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

Hong Wang \cdot Xiaoya Xi
e \cdot Quannan Zu \cdot Ming Lu \cdot Rong
fa Chen \cdot

Zhiren Yang · Yongqiang Gao · Zhangui Tang

Received: October 26, 2022 / Accepted: November 24, 2022 / Published online: December 9, 2022 $\ensuremath{\textcircled{}}$ The Author(s) 2022

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

Hong Wang and Xiaoya Xie are co-first authors.

H. Wang

Jinan University, Guangzhou 510632, Guangdong, People's Republic of China

X. Xie Macau University of Science and Technology, Macau, People's Republic of China e-mail: 1220008547@student.must.edu.mo

Q. Zu · M. Lu College of Management and Economics, Tianjin University, Tianjin 300072, People's Republic of China

Q. Zu e-mail: 59474566@qq.com

M. Lu e-mail: China.luming_cn@tju.edu.cn

R. Chen · Z. Yang The State Key Laboratory Management and Control for Complex Systems, Institute of Automation, Chinese Academy of Sciences, Beijing 100190, People's Republic of China 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

R. Chen e-mail: rongfa.chen@ia.ac.cn

Z. Yang e-mail: zhiren.yang@ia.ac.cn

H. Wang $(\boxtimes) \cdot Y$. Gao Department of Cardiology, The People's Hospital of Guangxi Zhuang Autonomous Region, Nanning 530021, Guangxi, People's Republic of China e-mail: iriswh2014@163.com

Y. Gao e-mail: 1737883971@qq.com

Z. Tang

Department of Cardiology, Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology, Tongji, Wuhan, People's Republic of China e-mail: zhangui.tang@yahoo.com 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, repeated revascularization. Ticagrelor or 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:Percutaneouscoronaryintervention;Type2diabetesmellitus;Ticagrelor;Dualantiplatelettherapy;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 longterm 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 Rev-Man 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.

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 Outcomes reported

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

 Table 1 continued

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

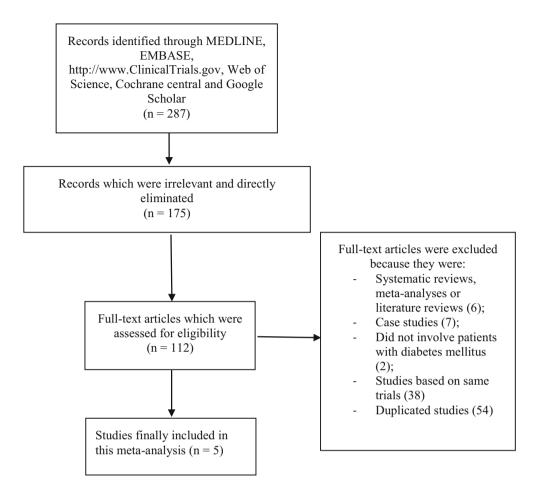


Fig. 1 Flow diagram representing the study selection

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

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

Table 2 Main features of the studies

T2DM type 2 diabetes mellitus, DAPT dual antiplatelet therapy

Table 3 Baseline features of the participants

	1 1				
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.

