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ORIGINAL RESEARCH

Cardiovascular Outcomes Observed with Ticagrelor versus Clopidogrel in Type 2 Diabetes Mellitus Patients with Acute Coronary Syndrome: A Meta-analysis

Zhiming Jiang · Le Liu · Pravesh Kumar Bundhun

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ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) is often associated with macrovascular complications including cardiovascular diseases (CVDs), resulting in acute coronary syndrome (ACS). Newer potent antiplatelet agents have recently been approved for use in clinical practice. In this analysis, we aimed to systematically compare the cardiovascular outcomes observed with ticagrelor versus clopidogrel in T2DM patients with ACS.

Methods: From August to September 2022, electronic databases were searched for publications that compared cardiovascular outcomes observed with ticagrelor versus clopidogrel in patients with T2DM. The statistical analysis was carried out using RevMan 5.4 software. A random effect statistical model was used to analyze the data. Risk ratios (RR) with 95% confidence intervals (CIs) were used to represent the data post analysis.

Results: A total of 5868 participants with T2DM were included in this analysis, of which 1944 participants were assigned to the ticagrelor group and 3924 participants were assigned to the clopidogrel group. Our analysis showed that ticagrelor was associated with a significantly lower risk of major adverse cardiac events (MACEs) (RR: 0.64, 95% CI: 0.49–0.84; $P = 0.001$), all-cause mortality (RR: 0.65, 95% CI: 0.51–0.83; $P = 0.0004$), and cardiac death (RR: 0.60, 95% CI: 0.43–0.84; $P = 0.003$) in comparison to clopidogrel. However, the risks of repeated revascularization (RR: 1.48, 95% CI: 0.44–4.99; $P = 0.53$), stent thrombosis (RR: 0.70, 95% CI: 0.18–2.71; $P = 0.60$), reinfarction (RR: 0.85, 95% CI: 0.58–1.23; $P = 0.39$), and stroke (RR: 0.56, 95% CI: 0.14–2.21; $P = 0.41$) were similar. Ticagrelor was associated with a significantly higher risk of minor bleeding (RR: 1.53, 95% CI: 1.07–2.19; $P = 0.02$), whereas the risk for major bleeding (RR: 1.08, 95% CI: 0.55–2.10; $P = 0.82$) was not significantly different.

Conclusions: In these T2DM patients with ACS, a significantly lower risk of major adverse cardiovascular events including all-cause mortality was observed in the ticagrelor group compared with the clopidogrel group. However, T2DM patients who were assigned to ticagrelor showed a significantly higher minor bleeding risk.

Z. Jiang
Department of Cardiology, The Fourth Hospital of Changsha, Changsha 410000, Hunan, People's Republic of China
e-mail: jiangzhimingll@163.com

L. Liu (✉)
Department of Cardiology, The Eighth Hospital of Changsha, Changsha 410001, Hunan, People's Republic of China
e-mail: cssdbyyxxg@163.com

P. K. Bundhun
Department of Internal Medicine, Bruno Cheong Hospital, Central Flacq 40614, Mauritius
e-mail: pravesh021@gmail.com

Larger clinical trials should be able to confirm these hypotheses.

PLAIN LANGUAGE SUMMARY

Type 2 diabetes mellitus (T2DM) is increasing all over the world, and is often associated with macrovascular complications including cardiovascular diseases (CVDs), leading to acute coronary syndrome (ACS).

Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel is recommended in these patients.

However, due to clopidogrel hyporesponsiveness, especially in patients with T2DM, a more potent antiplatelet is needed.

Recently, newer, more potent antiplatelet agents have been approved for use in clinical practice.

A significantly lower risk of major adverse cardiovascular outcomes including all-cause mortality was observed with ticagrelor compared with clopidogrel in these patients with T2DM.

However, ticagrelor was associated with a significantly higher minor bleeding risk.

Keywords: Type 2 diabetes mellitus; Diabetes therapy; Ticagrelor; Clopidogrel; Percutaneous coronary intervention; Acute coronary syndrome; Antiplatelet therapy; Cardiovascular outcomes

Key Summary Points

Type 2 diabetes mellitus (T2DM) is increasing all over the world, and is often associated with macrovascular complications including cardiovascular diseases (CVDs), leading to acute coronary syndrome (ACS)

Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel is recommended in these patients

However, due to clopidogrel hyporesponsiveness, especially in patients with T2DM, a more potent antiplatelet is needed

Recently, newer, more potent antiplatelet agents have been approved for use in clinical practice

A significantly lower risk of major adverse cardiovascular outcomes including all-cause mortality was observed with ticagrelor compared to clopidogrel in these patients with T2DM

However, ticagrelor was associated with a significantly higher minor bleeding risk

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is rising worldwide, and is often associated with macrovascular complications including cardiovascular diseases (CVDs), which could lead to acute coronary syndrome (ACS) [1, 2]. Following percutaneous coronary intervention (PCI) in these patients, guidelines have recommended dual antiplatelet therapy (DAPT) with aspirin and clopidogrel [3]. However, due to clopidogrel hyporesponsiveness [4], especially in patients with T2DM, which is often associated with platelet hyperactivity [5], a more potent antiplatelet is needed [6]. Recently, new potent antiplatelet agents including ticagrelor and prasugrel have been approved for use in clinical practice [7]. Ticagrelor has recently been prescribed to patients with T2DM and coexisting CVDs [8]. However, ticagrelor has seldom been systematically compared with clopidogrel through a meta-analysis in patients with T2DM. In this analysis, we aimed to systematically compare the cardiovascular outcomes observed with ticagrelor versus clopidogrel in T2DM patients with ACS.

