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REVIEW

Treatment of the New Era: Long-Term Ticagrelor Monotherapy for the Treatment of Patients with Type 2 Diabetes Mellitus following Percutaneous Coronary Intervention: A Meta-analysis

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ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) is a risk factor for the development of coronary artery disease (CAD). In patients with acute coronary syndrome (ACS), guidelines recommend a potent P2Y12 inhibitor in addition to aspirin. For those with complicated and advanced CAD requiring complex percutaneous coronary intervention (PCI), the risk for adverse ischemic events is even higher. Prolonged dual antiplatelet therapy (DAPT) use is controversial. A new antiplatelet regimen after PCI should be considered. In this analysis, we aimed to systematically show the impact of long-term ticagrelor monotherapy after a short course of DAPT use on the outcomes in patients with T2DM following PCI.

Methods: Electronic databases were searched

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for relevant publications. Studies that were based on patients with T2DM and that included patients with T2DM were selected on the basis of the inclusion and exclusion criteria. Statistical analysis was carried out with RevMan software. The data are presented as risk ratios (RR) with 95% confidence intervals (CI).

Results: A total of 8621 patients were included in this analysis, whereby 4357 participants with T2DM were assigned to ticagrelor monotherapy and 4264 were assigned to DAPT. Our results showed long-term ticagrelor monotherapy after a short course of DAPT use to be associated with a significantly lower risk of major adverse cardiac events (RR 0.86, 95% CI 0.77–0.98; $P = 0.02$) and all-cause mortality (RR 0.77, 95% CI 0.60–0.98; $P = 0.03$). However, no significant difference was observed in cardiac death, myocardial infarction, stroke, stent thrombosis, or repeated revascularization. Ticagrelor monotherapy was associated with significantly lower risk of thrombolysis in myocardial infarction (TIMI) defined minor or major bleeding (RR 0.71, 95% CI 0.54–0.93; $P = 0.01$) compared with the DAPT regimen.

Conclusion: Long-term ticagrelor monotherapy after a short course of DAPT use showed better results in patients with T2DM following PCI. Therefore, ticagrelor monotherapy after a short course of DAPT use could be considered an evolution in antiplatelet therapy of this decade for the treatment of patients with T2DM after PCI. However, newer studies with a larger population size and cost-effectiveness are factors that should further be considered.

Keywords: Percutaneous coronary intervention; Type 2 diabetes mellitus; Ticagrelor; Dual antiplatelet therapy; Monotherapy; Bleeding

Key Summary Points

Type 2 diabetes mellitus (T2DM) is a risk factor for the development of coronary artery disease (CAD).
In patients with acute coronary syndrome (ACS), guidelines recommend a potent P2Y12 inhibitor in addition to aspirin.
In patients with complicated and advanced CAD requiring complex percutaneous coronary intervention (PCI), the risk for adverse ischemic events is even higher.
Prolonged dual antiplatelet therapy (DAPT) use is controversial.
A new antiplatelet regimen after PCI should be considered.
In this analysis, we aimed to systematically show the impact of long-term ticagrelor monotherapy after a short course of DAPT use on outcomes in patients with T2DM following PCI.
Long-term ticagrelor monotherapy after a short course of DAPT use showed better results in patients with T2DM following PCI.
Therefore, ticagrelor monotherapy after a short course of DAPT use could be considered an evolution in antiplatelet therapy of this decade for the treatment of patients with T2DM after PCI.
However, newer studies with a larger population size and cost-effectiveness are factors that should further be considered.

INTRODUCTION

Coronary artery disease (CAD) is on the rise [1]. Type 2 diabetes mellitus (T2DM) is a risk factor for the development of CAD [2], and there is clear evidence that the proportion of CAD in

patients with T2DM is higher than that in patients without T2DM [3]. Percutaneous coronary intervention (PCI) has been the most common invasive revascularization procedure for patients with occluded coronary arteries. To prevent stent-related and stent-unrelated ischemic events, guidelines recommend the use of dual antiplatelet therapy (DAPT) [4], including aspirin and a P2Y12 platelet receptor inhibitor. Current guidelines recommend DAPT with aspirin and clopidogrel for a duration of 6 months in patients with stable CAD after PCI. In patients with acute coronary syndrome (ACS), guidelines recommend a more potent P2Y12 inhibitor such as ticagrelor or prasugrel in addition to aspirin.

In patients with complicated and advanced CAD requiring complex PCI for revascularization, the risk for adverse ischemic events is even higher. Prolonged dual antiplatelet therapy (DAPT) use is controversial. It might be associated with increased bleeding events, and higher risk of morbidity and mortality [5]. In addition, in patients with T2DM, highly active platelets have been observed [6], and due to platelet hyperactivity in such patients, aspirin and clopidogrel hyporesponsiveness has been noted [7]. Therefore, a more potent antiplatelet regimen that does not cause any increase in bleeding events would be required.

Recent studies have shown that short-term DAPT use with aspirin and ticagrelor followed by long-term ticagrelor monotherapy could reduce bleeding events without any increase in cardiovascular events [8]. Therefore, in this analysis, we aimed to systematically show the impact of long-term ticagrelor monotherapy after a short course of DAPT use on outcomes in patients with T2DM following PCI.