Study or Subgroup		herapy Total	DAP		Weight	Risk Ratio	Risk Ratio M-H Fixed 95% Cl	Risk of Bias
.1.1 Major adverse ca	Events ardiac events	rotal	events	rotal	weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	ABCDEF
Dominick2020	59	1319	75	1301	7.0%	0.78 [0.56, 1.08]		
Gao2020A	248	1614	263	1575	24.5%	0.92 [0.78, 1.08]	-	
Gao2020B	88	428	106	410	10.0%	0.80 [0.62, 1.02]	-	
Hann2019	16	570	13	552	1.2%	1.19 [0.58, 2.45]		
Johnson2020	1	8	1	9	0.1%	1.13 [0.08, 15.19]		
Yun2021	13	418	21	417	1.9%	0.62 [0.31, 1.22]		
Subtotal (95% CI)		4357		4264	44.7%	0.86 [0.77, 0.98]	•	
Fotal events Heterogeneity: Chi² = 3 Fest for overall effect: 2		'); I² = 0%	479					
I.1.2 All-cause mortal	lity							
Dominick2020	17	1319	25	1301	2.3%	0.67 [0.36, 1.24]		
Gao2020A	49	1614	58	1575	5.4%	0.82 [0.57, 1.20]		
Gao2020B	30	428	37	410	3.5%	0.78 [0.49, 1.23]		
Hann2019	8	570	7	552	0.7%	1.11 [0.40, 3.03]		
lohnson2020	0	8	1	9	0.1%	0.37 [0.02, 7.99]		
Yun2021 Subtotal (95% CI)	8	418	14	417	1.3%	0.57 [0.24, 1.34]		
	110	4357	142	4264	13.3%	0.77 [0.60, 0.98]	•	
Fotal events Heterogeneity: Chi ² = 1 Fest for overall effect: Z); I ² = 0%	142					
.1.3 Cardiac death								
Dominick2020	15	1319	19	1301	1.8%	0.78 [0.40, 1.53]	-+	
Hann2019	5	570	5	552	0.5%	0.97 [0.28, 3.33]		
Yun2021	5	418	8	417	0.7%	0.62 [0.21, 1.89]		
Subtotal (95% CI)		2307		2270	3.0%	0.77 [0.46, 1.30]	-	
Fotal events ⊣eterogeneity: Chi² = 0 Fest for overall effect: Z); I² = 0%	32					
.1.4 Myocardial Infan	ction							
Dominick2020	40	1319	52	1301	4.8%	0.76 [0.51, 1.14]		
Gao2020A	64	1614	55	1575	5.1%	1.14 [0.80, 1.62]		
Gao2020B	26	428	27	410	2.5%	0.92 [0.55, 1.55]	-	
lann2019	5	570	7	552	0.7%	0.69 [0.22, 2.17]		
lohnson2020	1	8	0	9	0.0%	3.33 [0.15, 71.90]		-
Yun2021 Subtotal (95% CI)	5	418 4357	5	417 4264	0.5% 13.7%	1.00 [0.29, 3.42] 0.94 [0.75, 1.18]		
Fotal events Heterogeneity: Chi ² = 3 Fest for overall effect: 2			146	1201	1011 /0	0.01 [0.10, 110]		
	L = 0.30 (P = 0.02)							
1.1.5 Stroke								
Dominick2020	8	1319	5	1301	0.5%	1.58 [0.52, 4.81]		
Hann2019		570	2	552	0.2%	2.42 [0.47, 12.43]		
	5	418	1	417 2270	0.1% 0.8%	0.33 [0.01, 8.14]		
Yun2021	0	2207						
Yun2021 Subtotal (95% CI)	0	2307	0	2270	0.070	1.56 [0.66, 3.68]		
Yun2021 Subtotal (95% CI) Fotal events Heterogeneity: Chi ² = 1	0 13 .18, df = 2 (P = 0.56		8	2270	0.078	1.30 [0.00, 3.00]		
Yun2021 Subtotal (95% CI) Fotal events Heterogeneity: Chi ² = 1 Fest for overall effect: 2 I.1.6 Stent thrombosis	0 .13 .18, df = 2 (P = 0.56 Z = 1.02 (P = 0.31) s	i); I ² = 0%						
Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1 Fest for overall effect: 2 I.1.6 Stent thrombosi Dominick2020	0 .18, df = 2 (P = 0.56 Z = 1.02 (P = 0.31) s 6	i); I² = 0% 1319	9	1301	0.8%	0.66 [0.23, 1.84]		
Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 1.1.6 Stent thrombosi: Dominick2020 Hann2019	0 .18, df = 2 (P = 0.56 Z = 1.02 (P = 0.31) s 6 1	i); l² = 0% 1319 570	9 1	1301 552	0.8% 0.1%	0.66 [0.23, 1.84] 0.97 [0.06, 15.44]		
Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 1.1.6 Stent thrombosi Dominick2020 Hann2019 Yun2021	0 .18, df = 2 (P = 0.56 Z = 1.02 (P = 0.31) s 6	i); ² = 0% 1319 570 418	9	1301 552 417	0.8% 0.1% 0.3%	0.66 [0.23, 1.84] 0.97 [0.06, 15.44] 1.33 [0.30, 5.91]		
Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: Z 1.1.6 Stent thrombosi: Dominick2020 Hann2019 Yun2021 Subtotal (95% CI)	0 13 .18, df = 2 (P = 0.56 Z = 1.02 (P = 0.31) s 6 1 4	i); l² = 0% 1319 570	9 1 3	1301 552	0.8% 0.1%	0.66 [0.23, 1.84] 0.97 [0.06, 15.44]		
Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1 Fest for overall effect: 2 1.6 Stent thrombosis Dominick2020 Hann2019 Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 0	0 13 .18, df = 2 (P = 0.56 Z = 1.02 (P = 0.31) s 6 1 4 11 0.59, df = 2 (P = 0.74	i); I ² = 0% 1319 570 418 2307	9 1	1301 552 417	0.8% 0.1% 0.3%	0.66 [0.23, 1.84] 0.97 [0.06, 15.44] 1.33 [0.30, 5.91]		