METHODS

Search Databases

Databases including MEDLINE (subset PubMed), EMBASE, http://www.ClinicalTrials.gov, Web of Science, Mendeley, Google scholar. and the Cochrane database were searched from August to the end of September 2022 for publications that compared cardiovascular outcomes between ticagrelor and clopidogrel in T2DM patients with ACS. Reference lists of relevant publications were also checked for suitable articles.

Search Terms and Search Strategies

The following search terms or phrases were used during the search process:

"ticagrelor, clopidogrel, and diabetes mellitus";

"ticagrelor, clopidogrel, and type 2 diabetes mellitus";

"ticagrelor, clopidogrel, and T2DM";

"ticagrelor, clopidogrel, diabetes mellitus, and percutaneous coronary intervention";

"ticagrelor, clopidogrel, diabetes mellitus, and PCI";

"ticagrelor, clopidogrel, diabetes mellitus, and coronary revascularization";

"ticagrelor, clopidogrel, diabetes mellitus, and acute coronary syndrome";

"ticagrelor, clopidogrel, diabetes mellitus, and STEMI";

"ticagrelor, clopidogrel, diabetes mellitus, and ACS''.

Only English publications were considered for this paper.

Inclusion and Exclusion Criteria

Studies were included if:

(a) they were randomized trials or observational studies comparing the cardiovascular outcomes in patients with T2DM treated by ticagrelor versus clopidogrel for ACS or following PCI;
(b) they were published in English;
(c) they reported dichotomous variables.

Studies were excluded if:

(a) they were meta-analyses, systematic reviews, letter to editors, case studies, or literature reviews;
(b) they did not involve patients with diabetes mellitus;
(c) they did not report cardiovascular outcomes;
(d) they were published in another language apart from English;
(e) they consisted of continuous variables;
(f) they were duplicated studies.

Outcomes and Definitions

The cardiovascular outcomes that were reported in the original studies have been listed in Table 1.

The following endpoints were assessed in this analysis:

(a) Major adverse cardiovascular events (MACEs) consisting of the composite endpoints including mortality, myocardial infarction, and revascularization; and when stroke was included, this composite endpoint was referred to as major adverse cardiovascular and cerebrovascular events (MACCEs);
(b) all-cause mortality;
(c) cardiac death;
(d) repeated revascularization;
(e) stent thrombosis;
(f) reinfarction;
(g) stroke;
(h) major bleeding: any major bleeding reported including thrombolysis in myocardial infarction (TIMI) defined major bleeding [9] and bleeding defined according to the academic research consortium (BARC), bleeding [9] type 3–5.
(i) Minor bleeding: any minor bleeding reported including TIMI defined minor bleeding and BARC bleeding type 1 and 2.

Table 1 Outcomes reported

Studies	Clinical outcomes
Ahn 2019 [13]	All-cause mortality, cardiac death, stroke, recurrent MI, major bleeding, TVR and TLR, MACCEs, stent thrombosis
He 2021 [14]	MACEs, nonfatal MI, TVR, rehospitalization, ischemic stroke, all-cause mortality, BARC type 1–5
Li 2019 [15]	MI, angina, heart failure, stent thrombosis, all-cause mortality, hemorrhage
Liu 2019 [16]	Death, MI, TVR, stroke, bleeding event, massive bleeding, mild-to-moderate bleeding
Liu 2020 [17]	Bleeding events, minimal bleeding
Mohareb 2020 [18]	Major bleeding, intracranial hemorrhage, gastrointestinal bleeding, acute stent thrombosis, subacute stent thrombosis, nonfatal MI, cardiovascular death, MACEs
Wang 2020 [19]	All-cause mortality, hospitalization, in-hospital TIMI, major and minor bleeding

Abbreviations: MI: myocardial infarction; TVR: target vessel revascularization; TLR: target lesion revascularization; MACCEs: major adverse cardiovascular and cerebrovascular events; BARC: bleeding defined according to the academic research consortium; TIMI: thrombolysis in myocardial infarction

Data Extraction and Quality Assessment

Two authors independently extracted data from the selected original studies. Data included authors' names; year of publication; participants' enrollment time; type of studies; total number of T2DM participants who were assigned to the ticagrelor versus the clopidogrel group, respectively; the type of coronary artery disease; the number of events associated with each endpoint; baseline features including age, gender, comorbidities such as hypertension, dyslipidemia, smoking history, and oral antihyperglycemic agents, as well as the percentage of participants on insulin therapy. Data were carefully extracted and cross-checked by the two authors. Any disagreement that occurred during this data extraction process was discussed with the corresponding author who was responsible for making the final decision.

The methodological assessment of the randomized trials was carried out using the Cochrane tool [10], while the methodological quality of the observational studies was carried out using the Newcastle Ottawa Scale (NOS) [11]. Grades from A to C were allotted to the studies denoting low to high risk of bias.