METHODS

Search Databases

Electronic databases, including MEDLINE, EMBASE, Web of Science, Google Scholar, and Cochrane databases, and http://www.ClinicalTrials.gov were searched for relevant publications based on the comparison of ticagrelor monotherapy after short-term DAPT use versus DAPT (with P2Y12 inhibitor and aspirin) following PCI. On the basis of the search results, studies that were based on patients with T2DM and studies that included patients with T2DM were selected with reference to the inclusion and exclusion criteria.

Search Strategies

During the search process, the following search terms or phrases were used:

> "ticagrelor and percutaneous coronary intervention"; "ticagrelor monotherapy and percutaneous coronary intervention"; "ticagrelor monotherapy and diabetes mellitus and percutaneous coronary intervention"; "P2Y12 inhibitors and percutaneous coronary intervention".

The term "percutaneous coronary intervention" was also replaced by the terms "coronary revascularization"; "coronary stenting"; "coronary angioplasty".

The abbreviation "PCI" was also used to replace the term "percutaneous coronary intervention".

Inclusion and Exclusion Criteria

Studies were selected if they satisfied the following inclusion criteria:

(a) They were randomized trials or observational studies comparing ticagrelor monotherapy after a short course of DAPT use versus DAPT following PCI;
(b) They were based on patients with T2DM or they included patients with T2DM;
(c) They reported adverse cardiovascular outcomes and bleeding events as their clinical endpoints;
(d) They were published in English.

The criteria for exclusion were:

(a) Studies that were case studies, meta-analyses, systematic reviews, or literature reviews;

(b) Studies that did not involve patients with T2DM;
(c) Studies that reported only an experimental group without any control group;
(d) Studies that were published in a language apart from English;
(e) Duplicated studies.

Definitions, Outcomes, and Follow-Up

The outcomes reported in each of the original studies are listed in Table 1. Those outcomes that were reported at least in two different studies were considered relevant for analysis, and were therefore considered as the endpoints of this analysis. The following endpoints were assessed in this meta-analysis:

- Major adverse cardiac events (MACEs), including all-cause mortality/cardiac death, myocardial infarction, and revascularization; however, since major adverse cardiovascular and cerebrovascular events (MACCEs) were reported in certain studies and they included stroke along with the same composition of MACEs, we have merged MACCEs with the MACEs category;
- All-cause mortality;
- Cardiac death;
- Myocardial infarction (MI);
- Repeated revascularization including target vessel revascularization (TVR) and target lesion revascularization (TLR);
- Stroke;
- Stent thrombosis;
- Thrombolysis in myocardial infarction (TIMI) defined major and minor bleeding [9];
- Bleeding defined by the academic research consortium (BARC) [10], grades 2, 3, or 5;
- Any minor bleeding events including TIMI minor bleeding or any other minor bleeding.

The follow-up time period is also listed in Table 1.

Long-term ticagrelor use was defined as the use of ticagrelor for a longer duration after DAPT was stopped (most of the studies reported DAPT use for only 3 months, and then ticagrelor monotherapy for 1–2 years follow-up).

Data Extraction and Quality Assessment

All the authors independently extracted data from the selected articles. Relevant information, including the names of authors, the relevant trials whose data were used, the time period of participants' enrollment, the year of publication, the total number of participants with T2DM who were assigned to the ticagrelor monotherapy group and the DAPT group, respectively, the outcomes that were reported in each of the original studies, the baseline features of the participants including gender, mean age, and comorbidities, and the total number of events associated with each outcome in both the experimental and the control groups, was carefully extracted by the authors.

Any disagreement during the data extraction process was carefully discussed among the authors, and a final decision was made by the corresponding author.

All the data that have been used in this analysis were directly or indirectly obtained from randomized trials. The methodological assessment of the trials were carried out on the basis of the recommendations of the Cochrane collaboration [11]. To account for risk of bias, a grade was allotted to represent low, intermediate, or high risk of bias among the studies.

Statistical Analysis

The statistical analysis was carried out by RevMan software version 5.4. Risk ratios (RR) with 95% confidence intervals (CI) were used to represent the data following analysis. Heterogeneity was assessed by two simple statistical tool, (a) the Q statistic test whereby an endpoint analysis with a P value less or equal to 0.05 was considered statistically significant and an endpoint analysis with a P value greater than 0.05 considered as statistically insignificant, and (b) the I^2 statistic test whereby a higher heterogeneity was expected with an increased value of I^2, and a low I^2 value was associated with a low heterogeneity. If I^2 was less than 50%, a fixed effect statistical model was used during the analysis; otherwise, a random effect statistical model was used.