'un2021 Subtotal (95% CI) 'otal events' teterogeneity: Chi² = 1 'est for overall effect: Z .1.6 Stent thrombosic Jominick2020 tann2019 'un2021 Subtotal (95% CI) 'otal events teterogeneity: Chi² = 0 'est for overall effect: Z .1.7 Repeated Revas	0 13 .18, df = 2 (P = 0.56 Z = 1.02 (P = 0.31) s 6 1 4 0.59, df = 2 (P = 0.74 Z = 0.44 (P = 0.66) cularization	i); l² = 0% 1319 570 418 2307 ↓); l² = 0%	9 1 3	1301 552 417	0.8% 0.1% 0.3%	0.66 [0.23, 1.84] 0.97 [0.06, 15.44] 1.33 [0.30, 5.91]		
$\label{eq:constraints} \begin{split} & (un2021) \\ & \text{Subtotal (95% CI)} \\ & \text{fotal events} \\ & \text{feterogeneity: Chi^2 = 1} \\ & \text{ferst for overall effect: 2} \\ & \text{i.1.6 Stent thrombosi} \\ & \text{Jonminick2020} \\ & \text{tann2019} \\ & \text{fun2021} \\ & \text{Subtotal (95% CI)} \\ & \text{fotal events} \\ & \text{feterogeneity: Chi^2 = 0} \\ & \text{feterogeneity: Chi^2 = 0} \\ & \text{fest for overall effect: 2} \\ & \text{J.1.7 Repeated Revas} \\ & \text{Sao2020A} \end{split}$	0 13 18, df = 2 (P = 0.56) 2 = 1.02 (P = 0.31) 8 6 1 4 11 0.59, df = 2 (P = 0.74) Z = 0.44 (P = 0.66) cularization 176	 i); l² = 0% 1319 570 418 2307 i); l² = 0% 1614 	9 1 3 13 184	1301 552 417 2270 1575	0.8% 0.1% 0.3% 1.2%	0.66 [0.23, 1.84] 0.97 [0.06, 15.44] 1.33 [0.30, 5.91] 0.84 [0.38, 1.86] 0.93 [0.77, 1.13]		
Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1 Fest for overall effect: 2 1.1.6 Stent thrombosii Dominick2020 Han2021 Subtotal (95% CI) Fotal events Heterogeneity: Chi ² = 0 Fest for overall effect: 2 L1.17 Repeated Revas Sao2020A Sao2020B	0 13 18, df = 2 (P = 0.56) Z = 1.02 (P = 0.31) s 6 1 4 0.59, df = 2 (P = 0.74) Z = 0.44 (P = 0.66) cularization 176 49	i); ² = 0% 1319 570 418 2307 .); ² = 0% 1614 428	9 1 3 13 184 64	1301 552 417 2270 1575 410	0.8% 0.1% 0.3% 1.2% 17.2% 6.0%	0.66 [0.23, 1.84] 0.97 [0.06, 15.44] 1.33 [0.30, 5.91] 0.84 [0.38, 1.86] 0.93 [0.77, 1.13] 0.73 [0.52, 1.04]		
/un2021 \$ubtotal (95% CI) fotal events teterogeneity: Chi² = 1 Fest for overall effect: 2 J.1.6 Stent thrombosi Jominick2020 tann2019 /un2021 Subtotal (95% CI) fotal events teterogeneity: Chi² = 0 fest for overall effect: 2 J.1.7 Repeated Revas 3ao2020A 3ao2020B Johnson2020	0 13 $.18, df = 2 (P = 0.56)$ $z = 1.02 (P = 0.31)$ s 6 1 4 $0.59, df = 2 (P = 0.74)$ $z = 0.44 (P = 0.66)$ 176 49 1	i); ² = 0% 1319 570 418 2307 1); ² = 0% 1614 428 8	9 1 3 13 184 64 0	1301 552 417 2270 1575 410 9	0.8% 0.1% 0.3% 1.2% 17.2% 6.0% 0.0%	0.66 [0.23, 1.84] 0.97 [0.06, 15.44] 1.33 [0.30, 5.91] 0.84 [0.38, 1.86] 0.93 [0.77, 1.13] 0.73 [0.52, 1.04] 3.33 [0.15, 71.90]		
Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi² = 1 Fest for overall effect: 2 Joninick2020 Jann2019 Yun2021 Subtotal (95% CI) Fotal events Heterogeneity: Chi² = 0 Fest for overall effect: 2 Jubtotal (95% CI) Fotal events Heterogeneity: Chi² = 0 Sao202020A Bao2020A Johnson2020 Yun2021	0 13 18, df = 2 (P = 0.56) Z = 1.02 (P = 0.31) s 6 1 4 0.59, df = 2 (P = 0.74) Z = 0.44 (P = 0.66) cularization 176 49	i); ² = 0% 1319 570 418 2307 (); ² = 0% 1614 428 8 418	9 1 3 13 184 64	1301 552 417 2270 1575 410 9 417	0.8% 0.1% 0.3% 1.2% 17.2% 6.0% 0.0% 0.2%	0.66 [0.23, 1.84] 0.97 [0.06, 15.44] 1.33 [0.30, 5.91] 0.84 [0.38, 1.86] 0.93 [0.77, 1.13] 0.73 [0.52, 1.04] 3.33 [0.15, 71.90] 2.49 [0.49, 12.78]		
Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi² = 1 Test for overall effect: 2 Jonnick2020 Hann2019 Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi² = 0 Fest for overall effect: 2 Subtotal (95% CI)	0 13 18, df = 2 (P = 0.56) 2 = 1.02 (P = 0.31) 5 6 1 0.59, df = 2 (P = 0.74) 2 = 0.44 (P = 0.66) 176 49 1 5	i); ² = 0% 1319 570 418 2307 1); ² = 0% 1614 428 8	9 1 3 13 184 64 0 2	1301 552 417 2270 1575 410 9	0.8% 0.1% 0.3% 1.2% 17.2% 6.0% 0.0%	0.66 [0.23, 1.84] 0.97 [0.06, 15.44] 1.33 [0.30, 5.91] 0.84 [0.38, 1.86] 0.93 [0.77, 1.13] 0.73 [0.52, 1.04] 3.33 [0.15, 71.90]		
Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 Total events Heterogeneity: Chi ² = 0 Total events Heterogeneity: Chi ² = 0 Test for overall effect: 2 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 0 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 3 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 3	0 13 $18, df = 2 (P = 0.56)$ $z = 1.02 (P = 0.31)$ s 6 1 4 $0.59, df = 2 (P = 0.74)$ $z = 0.44 (P = 0.66)$ 176 49 1 5 231 $0.67, df = 3 (P = 0.30)$	 i); ² = 0% 1319 570 418 2307 i); ² = 0% 1614 428 8 418 2468 	9 1 3 13 184 64 0 2 250	1301 552 417 2270 1575 410 9 417	0.8% 0.1% 0.3% 1.2% 17.2% 6.0% 0.0% 0.2%	0.66 [0.23, 1.84] 0.97 [0.06, 15.44] 1.33 [0.30, 5.91] 0.84 [0.38, 1.86] 0.93 [0.77, 1.13] 0.73 [0.52, 1.04] 3.33 [0.15, 71.90] 2.49 [0.49, 12.78]		
Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 1.1.6 Stent thrombosi: Dominick2020 Hann2019 Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 0 Sao2020A Sao2020B Johnson2020 Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 3 Test for overall effect: 2 For the subtotal (95% CI) Total events Heterogeneity: Chi ² = 3 Test for overall effect: 2 For the subtotal effect effect: 2 For the subtotal effect: 2 F	0 13 $18, df = 2 (P = 0.56)$ $z = 1.02 (P = 0.31)$ s 6 1 4 $0.59, df = 2 (P = 0.74)$ $z = 0.44 (P = 0.66)$ 176 49 1 5 231 $0.67, df = 3 (P = 0.30)$	 i); ² = 0% 1319 570 418 2307 i); ² = 0% 1614 428 8 418 2468 	9 1 3 13 184 64 0 2 250	1301 552 417 2270 1575 410 9 417 2411	0.8% 0.1% 0.3% 1.2% 17.2% 6.0% 0.0% 0.2%	0.66 [0.23, 1.84] 0.97 [0.06, 15.44] 1.33 [0.30, 5.91] 0.84 [0.38, 1.86] 0.93 [0.77, 1.13] 0.73 [0.52, 1.04] 3.33 [0.15, 71.90] 2.49 [0.49, 12.78]		
Num2021 Subtotal (95% CI) Total events Heterogeneity: Chi² = 1 Test for overall effect: 2 1.1.6 Stent thrombosi: Dominick2020 Hann2019 Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi² = 0 Fest for overall effect: 2 1.1.7 Repeated Revas Gao2020A Gao2020B Johnson2020 Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi² = 3 Test for overall effect: 2 Total events Total events Total events Test for overall effect: 2 Total events	0 13 $18, df = 2 (P = 0.56)$ $z = 1.02 (P = 0.31)$ s 6 1 4 $0.59, df = 2 (P = 0.74)$ $z = 0.44 (P = 0.66)$ 176 49 1 5 231 $0.67, df = 3 (P = 0.30)$	 i); ² = 0% 1319 570 418 2307 i); ² = 0% 1614 428 8 418 2468 j); ² = 189 	9 1 3 13 184 64 0 2 250	1301 552 417 2270 1575 410 9 417 2411	0.8% 0.1% 0.3% 1.2% 17.2% 6.0% 0.0% 0.2% 23.4%	0.66 [0.23, 1.84] 0.97 [0.06, 15.44] 1.33 [0.30, 5.91] 0.84 [0.38, 1.86] 0.93 [0.77, 1.13] 0.73 [0.52, 1.04] 3.33 [0.15, 71.90] 2.49 [0.49, 12.78] 0.90 [0.76, 1.06]		
Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 1.1.6 Stent thrombosi Dominick2020 Hann2019 Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 0 Test for overall effect: 2 1.1.7 Repeated Revas Gao2020A Gao2020B Johnson2020 Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 3 Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: Chi ² = 3	0 13 18, df = 2 (P = 0.56 Z = 1.02 (P = 0.31) s 6 1 4 0.59, df = 2 (P = 0.74 Z = 0.44 (P = 0.66) cularization 176 49 1 5 231 0.67, df = 3 (P = 0.30 Z = 1.25 (P = 0.21) 958 7.03, df = 30 (P = 0	 i); ² = 0% 1319 570 418 2307 i); ² = 0% 1614 428 8 418 2468 i); ² = 18% 22460 	9 1 3 13 184 64 0 2 250 5 1070	1301 552 417 2270 1575 410 9 417 2411	0.8% 0.1% 0.3% 1.2% 17.2% 6.0% 0.0% 0.2% 23.4%	0.66 [0.23, 1.84] 0.97 [0.06, 15.44] 1.33 [0.30, 5.91] 0.84 [0.38, 1.86] 0.73 [0.52, 1.04] 3.33 [0.15, 71.90] 2.49 [0.49, 12.78] 0.90 [0.76, 1.06]		- -
Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi² = 1 Test for overall effect: 2 1.1.6 Stent thrombosic Jominick2020 Han2019 Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi² = 0 Test for overall effect: 2 1.1.7 Repeated Revas Gao2020A Gao2020B Johnson2020 Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi² = 3 Test for overall effect: 2 Total events Heterogeneity: Chi² = 1 Total events Heterogeneity: Chi² = 3 Test for overall effect: 2 Total events Heterogeneity: Chi² = 1 Total events Heterogeneity: Chi² = 1 Test for overall effect: 2 Total events Heterogeneity: Chi² = 1 Test for subgroup differ	0 13 14, df = 2 (P = 0.56 Z = 1.02 (P = 0.31) 5 6 1 4 0.59, df = 2 (P = 0.74 Z = 0.44 (P = 0.66) cularization 176 49 1 5 231 1.67, df = 3 (P = 0.30 Z = 1.25 (P = 0.21) 958 7.03, df = 30 (P = 0.01)	 i); I² = 0% 1319 570 418 2307 i); I² = 0% 1614 428 8 418 2468 i); I² = 189 22460 97); I² = 0 	9 1 3 13 13 13 13 14 64 0 2 250 5 1070	1301 552 417 2270 1575 410 9 417 2411 22013	0.8% 0.1% 0.3% 1.2% 17.2% 6.0% 0.0% 0.2% 23.4%	0.66 [0.23, 1.84] 0.97 [0.06, 15.44] 1.33 [0.30, 5.91] 0.84 [0.38, 1.86] 0.93 [0.77, 1.13] 0.73 [0.52, 1.04] 3.33 [0.15, 71.90] 2.49 [0.49, 12.78] 0.90 [0.76, 1.06] 0.87 [0.80, 0.95]	U.1. 1 10 1 Ticagrelor mono] Favours [DAPT]	-
Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi² = 1 Fest for overall effect: Z Jonninck2020 Jann2019 Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi² = 0 Fest for overall effect: Z J.1.7 Repeated Revas Sao2020A Sao2020B Johnson2020 Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi² = 1 Fest for overall effect: Z Total events Heterogeneity: Chi² = 1 Fest for overall effect: Z Total events Heterogeneity: Chi² = 1 Fest for overall effect: Z Total events Heterogeneity: Chi² = 1 Fest for overall effect: Z Total events Heterogeneity: Chi² = 1 Fest for overall effect: Z Fest for overall effect: A Jashordow sequence	0 13 14, df = 2 (P = 0.56 Z = 1.02 (P = 0.31) s 6 1 0.59, df = 2 (P = 0.74 Z = 0.44 (P = 0.66) cularization 176 49 1 5 231 1.67, df = 3 (P = 0.30 Z = 1.25 (P = 0.21) 958 7.03, df = 30 (P = 0.21) 958 7.03, df = 30 (P = 0.001) rences: Chi ² = 3.63, generation (selectio	1319 570 418 2307 1614 428 8 418 2468 2468 2468 2468 2468 2468 2468 246	9 1 3 13 13 13 13 14 64 0 2 250 5 1070	1301 552 417 2270 1575 410 9 417 2411 22013	0.8% 0.1% 0.3% 1.2% 17.2% 6.0% 0.0% 0.2% 23.4%	0.66 [0.23, 1.84] 0.97 [0.06, 15.44] 1.33 [0.30, 5.91] 0.84 [0.38, 1.86] 0.93 [0.77, 1.13] 0.73 [0.52, 1.04] 3.33 [0.15, 71.90] 2.49 [0.49, 12.78] 0.90 [0.76, 1.06] 0.87 [0.80, 0.95]		-
Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 1.1.6 Stent thrombosic Dominick2020 Hann2019 Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 0 Test for overall effect: 2 1.1.7 Repeated Revas Gac2020A Gac2020B Johnson2020 Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 3 Test for overall effect: 2 Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 Total events Heterogeneity: Chi ² = 1 Test for bias legend (A) Random sequence (B) Allocation concealir	0 13 .18, df = 2 (P = 0.56) z = 1.02 (P = 0.31) s 6 1 4 11 .59, df = 2 (P = 0.74) z = 0.44 (P = 0.66) cularization 176 49 1 5 231 .67, df = 3 (P = 0.32) z = 1.25 (P = 0.21) 958 7.03, df = 30 (P = 0.001) rences: Ch ² = 3.63, generation (selection bias)	1319 570 418 2307 1614 428 8 8 2468 2468 2468 2468 2468 2468 2469 22460 97); I ² = 0(P = 10) 97; I ² = 6 (P = 10) 4 = 7 (P = 10)4 = 7 (P = 10) 4 = 7	9 1 3 13 13 184 64 0 2 250 6 1070 %	1301 552 417 2270 1575 410 9 417 2411 22013	0.8% 0.1% 0.3% 1.2% 17.2% 6.0% 0.0% 0.2% 23.4%	0.66 [0.23, 1.84] 0.97 [0.06, 15.44] 1.33 [0.30, 5.91] 0.84 [0.38, 1.86] 0.93 [0.77, 1.13] 0.73 [0.52, 1.04] 3.33 [0.15, 71.90] 2.49 [0.49, 12.78] 0.90 [0.76, 1.06] 0.87 [0.80, 0.95]		
Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi² = 1 Test for overall effect: 2 Jonninck2020 Hann2019 Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi² = 0 Test for overall effect: 2 Aun2021 Subtotal (95% CI) Total events Heterogeneity: Chi² = 0 Johnson2020 Subtotal (95% CI) Total events Heterogeneity: Chi² = 1 Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: Chi² = 1 Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: Chi² = 1 Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: Chi² = 1 Test for overall effect: 2	0 13 18, df = 2 (P = 0.56 Z = 1.02 (P = 0.31) s 6 1 0.59, df = 2 (P = 0.74 Z = 0.44 (P = 0.66) cularization 176 49 1 5 231 .67, df = 3 (P = 0.30 Z = 1.25 (P = 0.21) 958 7.03, df = 30 (P = 0.001) rences: Chi ² = 3.63, generation (selection bias) ints and personnel (($\begin{aligned} & 1319\\ & 570\\ & 418\\ & 2307 \end{aligned}$	9 1 3 13 13 184 64 0 2 250 6 1070 %	1301 552 417 2270 1575 410 9 417 2411 22013	0.8% 0.1% 0.3% 1.2% 17.2% 6.0% 0.0% 0.2% 23.4%	0.66 [0.23, 1.84] 0.97 [0.06, 15.44] 1.33 [0.30, 5.91] 0.84 [0.38, 1.86] 0.93 [0.77, 1.13] 0.73 [0.52, 1.04] 3.33 [0.15, 71.90] 2.49 [0.49, 12.78] 0.90 [0.76, 1.06] 0.87 [0.80, 0.95]		-
Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi² = 1 Test for overall effect: 2 1.1.6 Stent thrombosi- Dominick2020 Han2019 Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi² = 0 Heterogeneity: Chi² = 0 Johnson2020 Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi² = 3 Subtotal (95% CI) Total events Heterogeneity: Chi² = 1 Test for overall effect: 2 Total events Heterogeneity: Chi² = 1 Test for overall effect: 2 Test for overall effect: 2 <td>0 13 .18, df = 2 (P = 0.56 Z = 1.02 (P = 0.31) s 6 1 .59, df = 2 (P = 0.74 Z = 0.44 (P = 0.66) cularization 176 49 1 .67, df = 3 (P = 0.30 Z = 1.25 (P = 0.21) 958 7.03, df = 30 (P = 0.31) set a 2 (P = 0.36), generation (selection bias) unts and personnel (q) assessment (delection bias)</td> <td>$\begin{array}{l} 1319\\ 570\\ 418\\ 2307\\ 1614\\ 428\\ 8\\ 418\\ 2468\\ 2468\\ 2468\\ 97); \ ^2=0\%\\ 22460\\ 97); \ ^2=189\\ 22460\\ 97); \ ^2=0\\ 6\ (P^{-1})\\ 1016\\$</td> <td>9 1 3 13 13 184 64 0 2 250 6 1070 %</td> <td>1301 552 417 2270 1575 410 9 417 2411 22013</td> <td>0.8% 0.1% 0.3% 1.2% 17.2% 6.0% 0.0% 0.2% 23.4%</td> <td>0.66 [0.23, 1.84] 0.97 [0.06, 15.44] 1.33 [0.30, 5.91] 0.84 [0.38, 1.86] 0.93 [0.77, 1.13] 0.73 [0.52, 1.04] 3.33 [0.15, 71.90] 2.49 [0.49, 12.78] 0.90 [0.76, 1.06] 0.87 [0.80, 0.95]</td> <td></td> <td>-</td>	0 13 .18, df = 2 (P = 0.56 Z = 1.02 (P = 0.31) s 6 1 .59, df = 2 (P = 0.74 Z = 0.44 (P = 0.66) cularization 176 49 1 .67, df = 3 (P = 0.30 Z = 1.25 (P = 0.21) 958 7.03, df = 30 (P = 0.31) set a 2 (P = 0.36), generation (selection bias) unts and personnel (q) assessment (delection bias)	$\begin{array}{l} 1319\\ 570\\ 418\\ 2307\\ 1614\\ 428\\ 8\\ 418\\ 2468\\ 2468\\ 2468\\ 97); \ ^2=0\%\\ 22460\\ 97); \ ^2=189\\ 22460\\ 97); \ ^2=0\\ 6\ (P^{-1})\\ 1016\\$	9 1 3 13 13 184 64 0 2 250 6 1070 %	1301 552 417 2270 1575 410 9 417 2411 22013	0.8% 0.1% 0.3% 1.2% 17.2% 6.0% 0.0% 0.2% 23.4%	0.66 [0.23, 1.84] 0.97 [0.06, 15.44] 1.33 [0.30, 5.91] 0.84 [0.38, 1.86] 0.93 [0.77, 1.13] 0.73 [0.52, 1.04] 3.33 [0.15, 71.90] 2.49 [0.49, 12.78] 0.90 [0.76, 1.06] 0.87 [0.80, 0.95]		-
Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi² = 1 Test for overall effect: 2 Jonminck2020 Jann2019 Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi² = 0 Fest for overall effect: 2 J.1.7 Repeated Revas Bac/2020A Bac/2020B Johntons2020 Yun2021 Subtotal (95% CI) Total events Heterogeneity: Chi² = 3 Fest for overall effect: 2 Total (95% CI) Total events Heterogeneity: Chi² = 1 Fest for overall effect: 2 Total (95% CI) Total events Heterogeneity: Chi² = 1 Fest for overall effect: 2 Total (95% CI) Total events Best for overall effect: 2 Test for overall effect: 2 Gotal events Best for ov	0 13 18, df = 2 (P = 0.56) Z = 1.02 (P = 0.31) 8 6 1 1 0.59, df = 2 (P = 0.74) Z = 0.44 (P = 0.66) 176 49 1 5 231 0.67, df = 3 (P = 0.30) Z = 1.25 (P = 0.21) 958 7.03, df = 30 (P = 0.21) 958 7.03, df = 30 (P = 0.30) z = 3.23 (P = 0.001) rences: Chi ² = 3.63, generation (selection bias) inst and personnel (detace e data (attriton bias)	$\begin{array}{l} 1319\\ 570\\ 418\\ 2307\\ 1614\\ 428\\ 8\\ 418\\ 2468\\ 2468\\ 2468\\ 97); \ ^2=0\%\\ 22460\\ 97); \ ^2=189\\ 22460\\ 97); \ ^2=0\\ 6\ (P^{-1})\\ 1016\\$	9 1 3 13 13 184 64 0 2 250 6 1070 %	1301 552 417 2270 1575 410 9 417 2411 22013	0.8% 0.1% 0.3% 1.2% 17.2% 6.0% 0.0% 0.2% 23.4%	0.66 [0.23, 1.84] 0.97 [0.06, 15.44] 1.33 [0.30, 5.91] 0.84 [0.38, 1.86] 0.93 [0.77, 1.13] 0.73 [0.52, 1.04] 3.33 [0.15, 71.90] 2.49 [0.49, 12.78] 0.90 [0.76, 1.06] 0.87 [0.80, 0.95]		-