Statistical Analysis

The statistical analysis was carried out by the new version of the RevMan software, version 5.4. Risk ratios (RR) with 95% confidence intervals (CIs) were used to represent the data post analysis. A random effect statistical model was used to analyze the data. Heterogeneity was assessed by the Q statistic test, whereby a P-value ≤ 0.05 was considered statistically significant. Heterogeneity was also assessed by the I^2 test, whereby a lower I^2 percentage denoted lower heterogeneity, and a higher I^2 value denoted increasing heterogeneity.

Sensitivity analysis was carried out by an exclusion method, whereby each original study included in the final analysis was excluded one by one, and a new analysis was carried out each time and compared with the main result of this analysis for any statistical difference.

This meta-analysis included less than ten studies,therefore, publication bias was visually assessed through funnel plots.

Compliance with Ethical Guidelines

This study is a meta-analysis, and does not involve experiment on humans or animals carried out by any of the authors. Hence, ethical or board review approval was not required. Data were extracted from previously published original studies.

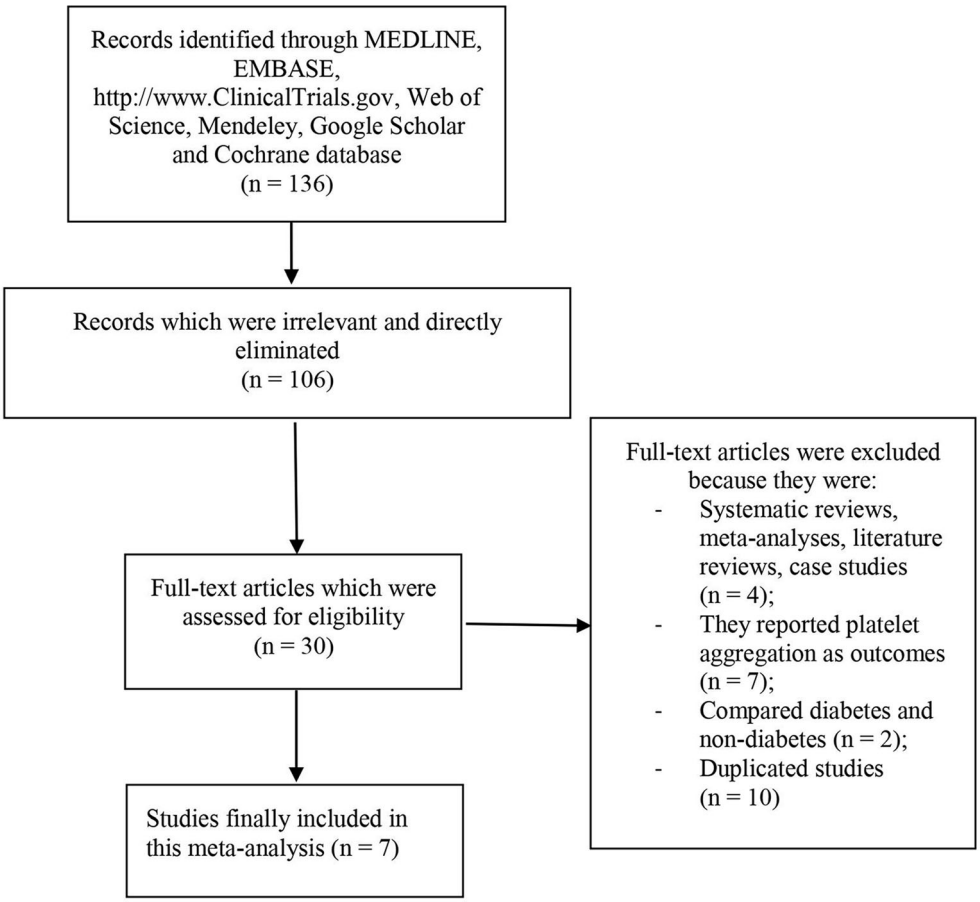


Fig. 1 Flow diagram showing the study selection

RESULTS

Search Outcomes

The preferred reporting items in systematic reviews and meta-analyses (PRISMA) guideline [12] was followed. Our search resulted in a total of 136 publications. The authors carefully assessed the abstracts and titles. Following this initial assessment, 106 publications were eliminated since they were not based on the scope and idea of this research paper. Therefore, 30 full text articles were assessed for eligibility.

Another assessment of the full text articles was carried out. Based on this second assessment, elimination was carried out based on the criteria for inclusion and exclusion. Publications were eliminated because they did not compare the outcomes in patients with T2DM who were assigned to either ticagrelor or clopidogrel, but instead, compared outcomes in T2DM and non-diabetes mellitus, they reported platelet aggregations as endpoints that did not satisfy the inclusion and exclusion criteria of this research, or they were duplicated studies.

Finally, seven studies [13–19] were included in this analysis, as shown in Fig. 1.

