a nationwide cohort study [29] based on patients with ESRD and who were on hemodialysis, the authors demonstrated that in such patients receiving DAPT for acute MI, ticagrelor and clopidogrel were comparable with regards to the composite endpoint and bleeding events.

It is vital to also mention that ticagrelor versus clopidogrel showed different treatment effects among patients from different ethnicities. For example, in East Asian participants with ACS, ticagrelor and clopidogrel displayed similar effects [30]. Administration of either ticagrelor or clopidogrel in ACS patients from East Asia showed no statistical difference in terms of major adverse events and cardiovascular death or all-cause mortality. However, ticagrelor was associated with a significantly higher major bleeding risk. Moreover, in Korean patients with ACS intended for invasive management among 800 Korean participants with ACS, clinically significant bleeding was observed with ticagrelor [31]. Major bleeding and fatal bleeding were significantly higher in the ticagrelor group when compared with the clopidogrel group. When Asian and non-Asian participants from the PLATO trial were compared based on the use of ticagrelor versus clopidogrel, even though cardiovascular events were higher in Asian participants, the effects of ticagrelor versus clopidogrel were not significantly different between the Asian and non-Asian populations [32]. In the prespecified interim analysis of Comparison of Efficacy and Safety between TIcagrelor and Clopidogrel In Chinese (COSTIC) [33], ticagrelor was superior to clopidogrel with regard to major vascular thrombotic outcomes at 1 month, especially in patients with ACS, but both antiplatelet groups had similar thrombotic outcomes at 7 days, 6 months and 12 months. However, ticagrelor consistently caused significantly more BARC type 2 bleeding in these Chinese patients.

Su et al. demonstrated the effects of antiplatelet therapy on cardiovascular and kidney outcomes in patients with CKD through a systematic review and meta-analysis [27]. In their review, they concluded that antiplatelet therapy might reduce the occurrence of major cardiovascular events and hemodialysis vascular access failure in CKD patients. Even though there seemed to be a net benefit compared with risk using antiplatelet agents in patients with CKD, significant bleeding risk was a potential drawback. Hence, careful monitoring was required when using antiplatelet therapy in these patients. In another meta-analysis, the effect of antiplatelet therapy on bleeding outcomes was assessed in 9969 participants with CKD [34]. The authors showed antiplatelets to increase serious bleeding in these patients. However, their definitions for bleeding outcomes and trial duration were heterogeneous. Moreover, from the TICO (Ticagrelor Monotherapy After 3 Months in Patients Treated With New Generation Sirolimus-Eluting Stent for Acute Coronary Syndrome) trial, whereby 2660 participants were included, an estimated glomerular filtration rate < 60 mL/min/1.73 m^2 was associated with an increased risk of major bleeding (TIMI-defined major bleeding and BARC 3a–5b bleeding) after ticagrelor therapy [35]. Therefore, a significantly higher major bleeding risk with ticagrelor therapy cannot be ruled out at present, requiring further larger studies. In addition, insights from the Canadian Observational Antiplatelet Study (COAPT) based on the use and outcomes of DAPT for ACS patients with CKD showed that patients with CKD were mostly prescribed less-potent antiplatelet agents compared with patients without CKD [36]. Among those CKD patients who were prescribed potent antiplatelets, more bleeding risks were observed compared with patients without CKD.

In our study, during the data analysis for all-cause mortality, data from all the studies pointed toward a lower estimate, except for the study by Li et al. In this study, even though patients in the ticagrelor group were younger (mean age 64.0 versus 67.0 years), a higher percentage of participants were suffering from acute MI (93.3% for the ticagrelor group versus 78.9% for the clopidogrel group) and diabetes mellitus. Also, a higher proportion of patients in the ticagrelor group were on angiotensin-converting enzyme inhibitors (ACEI) and statin when compared with participants in the clopidogrel group. This might have reflected in a tendency

of higher ischemic stroke in such patients. Data from other studies did not significantly differ.

Nevertheless, this study also has limitations. First of all, there were only a few studies that reported bleeding outcomes and, therefore, during data analysis, less studies were involved when assessing bleeding outcomes in comparison with adverse cardiovascular outcomes. Another limitation is that studies from randomized trials and retrospective and prospective observational cohorts were combined and analyzed. This might have a minor impact on the results due to the introduction of bias from observational studies. Fortunately, a random-effect statistical model was used during data analysis. This randomized-effect model assumed heterogeneity among mixed studies that were combined especially if the study designs were different, even if a heterogeneity test did not show significant results. This random-effect model assumed that the size of the effects of treatment differed among the studies. Therefore, differences in variation among the studies were believed not only to be due to random error, but also between study variability in the results. Hence, the weighting did not decrease largely for studies with a small number of patients. In a random-effect model, studies were given relatively similar weights irrespective of the study population size. When several small studies of different methodological types have been used, a sensitivity analysis was performed to control the small study effect.