Table 1 Outcomes reported

Studies	Cardiovascular outcomes	Bleeding outcomes	Follow-up time period	DAPT medications	Type of participants
Dominick 2020 [12]	Death, MI or stroke, all-cause death, MI, cardiac death, ischemic stroke, stent thrombosis (definite/probable)	BARC 2, 3, or 5, BARC 3 or 5, TIMI minor or major, GUSTO moderate or severe, ISTH major	12 months	DAPT with ticagrelor plus aspirin for 3 months, then ticagrelor monotherapy 90 mg twice daily, afterwards versus DAPT with ticagrelor and aspirin	Non-STE ACS
Gao 2020 [13]	All-cause mortality, MI, any revascularization, TVR, patient-oriented composite endpoint including all-cause mortality, stroke, MI, or any revascularization	BARC type 3 or 5 bleeding, BARC type 2 bleeding, BARC type 2, 3, or 5 bleeding	24 months	DAPT with ticagrelor plus aspirin for 3 months then ticagrelor monotherapy 90 mg twice daily afterwards versus DAPT with (ticagrelor or clopidogrel) plus aspirin	Stable coronary artery disease and ACS
Hann 2019 [14]	MACCE, all-cause mortality, MI, stroke, cardiac death, stent thrombosis	BARC type 2–5 bleeding, major bleeding	12 months	DAPT with ticagrelor plus aspirin for 3 months then ticagrelor monotherapy 90 mg twice daily afterwards versus DAPT with (ticagrelor, clopidogrel, or prasugrel) plus aspirin	Stable coronary artery disease and ACS
Johnson 2020 [15]	MACE, death, MI, revascularization	BARC type 1	1 month	Ticagrelor monotherapy 90 mg twice daily versus DAPT with ticagrelor plus aspirin	Stable coronary artery disease and ACS

Table 1 continued

Studies	Cardiovascular outcomes	Bleeding outcomes	Follow-up time period	DAPT medications	Type of participants
Yun 2021 [16]	All-cause death, cardiac death, MI, stent thrombosis, ischemic stroke, TVR, non-TVR, any revascularization	Fatal bleeding, BARC 3A, 3B, 3C bleeding, BARC 3 or 5 bleeding, TIMI major bleeding, TIMI minor bleeding, all TIMI bleeding	12 months	DAPT with ticagrelor plus aspirin for 3 months, then ticagrelor monotherapy 90 mg twice daily, afterwards versus DAPT with ticagrelor and aspirin	Patients with ACS

MI myocardial infarction, *MACCE* major adverse cardiovascular and cerebrovascular events, *MACEs* major adverse cardiac events, *TVR* target vessel revascularization, *BARC* bleeding defined by the academic research consortium, *TIMI* thrombolysis in myocardial infarction, *GUSTO* global strategies for opening occluded coronary arteries, *ISTH* International Society on Thrombolysis and Hemostasis, *DAPT* dual antiplatelet therapy, *ACS* acute coronary syndrome, *Non-STE* non-ST elevation

In addition, to confirm that the final results were not influenced by data of any particular original studies, for example those with larger number of participants or events, a sensitivity analysis was carried out. This sensitivity analysis was carried out in such a way that each study was excluded one by one, and a new analysis was carried out each time to assess for any significant change in the main results.

Compliance with Ethical Guidelines

This analysis consisted of data that were previously published. No authors were involved in experiments on animals or human beings. Therefore, ethical or board review approval was not required for this analysis.

RESULTS

Search Results

The Preferred Reporting Items for Meta-Analysis (PRISMA) guideline was followed [12]. Our search resulted in a total number of 287 publications. On the basis of a general assessment of the titles and abstracts, an initial elimination of nonrelevant publications was carried out. Thereafter, only 112 full-text articles were assessed for eligibility. On the basis of the inclusion and exclusion criteria, further studies were eliminated due to the following reasons:

(a) Meta-analyses, systematic reviews, or literature reviews (6);
(b) Case studies (7);
(c) Did not involve patients with diabetes mellitus (2);
(d) Studies based on same trials either as a substudy or a new study based on a similar trial (38);
(e) Duplicated studies (54).

Finally, only five studies [13–17] based on randomized trials were selected for this analysis.

Figure 1 demonstrates the flow diagram for the study selection.

Main Features of the Original Studies

A total number of 8621 patients were included in this analysis whereby 4357 participants with T2DM were assigned to the ticagrelor monotherapy and 4264 were assigned to the DAPT groups. The main features of the original studies are listed in Table 2. All the studies were