General and Baseline Features of the Studies

The general features of the studies are listed in Table 2. A total of 5868 participants with T2DM were included in this analysis, of which 1944 participants were assigned to the ticagrelor group and 3924 participants were assigned to the clopidogrel group. Patients with ACS were included in this analysis. The studies reported a

Table 2 General features of the studies

Studies	No. of T2DM participants assigned to the ticagrelor group (*n*)	No. of T2DM participants assigned to the clopidogrel group (*n*)	Types of coronary artery disease	Follow-up time period	Bias risk grade
Ahn 2019 [13]	1000	2985	AMI with successful PCI	1 and 12 months	B
He 2021 [14]	133	133	ACS patients	6 months	B
Li 2019 [15]	100	100	STEMI	1 and 6 months	B
Liu 2019 [16]	108	100	STEMI	–	B
Liu 2020 [17]	20	19	Chronic coronary syndrome undergoing PCI	–	B
Mohareb 2020 [18]	218	222	ACS undergoing PCI	12 months	B
Wang 2020 [19]	365	365	AMI with successful PCI	6, 12, and 24 months	B
Total no. of participants (*n*)	1944	3924			

Abbreviations: T2DM: type 2 diabetes mellitus; AMI: acute myocardial infarction; PCI: percutaneous coronary intervention; ACS: acute coronary syndrome; STEMI: ST elevated myocardial infarction

Table 3 Baseline features of the participants

Studies	Age (years) Tica/Clop	Males (%) Tica/Clop	HBP (%) Tica/Clop	DYS (%) Tica/Clop	Smoker (%) Tica/Clop	On insulin therapy (%) Tica/Clop	On OHA (%) Tica/Clop
Ahn 2019 [13]	61.5/66.1	77.2/67.9	57.3/65.1	12.6/14.8	42.5/35.5	5.40/7.50	85.0/79.3
He 2021 [14]	64.0/64.0	29.3/35.3	60.2/72.2	21.1/21.8	54.9/51.1	39.1/32.3	33.1/39.9
Li 2019 [15]	70.8/79.1	55.0/61.0	38.8/26.0	34.7/38.8	53.1/57.1	–	–
Liu 2019 [16]	68.3/69.1	53.7/58.0	51.8/48.0	31.5/36.0	48.1/46.0	–	–
Liu 2020 [17]	62.9/63.3	60.0/78.9	75.0/73.7	60.0/68.4	40.0/36.8	30.0/26.3	75.0/79.0
Mohareb 2020 [18]	49.8/47.9	67.5/64.0	37.5/42.3	42.8/45.9	21.3/25.2	–	–
Wang 2020 [19]	62.7/63.0	74.8/75.1	73.4/74.5	46.6/46.3	37.5/38.2	–	–

Abbreviations: Tica: ticagrelor group; Clop: clopidogrel group; HBP: high blood pressure; DYS: dyslipidemia; OHA: oral hypoglycemic agents

follow-up time period ranging from 6 to 24 months.

The baseline characteristics of the participants are listed in Table 3. Mean age varied from 47.9 to 79.1 years, with the number of male participants ranging from 29.3% to 78.9% depending on the study. Hypertension (26.0–74.5%), dyslipidemia (12.6–68.4%), smokers (21.3–57.1%), and participants on insulin therapy (5.40–39.1%) or oral antihyperglycemic agents (33.1–85.0%) are also reported in Table 3.

Main Results of this Analysis

Our analysis showed that ticagrelor was associated with a significantly lower risk of MACEs (RR: 0.64, 95% CI: 0.49–0.84; $P = 0.001$), all-cause mortality (RR: 0.65, 95% CI: 0.51–0.83; $P = 0.0004$), and cardiac death (RR: 0.60, 95% CI: 0.43–0.84; $P = 0.003$) in comparison with clopidogrel in these patients with T2DM, as shown in Fig. 2. However, the risks of repeated revascularization (RR: 1.48, 95% CI: 0.44–4.99; $P = 0.53$), stent thrombosis (RR: 0.70, 95% CI: 0.18–2.71; $P = 0.60$), reinfarction (RR: 0.85, 95% CI: 0.58–1.23; $P = 0.39$), and stroke (RR: 0.56, 95% CI: 0.14–2.21; $P = 0.41$) were similarly manifested, as shown in Fig. 2.

When bleeding risks were assessed, ticagrelor was associated with a significantly higher risk of minor bleeding (RR: 1.53, 95% CI: 1.07–2.19; $P = 0.02$) as shown in Fig. 3, whereas the risk of major bleeding (RR: 1.08, 95% CI: 0.55–2.10; $P = 0.82$) was not significantly different with ticagrelor versus clopidogrel.

The results of this analysis are summarized in Table 4.