Also, selection bias was introduced by the clinicians themselves based on the choice of antiplatelet agents to be used by selective patients. For example, in a real-world registry (multicenter START-ANTIPLATELET registry) of patients with acute coronary syndrome, 45% were at higher risk of bleeding, and such patients were frequently treated with clopidogrel [37]. Another real-world study, the Improving Care for Cardiovascular Disease in China (CCC-ACS) project, comprising of 17,420 patients on clopidogrel and 4700 patients on ticagrelor, the authors clearly showed that ticagrelor was associated with a significantly higher risk of in-hospital major bleeding when compared with clopidogrel without any reduction in major adverse cardiovascular events among ACS participants with high bleeding risk, showing that clopidogrel was a better choice for such patients [38]. Furthermore, among real-world Chinese patients with ACS from the General Hospital of Shenyang Military Region (October 2011 to August 2014) who were treated by PCI, ticagrelor was effective only in patients with low bleeding risk; however, it was not recommended in patients with a moderate-to-high bleeding risk [39]. Hence, the choice of antiplatelet agents was sometimes dependent on the decision of the clinicians, based on the bleeding or thrombotic risk of the patients.

In addition, even though in several studies, patients were treated with DAPT including aspirin and clopidogrel or aspirin and ticagrelor, there were two studies in which the use of aspirin was not mentioned. Therefore, it was not clear whether in those two studies, CKD patients were assigned to DAPT or to a single antiplatelet therapy. However, aspirin use is often not recorded in most US claims databases, and it is comprehensible that most patients are on DAPT [40]. Aspirin therapy remains a highly utilized mean of preventing cardiovascular diseases in the USA [41]. Moreover, the other cardiovascular drugs used by patients were not taken into consideration and were ignored during the analysis. Also, there was not sufficient information about the type of drug eluting stents that were implanted during PCI. Since the types of coronary stents might also contribute to adverse cardiovascular outcomes following PCI, this might also have had an impact on the outcomes. Another limitation could be the fact that CKD patients with different stages were combined and analyzed. For example, patients with ESRD, patients with CKD stage III and IV were all combined and assessed. Since research based on this scope (antiplatelet agents in patients with CKD) is still scarce, it will be vital to rely on future studies with a larger population size.

This study is based on real-world data. Data related to patients' health status and/or the delivery of health care on a daily basis among CKD patients with cardiovascular diseases on either ticagrelor or clopidogrel, collected from different sources comprise real-world data in this study. Wide internet usage, social media, disease registries, e-health services, and other technology-driven services, have led to the availability of digital real-world data. Our study was based on real patients with CKD with co-existing cardiovascular diseases, obtained from randomized and nonrandomized studies. The impact of antiplatelet agents including ticagrelor and clopidogrel was carefully observed, and the number of events were compiled and analyzed using a random-effect statistical model. Real-world data, as reported in our study, could enhance the efficiency of clinical research and bridge the evidence gap between clinical research and application of knowledge during practice. However, future studies with real-world data comparing antiplatelet agents in CKD patients with cardiovascular diseases should be further followed-up.

5 Conclusions

When compared with clopidogrel, even though ticagrelor was not associated with higher risk of cardiovascular outcomes in these patients with CKD, it was associated with significantly higher BARC bleeding. Therefore, the safety outcomes of ticagrelor still require further evaluation in patients with CKD. Nevertheless, this hypothesis should only be confirmed with more powerful results that could usually only be achieved using large-scale randomized trials.

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Declarations

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Conflict of interest The authors Yinxue Guo, Pingyu Ge, Ziju Li, Jingxia Xiao and Lirui Xie declare that they have no competing interests.

Ethical approval This meta-analysis is based on previously published studies and does not contain any studies with human participants or animals performed by any of the authors. Therefore, no ethical approval was required.

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Consent for publication Not applicable.

Code availability Not applicable.

Data availability statement All data generated or analyzed during this study are included in this published article. References have been provided. The full text articles containing those data can be obtained from electronic databases including PubMed, EMBASE, Web of Science and so on.

Authors' contributions Yinxue Guo, Pingyu Ge, Ziju Li, Jingxia Xiao, and Lirui Xie were responsible for the conception and design, acquisition of data, analysis and interpretation of data, drafting the initial manuscript and revising it critically for important intellectual content. Yinxue Guo and Pingyu Ge wrote the final draft. All the authors approved the final manuscript as it has been written.

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