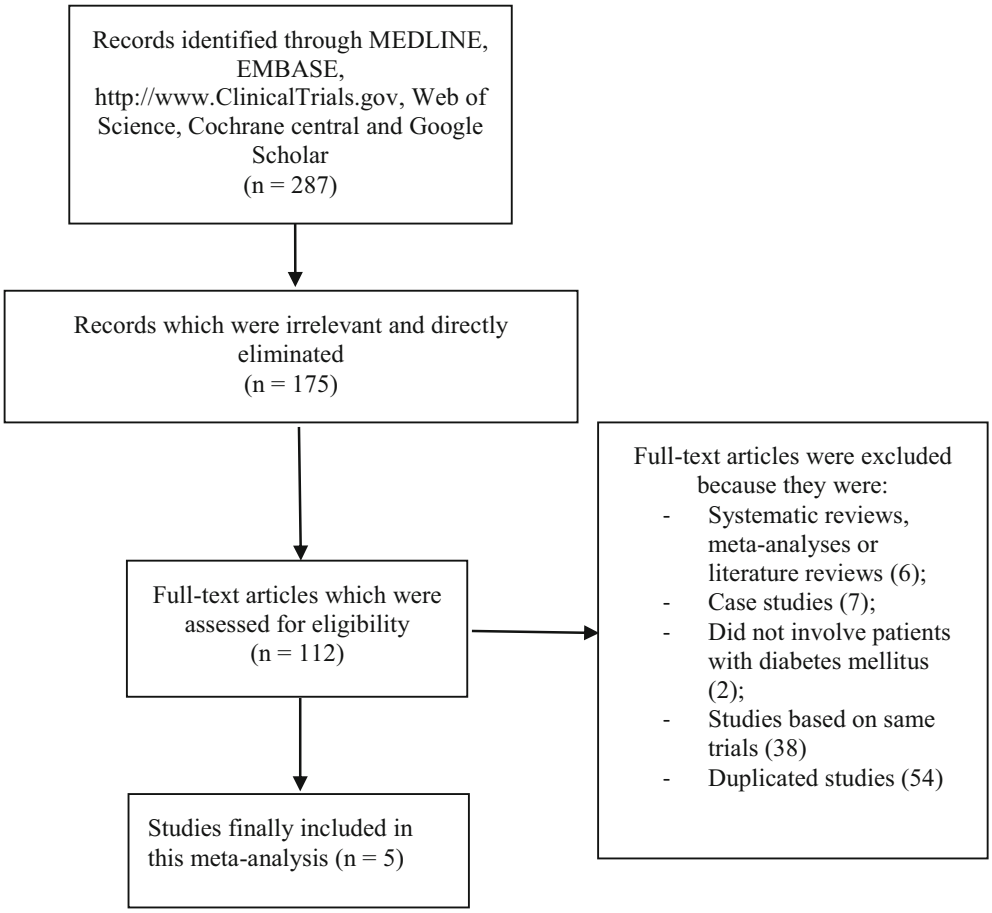

Fig. 1 Flow diagram representing the study selection

trials, and participants were enrolled from years 2013 to 2018. Studies Dominick 2020 [12] and Gao 2020 [13] included the highest number of participants.

Baseline Features of the Participants

The baseline features of the participants are listed in Table 3. The majority of the participants were male (69.3–80.0%), with a mean age of 63.3–68.2 years. The mean percentage of patients with hypertension (47.0–88.7%), with dyslipidemia (45.1–75.8%), and on insulin therapy (5.00–34.7%) are listed in Table 3.

Main Results of the Analysis

Our results showed ticagrelor monotherapy after a short course of DAPT use to be associated with a significantly lower risk of MACEs (RR 0.86, 95% CI 0.77–0.98; $P = 0.02$) and all-cause mortality (RR 0.77, 95% CI 0.60–0.98; $P = 0.03$) as shown in Fig. 2. However, no significant difference was observed in cardiac death (RR 0.77, 95% CI 0.46–1.30; $P = 0.32$), MI (RR 0.94, 95% CI 0.75–1.18; P = 0.62), stroke (RR 0.84, 95% CI 0.66–3.68; $P = 0.31$), stent thrombosis (RR 0.84, 95% CI 0.38–1.86; $P = 0.66$), or repeated revascularization (RR 0.90, 95% CI 0.76–1.06; $P = 0.21$) when ticagrelor monotherapy was compared with DAPT in patients with T2DM after PCI as shown in Fig. 2.

Our analysis also showed ticagrelor monotherapy to be associated with significantly

Table 2 Main features of the studies

Studies	Using data from	Enrollment time period (year)	Number of participants with T2DM with ticagrelor monotherapy (*n*)	Number of participants with T2DM with DAPT (*n*)	Bias risk grade
Dominick 2020	Trial	2015–2017	1319	1301	B
Gao 2020	Trial	2013–2015	1614 + 428	1575 + 410	B
Hann 2019	Trial	2014–2017	570	552	B
Johnson 2020	Trial	2015–2017	8	9	B
Yun 2021	Trial	2015–2018	418	417	B
Total number of patients (*n*)			4357	4264	

T2DM type 2 diabetes mellitus, *DAPT* dual antiplatelet therapy

Table 3 Baseline features of the participants

Studies	Mean age (years)	Males (%)	HBP (%)	DYS (%)	On insulin therapy (%)
Features	MT/DAPT	MT/DAPT	MT/DAPT	MT/DAPT	MT/DAPT
Dominick 2020	64.8/64.8	76.6/76.2	80.9/82.2	66.3/66.9	25.4/28.8
Gao 2020	68.2/68.2	69.3/69.3	88.7/88.7	75.8/75.8	34.7/34.7
Hann 2019	64.6/64.4	72.7/74.2	61.6/61.3	45.1/45.5	–
Johnson 2020	66.1/67.3	80.0/80.0	56.0/47.0	56.0/55.0	7.00/5.00
Yun 2021	63.3/63.3	73.3/73.3	68.3/68.3	64.1/64.1	10.0/9.59

HBP high blood pressure, *DYS* dyslipidemia, *MT* ticagrelor monotherapy, *DAPT* dual antiplatelet therapy with aspirin and ticagrelor

lower risk of TIMI defined minor or major bleeding (RR 0.71, 95% CI 0.54–0.93; $P = 0.01$) as shown in Fig. 3. However, "any minor bleeding" was similarly manifested (RR 1.14, 95% CI 0.89–1.46; $P = 0.31$) as shown in Fig. 3. In addition, the results for BARC 2, 3, or 5 bleeding (RR 0.87, 95% CI 0.62–1.22; $P = 0.43$) and BARC 3 or 5 bleeding (RR 0.75, 95% CI 0.45–1.26; $P = 0.28$) were not significantly different as shown in Fig. 4.

The results of this analysis have been summarized in Table 4.

Sensitivity analysis was also carried out. The result for TIMI minor or major bleeding was influenced by study Dominick 2020 [12], which consisted of 2620 participants compared with 835 participants from the other comparative study. For the remaining outcomes, consistent results were obtained throughout.