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

	Ticagrelor monot	herapy	DAP	т		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	ABCDEFG
1.2.1 Any minor blee	ding							
Gao2020A	83	1614	72	1575	32.1%	1.12 [0.83, 1.53]		
Gao2020B	31	428	23	410	10.4%	1.29 [0.77, 2.18]	- - -	
Johnson2020	2	8	4	9	1.7%	0.56 [0.14, 2.29]		
Yun2021	12	418	11	417	4.9%	1.09 [0.49, 2.44]		
Subtotal (95% CI)		2468		2411	49.0%	1.14 [0.89, 1.46]	•	
Total events	128		110					
Heterogeneity: Chi ² =	1.21, df = 3 (P = 0.75	5); I² = 0%						
Test for overall effect:	Z = 1.02 (P = 0.31)							
1.2.2 TIMI minor or n	najor bleeding							
Dominick2020	58	1319	86	1301	38.2%	0.67 [0.48, 0.92]	-=-	
Yun2021	24	418	29	417	12.8%	0.83 [0.49, 1.39]		
Subtotal (95% CI)		1737		1718	51.0%	0.71 [0.54, 0.93]	◆	
Total events	82		115					
Heterogeneity: Chi ² =	0.47, df = 1 (P = 0.49	9); l ² = 0%						
Test for overall effect:	Z = 2.48 (P = 0.01)							
Total (95% CI)		4205		4129	100.0%	0.92 [0.76, 1.10]	•	
Total events	210		225					
Heterogeneity: Chi ² =	7.90, df = 5 (P = 0.16	5); l² = 379	%			0.01	0.1 1 10	100
Test for overall effect:	Z = 0.93 (P = 0.35)						Ticagrelor mono] Favours [DAPT]	100
Test for subgroup diffe	erences: Chi ² = 6.39,	df = 1 (P =	= 0.01), l ⁱ	² = 84.3	\$%	1 avours [1		
Risk of bias legend								
(A) Random sequence	e generation (selectio	n bias)						
(B) Allocation conceal	ment (selection bias)							
(C) Blinding of particip	ants and personnel (performar	nce bias)					
(D) Blinding of outcom	ne assessment (detec	tion bias)						
(E) Incomplete outcom	ne data (attrition bias)							
(F) Selective reporting	(reporting bias)							
(G) Other bias								

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

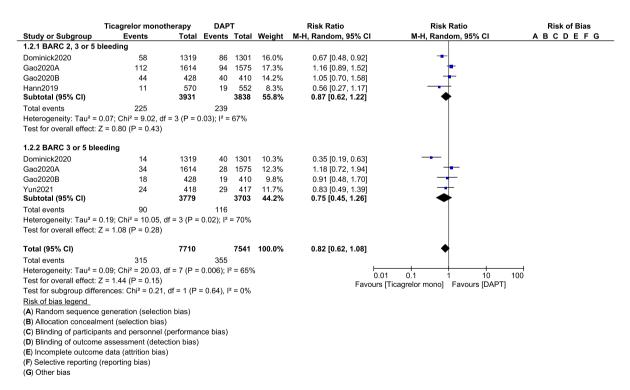


Fig. 4 Forest plot showing the comparison of BARC bleeding between ticagrelor monotherapy and dual antiplatelet therapy following PCI in patients with T2DM

Table 4 Summary of the main analysis

Outcomes	RR with 95%	P value	I^2
	CI		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].

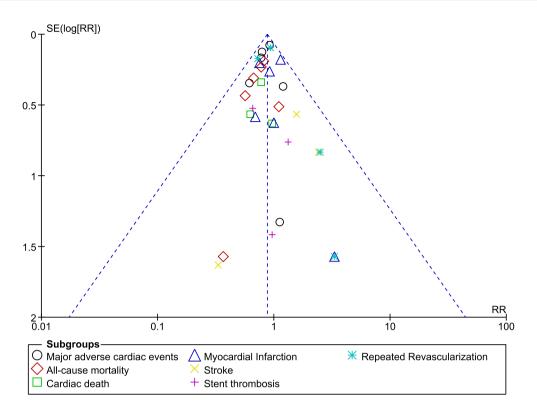


Fig. 5 Funnel plot showing publication bias (A)

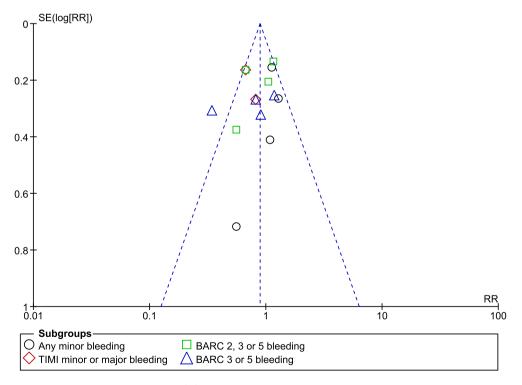


Fig. 6 Funnel plot showing publication bias (B)

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.