Sensitivity Analysis and Publication Bias

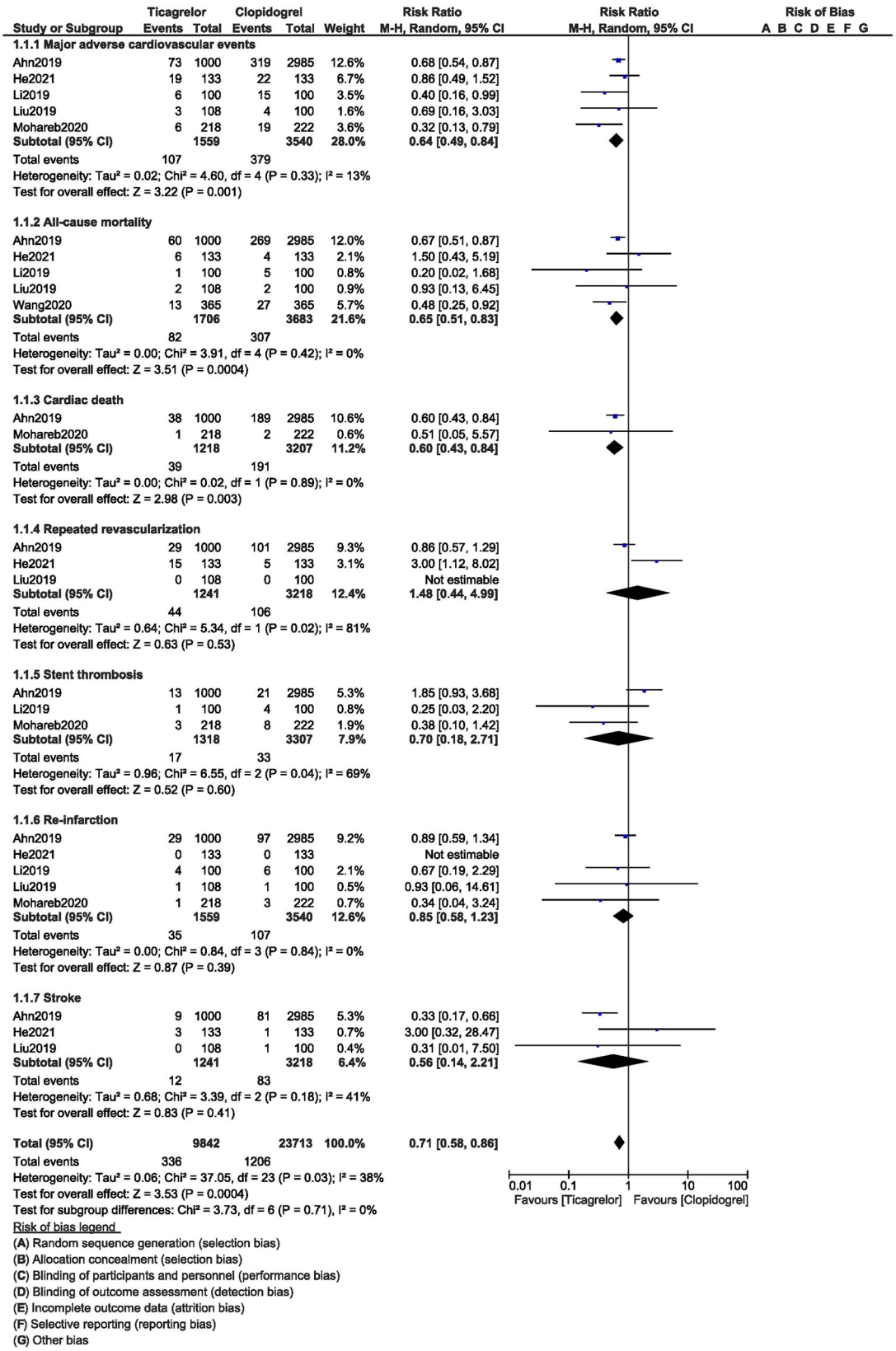
When the sensitivity analysis was carried out, consistent results were obtained throughout. When each study were excluded one at a time and a new analysis was carried out, the obtained result was not significantly different from the main results of this analysis. In addition, a simple analysis of funnel plots provided a vital test for the likely presence of bias in the meta-analyses. The funnel plot, which is a plot of effect estimates against sample size, could be visually assessed for asymmetrical findings that could predict discordance of results when meta-analyses are compared with larger trials. Therefore, by visually assessing the symmetry of the funnel plot (Fig. 4), we could confirm a low evidence of publication bias across the studies that assessed all the cardiovascular outcomes in these patients with T2DM. Publication bias is represented in Fig. 4.

DISCUSSION

In this meta-analysis, we compared the cardiovascular outcomes observed in T2DM patients with ACS who were assigned to a ticagrelor group versus those who were assigned to a clopidogrel group. Our results showed that ticagrelor was associated with a significantly lower risk of MACEs and mortality. However, the risk of minor bleeding was significantly higher with ticagrelor in comparison to clopidogrel in these patients with T2DM. Nevertheless, significant major bleeding was not observed with ticagrelor.

Similar to this analysis, a substudy from the PLATelet inhibition and patient Outcomes (PLATO) trial [20] that assessed ticagrelor versus clopidogrel in patients with ACS and diabetes mellitus showed the former to reduce ischemic events in ACS patients irrespective of diabetic status and glycemic control, without increasing the risk of major bleeding. It should be noted that this PLATO substudy included 4662 participants with T2DM, of which 1036 were on insulin therapy.