Publication bias was demonstrated through funnel plots in Figs. 5 and 6.

DISCUSSION

Recently, a new potential antiplatelet regimen with ticagrelor monotherapy after a short course of DAPT use has been shown to be effective in patients with CAD following PCI.

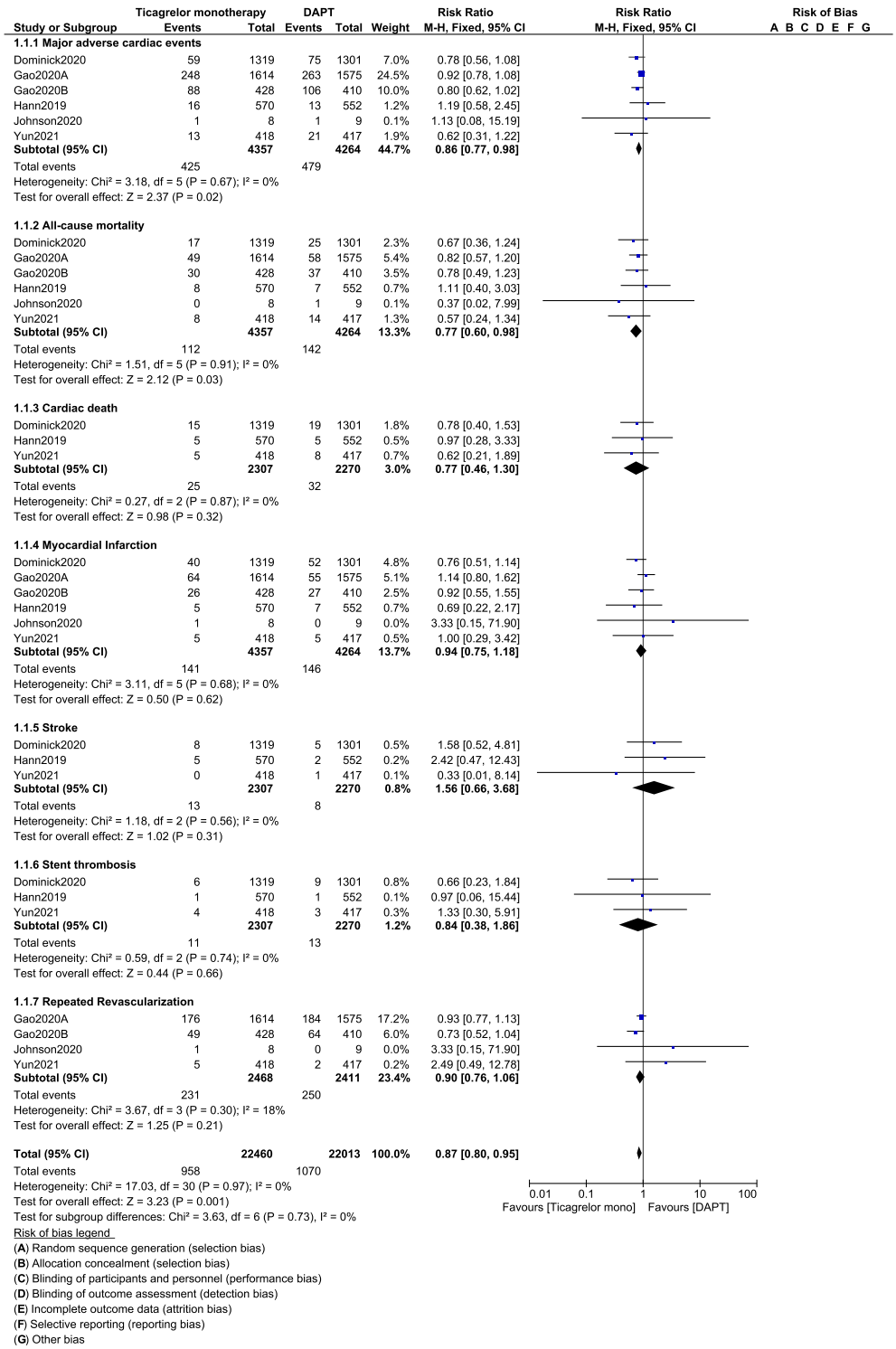

Fig. 2 Forest plot showing the comparison of cardiovascular outcomes between ticagrelor monotherapy and dual antiplatelet therapy following PCI in patients with T2DM