ACKNOWLEDGEMENTS

Funding. This research study was supported by the Guangxi Key Research and Development Program (Grant No. AB22035078); Guangxi Medical and Health Appropriate Technology Development and Promotion Application Project (Grant No. S2017077) and the Guangxi Nanning Qingxiu District Science and Technology Development Project (Grant No. 2014S06).

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.

Open Access. This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/bync/4.0/.

REFERENCES

- 1. Mishra S, Ray S, Dalal JJ, et al. Management standards for stable coronary artery disease in India. Indian Heart J. 2016;68(Suppl 3):S31–49.
- 2. Das RN. Relationship between diabetes mellitus and coronary heart disease. Curr Diabetes Rev. 2016;12(3):285–96.
- 3. Jensen ES, Olesen KKW, Gyldenkerne C, et al. Cardiovascular risk in patients with and without diabetes presenting with chronic coronary syndrome in 2004–2016. BMC Cardiovasc Disord. 2021;21(1): 579.
- 4. Capodanno D, Alfonso F, Levine GN, Valgimigli M, Angiolillo DJ. ACC/AHA versus ESC guidelines on

dual antiplatelet therapy: JACC guideline comparison. J Am Coll Cardiol. 2018;72(23 Pt A):2915–31.

- 5. Savarese G, Savonitto S, Lund LH, et al. Efficacy and safety of prolonged dual antiplatelet therapy: a meta-analysis of 15 randomized trials enrolling 85,265 patients. Eur Heart J Cardiovasc Pharmacother. 2016;2(4):218–28.
- 6. Rollini F, Franchi F, Muñiz-Lozano A, Angiolillo DJ. Platelet function profiles in patients with diabetes mellitus. J Cardiovasc Transl Res. 2013;6(3):329–45.
- 7. Yang T-H, Kim D-I, Kim D-K, et al. Detection of clopidogrel hyporesponsiveness using a point-of-care assay and the impact of additional cilostazol administration after coronary stent implantation in diabetic patients. Korean J Intern Med. 2011;26(2): 145–52.
- 8. Takahashi K, Serruys PW, Chichareon P, et al. Efficacy and safety of ticagrelor monotherapy in patients undergoing multivessel PCI. J Am Coll Cardiol. 2019;74(16):2015–27.
- 9. Steinhubl SR, Kastrati A, Berger PB. Variation in the definitions of bleeding in clinical trials of patients with acute coronary syndromes and undergoing percutaneous coronary interventions and its impact on the apparent safety of antithrombotic drugs. Am Heart J. 2007;154(1):3–11.
- 10. Fortuni F, Crimi G, Morici N, et al. Assessing bleeding in acute coronary syndrome using the Bleeding Academic Research Consortium definition. J Cardiovasc Med (Hagerstown). 2019;20(12): 818–24.
- 11. Higgins JP, et al. Assessing risk of bias in included studies. In: Cochrane handbook for systematic reviews of interventions. Wiley; 2008. p. 187–241.
- 12. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;21(339): b2700.
- 13. Angiolillo DJ, Baber U, Sartori S, et al. Ticagrelor with or without aspirin in high-risk patients with diabetes mellitus undergoing percutaneous coronary intervention. J Am Coll Cardiol. 2020;75(19): 2403–13.
- 14. Gao C, Tomaniak M, Takahashi K, et al. Ticagrelor monotherapy in patients with concomitant diabetes mellitus and chronic kidney disease: a post hoc analysis of the GLOBAL LEADERS trial. Cardiovasc Diabetol. 2020;19(1):179.

- 15. Hahn J-Y, Song YB, Oh J-H, et al. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE randomized clinical trial. JAMA. 2019;321(24):2428–37.
- 16. Johnson TW, Baos S, Collett L, et al. Pharmacodynamic comparison of ticagrelor monotherapy versus ticagrelor and aspirin in patients after percutaneous coronary intervention: the TEM-PLATE (ticagrelor monotherapy and platelet reactivity) randomized controlled trial. J Am Heart Assoc. 2020;9(24):e016495.
- 17. Yun KH, Cho JY, Lee SY, et al. Ischemic and bleeding events of ticagrelor monotherapy in korean patients with and without diabetes mellitus: insights from the TICO trial. Front Pharmacol. 2021;11:620906.
- Valgimigli M, Mehran R, Franzone A, et al. Ticagrelor monotherapy versus dual-antiplatelet therapy after PCI: an individual patient-level metaanalysis. JACC Cardiovasc Interv. 2021;14(4): 444–56.

- 19. Baber U, Dangas G, Angiolillo DJ, et al. Ticagrelor alone vs. ticagrelor plus aspirin following percutaneous coronary intervention in patients with non-ST-segment elevation acute coronary syndromes: TWILIGHT-ACS. Eur Heart J. 2020;41(37):3533–45.
- 20. Angiolillo DJ, Baber U, Mehran R. Ticagrelor monotherapy in patients with diabetes mellitus undergoing percutaneous coronary interventions: insights from the TWILIGHT trial. Cardiovasc Res. 2020;116(7):e70–2.
- 21. Zhang Z, Chen O. Efficacy and safety of ticagrelor in diabetes patients undergoing percutaneous coronary intervention: a meta-analysis of randomized controlled trials. J Cardiovasc Pharmacol. 2021;77(5):536–43.
- 22. Franzone A, McFadden E, Leonardi S, et al. Ticagrelor alone versus dual antiplatelet therapy from 1 month after drug-eluting coronary stenting. J Am Coll Cardiol. 2019;74(18):2223–34.