A post hoc analysis of the ad hoc PCI study [21], which was a prospective, open-label, randomized, multicenter, parallel-group, phase 4 pharmaco-dynamic study performed at 15 centers in the USA and involving patients with diabetes mellitus, showed that compared with clopidogrel, faster and enhanced platelet inhibition was achieved with ticagrelor. Similarly, in the OPTIMUS-6 study [22], which analyzed the pharmacodynamic and pharmacokinetic effects of a low maintenance dose ticagrelor regimen versus standard dose clopidogrel in


Ticagrelor
Clopidogrel
Risk Ratio
Risk Ratio
Risk of Bias
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
A B C D E F G
1.1.1 Major adverse cardiovascular events
Ahn2019 73 1000 319 2985 12.6% 0.68 [0.54, 0.87]
He2021 19 133 22 133 6.7% 0.86 [0.49, 1.52]
Li2019 6 100 15 100 3.5% 0.40 [0.16, 0.99]
Liu2019 3 108 4 100 1.6% 0.69 [0.16, 3.03]
Mohareb2020 6 218 19 222 3.6% 0.32 [0.13, 0.79]
Subtotal (95% CI) 1559 3540 28.0% 0.64 [0.49, 0.84]
Total events 107 379
Heterogeneity: Tau² = 0.02; Chi² = 4.60, df = 4 (P = 0.33); I² = 13%
Test for overall effect: Z = 3.22 (P = 0.001)
1.1.2 All-cause mortality
Ahn2019 60 1000 269 2985 12.0% 0.67 [0.51, 0.87]
He2021 6 133 4 133 2.1% 1.50 [0.43, 5.19]
Li2019 1 100 5 100 0.8% 0.20 [0.02, 1.68]
Liu2019 2 108 2 100 0.9% 0.93 [0.13, 6.45]
Wang2020 13 365 27 365 5.7% 0.48 [0.25, 0.92]
Subtotal (95% CI) 1706 3683 21.6% 0.65 [0.51, 0.83]
Total events 82 307
Heterogeneity: Tau² = 0.00; Chi² = 3.91, df = 4 (P = 0.42); I² = 0%
Test for overall effect: Z = 3.51 (P = 0.0004)
1.1.3 Cardiac death
Ahn2019 38 1000 189 2985 10.6% 0.60 [0.43, 0.84]
Mohareb2020 1 218 2 222 0.6% 0.51 [0.05, 5.57]
Subtotal (95% CI) 1218 3207 11.2% 0.60 [0.43, 0.84]
Total events 39 191
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 2.98 (P = 0.003)
1.1.4 Repeated revascularization
Ahn2019 29 1000 101 2985 9.3% 0.86 [0.57, 1.29]
He2021 15 133 5 133 3.1% 3.00 [1.12, 8.02]
Liu2019 0 108 0 100 Not estimable
Subtotal (95% CI) 1241 3218 12.4% 1.48 [0.44, 4.99]
Total events 44 106
Heterogeneity: Tau² = 0.64; Chi² = 5.34, df = 1 (P = 0.02); I² = 81%
Test for overall effect: Z = 0.63 (P = 0.53)
1.1.5 Stent thrombosis
Ahn2019 13 1000 21 2985 5.3% 1.85 [0.93, 3.68]
Li2019 1 100 4 100 0.8% 0.25 [0.03, 2.20]
Mohareb2020 3 218 8 222 1.9% 0.38 [0.10, 1.42]
Subtotal (95% CI) 1318 3307 7.9% 0.70 [0.18, 2.71]
Total events 17 33
Heterogeneity: Tau² = 0.96; Chi² = 6.55, df = 2 (P = 0.04); I² = 69%
Test for overall effect: Z = 0.52 (P = 0.60)
1.1.6 Re-infarction
Ahn2019 29 1000 97 2985 9.2% 0.89 [0.59, 1.34]
He2021 0 133 0 133 Not estimable
Li2019 4 100 6 100 2.1% 0.67 [0.19, 2.29]
Liu2019 1 108 1 100 0.5% 0.93 [0.06, 14.61]
Mohareb2020 1 218 3 222 0.7% 0.34 [0.04, 3.24]
Subtotal (95% CI) 1559 3540 12.6% 0.85 [0.58, 1.23]
Total events 35 107
Heterogeneity: Tau² = 0.00; Chi² = 0.84, df = 3 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.87 (P = 0.39)
1.1.7 Stroke
Ahn2019 9 1000 81 2985 5.3% 0.33 [0.17, 0.66]
He2021 3 133 1 133 0.7% 3.00 [0.32, 28.47]
Liu2019 0 108 1 100 0.4% 0.31 [0.01, 7.50]
Subtotal (95% CI) 1241 3218 6.4% 0.56 [0.14, 2.21]
Total events 12 83
Heterogeneity: Tau² = 0.68; Chi² = 3.39, df = 2 (P = 0.18); I² = 41%
Test for overall effect: Z = 0.83 (P = 0.41)
Total (95% CI) 9842 23713 100.0% 0.71 [0.58, 0.86]
Total events 336 1206
Heterogeneity: Tau² = 0.06; Chi² = 37.05, df = 23 (P = 0.03); I² = 38%
Test for overall effect: Z = 3.53 (P = 0.0004)
Test for subgroup differences: Chi² = 3.73, df = 6 (P = 0.71), I² = 0%
0.01 0.1 1 10 100
Favours [Ticagrelor] Favours [Clopidogrel]
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

◀**Fig. 2** Cardiovascular outcomes observed with ticagrelor versus clopidogrel in patients with T2DM

diabetes mellitus patients without previous MACEs undergoing elective PCI, the authors showed that a 60 mg twice daily dose of ticagrelor minimum dose regimen achieved better and more sustained platelet inhibition compared with the standard dose clopidogrel. The results were in favor of ticagrelor even in the Clopidogrel High Dose Versus Ticagrelor for Antiplatelet Maintenance in Diabetic Patients (CLOTILDIA) study [23]. The faster and more potent antithrombotic property of ticagrelor in patients with T2DM were further demonstrated in a study published by Zafar et al. [24].