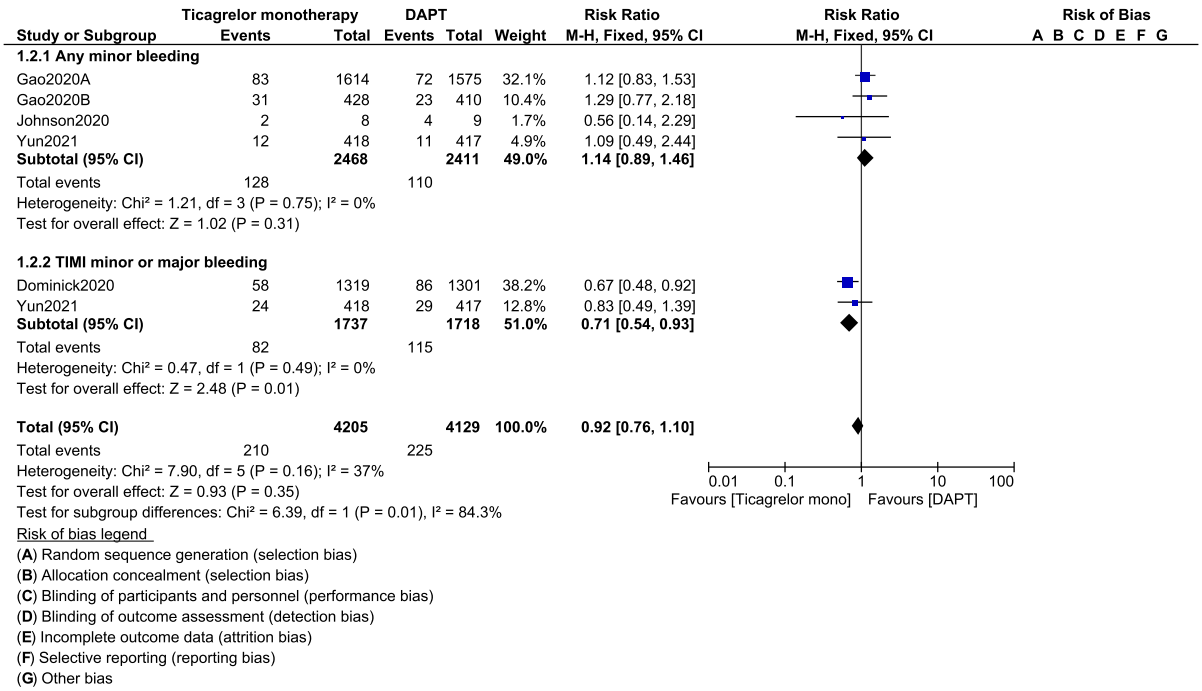

Fig. 3 Forest plot showing the comparison of minor bleeding and TIMI bleeding between ticagrelor monotherapy and dual antiplatelet therapy following PCI in patients with T2DM

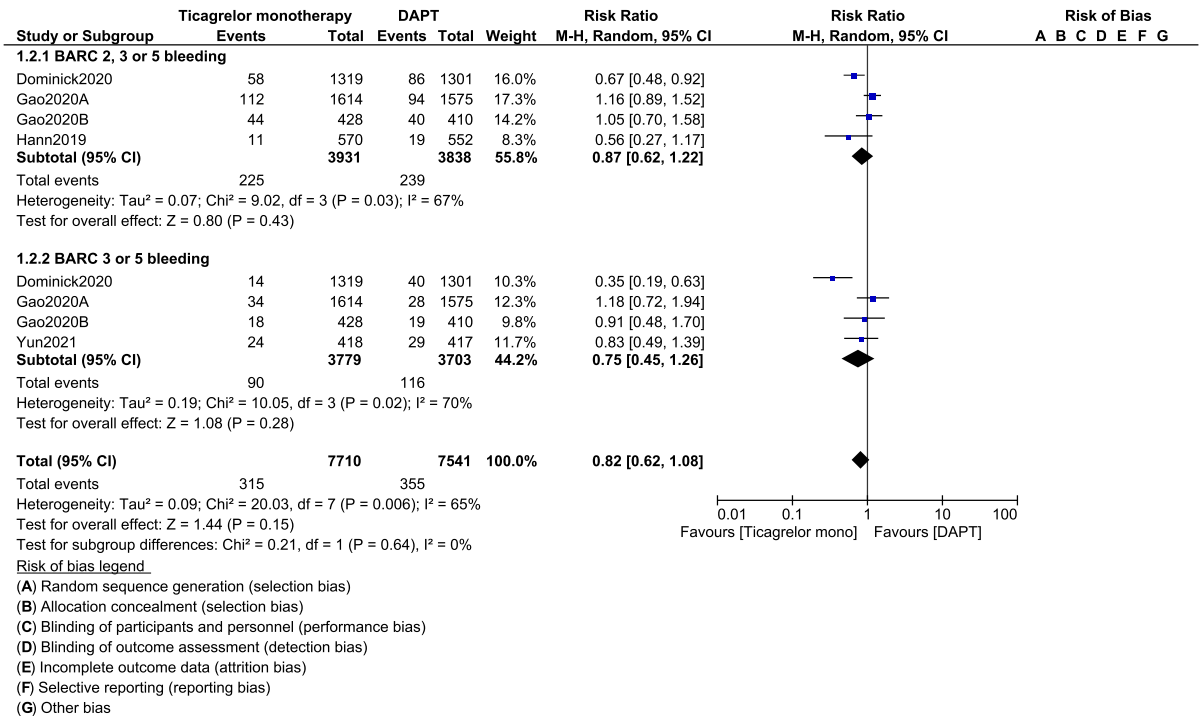

Fig. 4 Forest plot showing the comparison of BARC bleeding between ticagrelor monotherapy and dual antiplatelet therapy following PCI in patients with T2DM

Table 4 Summary of the main analysis

Outcomes	RR with 95% CI	*P* value	I^2 value (%)
Major adverse cardiac events	0.86 (0.77–0.98)	0.02	0
All-cause mortality	0.77 (0.60–0.98)	0.03	0
Cardiac death	0.77 (0.46–1.30)	0.32	0
Myocardial infarction	0.94 (0.75–1.18)	0.62	0
Repeated revascularization	0.90 (0.76–1.06)	0.21	18
Stroke	1.56 (0.66–3.68)	0.31	0
Stent thrombosis	0.84 (0.38–1.86)	0.66	0
Any minor bleeding	1.14 (0.89–1.46)	0.31	0
TIMI defined minor or major bleeding	0.71 (0.54–0.93)	0.01	0
BARC 2, 3, or 5 bleeding	0.87 (0.62–1.22)	0.43	67
BARC 3 or 5 bleeding	0.75 (0.45–1.26)	0.28	70

RR risk ratios, *CI* confidence intervals, *TIMI* thrombolysis in myocardial infarction, *BARC* bleeding defined according to the Academic Research Consortium

Our analysis has studied this new antiplatelet regimen in a population patients with T2DM.