Our results showed a significant decrease in MACEs with ticagrelor compared with clopidogrel in patients with T2DM. Current guidelines issued by the American Heart Association/American College of Cardiology recommend ticagrelor over clopidogrel for DAPT with aspirin in patients with ACS. The potent effect of ticagrelor could be because it works differently to clopidogrel. Even though it inhibits adenosine-5 diphosphate (ADP), which plays an important role in blood clotting, it does this by reversibly binding to the receptor P2Y12 on the surface of platelets [25]. Reversible binding means platelet activities could be restored at a later time once the concentration of ticagrelor decreases to a certain level. In contrast, clopidogrel binds irreversibly to the P2Y12 receptors of platelet surfaces, blocking platelets from aggregating for the remainder of their lifespan (about 10 days). Moreover, ticagrelor could work quicker than clopidogrel. Maximum platelet inhibition with ticagrelor could be reached within 2 h in comparison with clopidogrel, which could take over 8 h. Also, clopidogrel is a prodrug, meaning that it requires conversion in the liver to its active form before it can work.

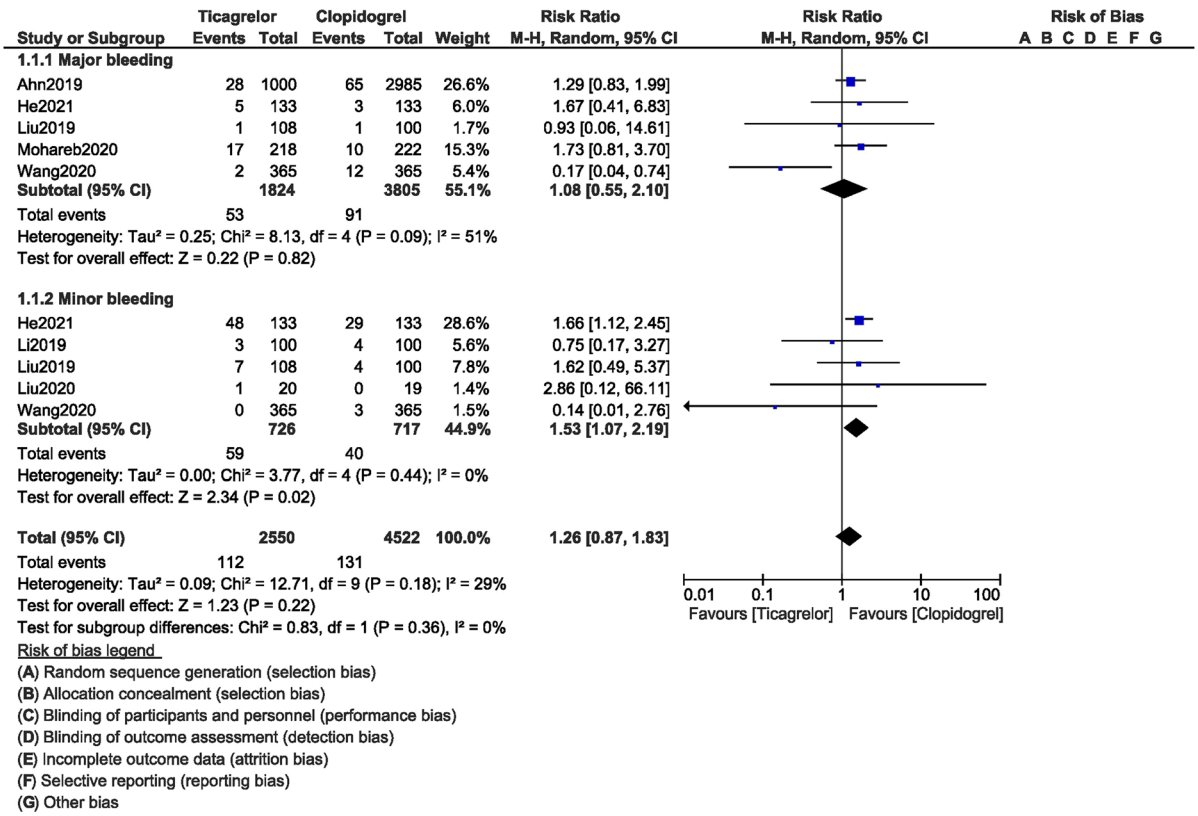


Fig. 3 Bleeding events observed with ticagrelor versus clopidogrel in patients with T2DM

Table 4 Main results of this analysis

Endpoints	RR with 95% CI	*P*-value	I^2 (%)
Major adverse cardiac events	0.64 (0.49–0.84)	0.001	13
All-cause mortality	0.65 (0.51–0.83)	0.0004	0
Cardiac death	0.60 (0.43–0.84)	0.003	0
Repeated revascularization	1.48 (0.44–4.99)	0.53	81
Stent thrombosis	0.70 (0.18–2.71)	0.60	69
Reinfarction	0.85 (0.58–1.23)	0.39	0
Stroke	0.56 (0.14–2.21)	0.14	41
Major bleeding	1.08 (0.55–2.10)	0.82	51
Minor bleeding	1.53 (1.07–2.19)	0.02	0