The current results showed long-term ticagrelor monotherapy to be associated with significantly lower risks of MACEs, all-cause mortality, and TIMI defined major and minor bleeding events. However, no significant results were obtained with cardiac death, MI, stroke, stent thrombosis, repeated revascularization, or BARC bleeding.

An individual patient level meta-analysis that compared ticagrelor monotherapy versus DAPT after PCI and showed the former to be associated with significantly lower risk of major bleeding without any increase in ischemic events [18]. It should be noted that this individual-patient-level meta-analysis was a combination of two randomized trials including 4424 participants with T2DM who underwent PCI from the GLOBAL LEADERS Adjudication substudy and the TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients After Coronary Intervention) Trial. Another substudy of the TWILIGHT trial including 2369 patients with T2DM [19] showed that, among patients with non-ST-elevated ACS who have completed an initial 3-month course of DAPT followed by ticagrelor monotherapy, participants who were assigned to ticagrelor monotherapy experienced lower meaningful bleeding events without increasing any other adverse cardiovascular events when compared with participants who were assigned to DAPT with ticagrelor and aspirin. In addition, in another substudy of the TWILIGHT trial [20], this finding was consistent among patients with and without T2DM. The authors concluded that there is a need to update practical guidelines on the antiplatelet management of high-risk patients undergoing PCI.

It should be noted that, in patients with T2DM, ticagrelor showed better outcomes when compared with clopidogrel or prasugrel in the DAPT regimen along with aspirin to prevent stent thrombosis, or non-stent thrombosis in patients who underwent PCI [21].

Another meta-analysis further supported the results of our current study [22]. The safety and efficacy of ticagrelor monotherapy after a short course of ticagrelor-based DAPT were compared with standard therapy in complex PCI. The pooled analysis did not show any significant change in major bleeding, MI, stent thrombosis, or ischemic stroke. However, ticagrelor monotherapy was associated with a significantly reduced risk of cardiovascular mortality, all-cause death, and any bleeding events.

In contrast to the results of this analysis, other published studies showed different results. In "GLOBAL LEADERS: a clinical study comparing two forms of anti-platelet therapy after stent implantation," ticagrelor monotherapy was started earlier, 1 month after DAPT use, and the 2-year outcomes showed ticagrelor monotherapy to be non-inferior and non-superior to the conventional therapy in preventing ischemic events, and the bleeding risk was not decreased [22].

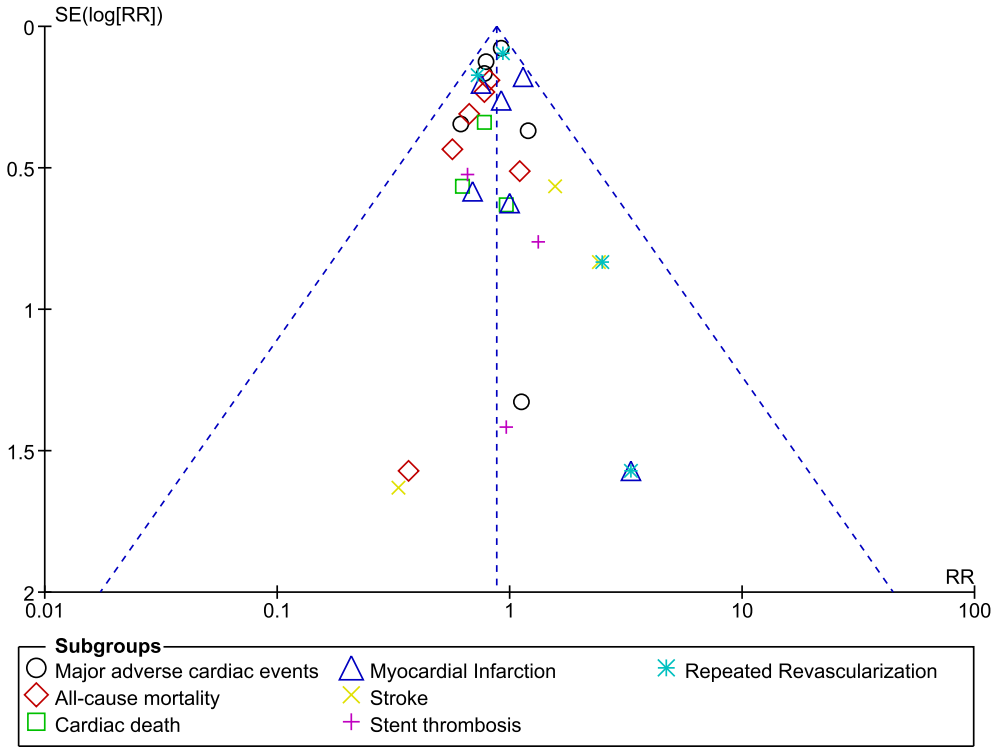

Fig. 5 Funnel plot showing publication bias (A)