Abbreviations: RR: risk ratios; CI: confidence intervals; MI: myocardial infarction; TVR: target vessel revascularization; TLR: target lesion revascularization; MACCEs: major adverse cardiovascular and cerebrovascular events; BARC: bleeding defined according to the academic research consortium; TIMI: thrombolysis in myocardial infarction

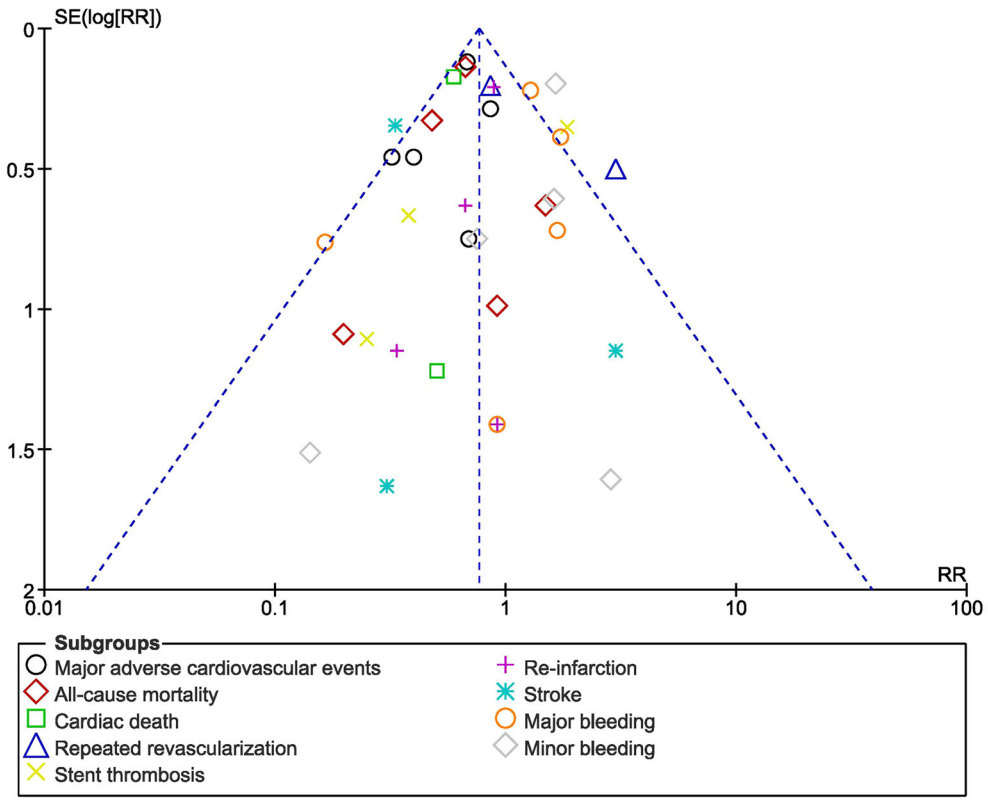


Fig. 4 Funnel plot showing publication bias

However, ticagrelor is not a prodrug, therefore it has a quicker onset of action.

Our current analysis was based on diabetes mellitus patients with ACS and in this category of patients, the results showed ticagrelor to be associated with a significantly lower risk of MACEs, but a significantly higher risk of minor bleeding in comparison to clopidogrel. However, in diabetes patients with stable coronary artery disease, ticagrelor in combination with aspirin was associated with a higher incidence of major bleeding [26].

Limitations

Similar to other studies, this analysis also limitations. First, due to the limited number of participants, the results might not be robust. Another limitation is that several clinical outcomes, such as dyspnea, heart failure, rehospitalization, gastrointestinal bleeding, intracranial bleeding, and so on, could not be analyzed because they were reported in only one study. Another limitation is that in one study, patients in the experimental group were assigned to both ticagrelor and prasugrel instead of ticagrelor alone. This might have a minor impact on the results. Moreover, in two studies, the follow-up time period was not mentioned, whereas in other studies where the follow-up time period was stated, and varied among studies. Another limitation is that the duration of diabetes mellitus, the cardiac medications used by the patients, and the percentage of patients with T2DM on insulin therapy or on oral antihyperglycemic agents were not taken into consideration. Also, in most of the original studies, the glycosylated hemoglobin was not reported for the patients, so it was not known whether blood sugar in those participants was well controlled or uncontrolled.

CONCLUSIONS

In these patients with T2DM, a significantly lower risk of major adverse cardiovascular events including all-cause mortality was observed in the ticagrelor group compared with the clopidogrel group. However, T2DM patients who were assigned to the ticagrelor group showed a significantly higher minor bleeding risk. Larger clinical trials should be able to confirm these hypotheses.

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Compliance with Ethics Guidelines. This meta-analysis is based on previously conducted studies and does not contain any new study with human participants or animals performed by any of the authors. Therefore, an ethical approval was not required.

Data Availability. All data generated or analyzed during this study are included in this published article. References of the original papers involving the data source which have been used in this paper have been listed in the main text of this current manuscript. All data are publicly available in electronic databases.

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