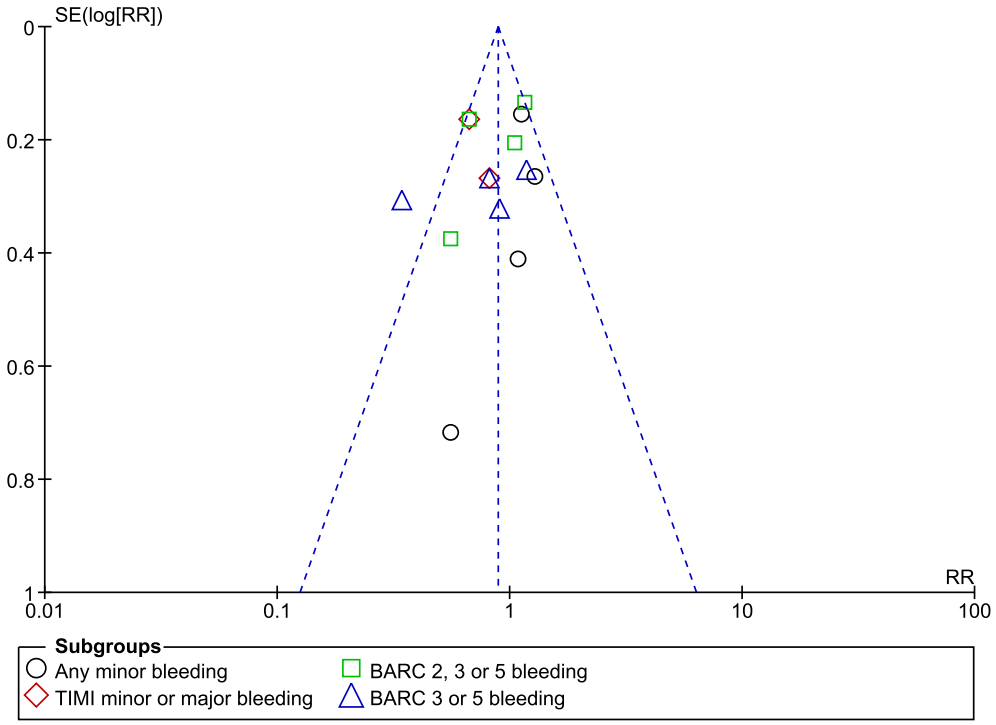

Fig. 6 Funnel plot showing publication bias (B)

This is the first meta-analysis comparing ticagrelor monotherapy after a short course of DAPT use versus DAPT in patients with T2DM, and this is the main strength of our study. CAD and ACS have been observed mostly in patients with T2DM, and there was a great need for a new antiplatelet regimen with better outcomes.

This analysis also has limitations. First of all, the total number of studies and the number of participants might have been too low to reach a robust result. At times, during the outcome analysis, only two studies were involved, and the final result obtained for this specific outcome was influenced by the study with the higher number of participants. This could be considered a limitation of this paper. Another limitation was the fact that the follow-up time period was not standard in all studies. In addition, in a few studies, the ticagrelor monotherapy group first involved DAPT during the first month, and then patients were assigned to ticagrelor monotherapy, and in other studies, the duration of DAPT before ticagrelor monotherapy use was 3 months. This could have had an impact on the results. Another limitation could be related to the bleeding outcomes. TIMI defined major bleeding and minor bleeding were not separately assessed. This was not possible since all the original studies reported TIMI major or minor bleeding altogether. Other bleeding events such as GUSTO bleeding, fatal bleeding were not assessed since they were not reported in the original studies. Another limitation could be the fact that the gravity of coronary artery disease was not considered. Moreover, one study, Johnson 2020 [15], had a follow-up time period of only 1 month compared with the other studies that had a follow-up time period of at least 12 months, and this could affect the final result. The mentioned study also compared ticagrelor monotherapy versus DAPT, whereas the other studies compared ticagrelor monotherapy after a short course of DAPT use in these patients with T2DM.

CONCLUSIONS

Long-term ticagrelor monotherapy after a short course of DAPT use showed better results in patients with T2DM following PCI. Therefore, ticagrelor monotherapy after a short course of DAPT use could be considered an evolution in antiplatelet therapy of this decade for the treatment of patients with T2DM after PCI. However, newer studies with a larger population size and cost-effectiveness are factors that should further be considered.

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Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authors' Contributions. Hong Wang, Xiaoya Xie, Quannan Zu, Ming Lu, Rongfa Chen, Zhiren Yang, Yongqiang Gao and Zhangui Tang were responsible for the conception and design, drafting the initial manuscript and revising it critically for important intellectual content. Hong Wang and Xiaoya Xie wrote the final draft. All the authors approved the final manuscript as it has been written.

Disclosures . The authors Hong Wang, Xiaoya Xie, Quannan Zu, Ming Lu, Rongfa Chen, Zhiren Yang, Yongqiang Gao and Zhangui Tang declare that they have nothing to disclose.

Compliance with Ethical Guidelines. This analysis consisted of data which were previously published. No authors were involved in carry out experiment on animals or human beings. Therefore, an ethical or board review approval was not required for this analysis.

Data Availability. All data are freely available in all electronic databases. References have been given.

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