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ORIGINAL RESEARCH

Ticagrelor Versus Prasugrel for the Treatment of Patients with Type 2 Diabetes Mellitus Following Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Antiplatelet therapy is very important following percutaneous coronary intervention (PCI). New generation $P2Y_{12}$ inhibitors (ticagrelor and prasugrel) might potentially replace clopidogrel for the treatment of post-interventional acute coronary syndrome (ACS). In this analysis, we aimed to systematically compare the post-interventional clinical outcomes and bleeding events observed with ticagrelor versus prasugrel in patients with type 2 diabetes mellitus (T2DM).

Methods: EMBASE, MEDLINE, the Cochrane Central Register of Controlled Trials, and www.ClinicalTrials.gov were carefully searched for publications comparing the post-coronary interventional outcomes following ticagrelor versus prasugrel use in patients with T2DM. Adverse clinical outcomes and bleeding events were considered as the endpoints. Statistical analysis was carried out by the Revman software (version 5.3). Odds ratios (OR) and 95% confidence intervals (CI) were used to represent the data during subgroup analysis.

Results: A total of 2004 participants with T2DM were included in this analysis. Following PCI, mortality (OR 1.00, 95% CI 0.57–1.76; $P = 0.99$, $I^2 = 19\%$), myocardial infarction (OR 0.86, 95% CI 0.42–1.75; $P = 0.67$, $I^2 = 0\%$), major adverse cardiac events (OR 0.73, 95% CI 0.42–1.27; $P = 0.27$, $I^2 = 0\%$), and stroke (OR 0.72, 95% CI 0.20–2.59; $P = 0.61$, $I^2 = 0\%$) were not significantly different between ticagrelor and prasugrel. In addition, total bleeding events (OR 0.87, 95% CI 0.55–1.40; $P = 0.58$, $I^2 = 6\%$), Thrombolysis in Myocardial Infarction (TIMI) defined minor bleeding (OR 2.39, 95% CI 0.58–9.91; $P = 0.23$, $I^2 = 0\%$), TIMI defined major bleeding (OR 1.42, 95% CI 0.27–7.45; $P = 0.68$, $I^2 = 0\%$), bleeding defined according to the Bleeding Academic Research Consortium (BARC) major bleeding (OR 0.55, 95% CI 0.22–1.36; $P = 0.20$, $I^2 = 0\%$), BARC minor bleeding (OR 1.44, 95% CI 0.52–3.99; $P = 0.48$, $I^2 = 0\%$), and total minimal bleeding (OR 3.12, 95% CI 0.55–17.59; $P = 0.20$, $I^2 = 0\%$) were also not significantly different.

Conclusion: Ticagrelor and prasugrel were not associated with significantly different adverse clinical outcomes and bleeding events in these patients with T2DM. Therefore, both antiplatelet agents might safely be used in patients with T2DM following coronary intervention.

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However, this head-to-head comparison still remains a major challenge which should be resolved in larger clinical trials.

Keywords: Bleeding events; Clinical outcomes; Percutaneous coronary intervention; Prasugrel; Ticagrelor; Type 2 diabetes mellitus

Abbreviations

CVD	Cardiovascular disease
CAD	Coronary artery disease
PCI	Percutaneous coronary intervention
T2DM	Type 2 diabetes mellitus

INTRODUCTION

Antiplatelet therapy is very important following percutaneous coronary intervention (PCI) to reduce the risk of post-interventional complications. However, bleeding risk might be a limiting factor of these blood thinners [1]. New generation $P2Y_{12}$ inhibitors (ticagrelor and prasugrel) might soon replace clopidogrel for the post-interventional treatment of patients with acute coronary syndrome (ACS) [2]. This was indicated in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI 38) and the PLATelet inhibition and patient Outcomes (PLATO) trials [3, 4].

The newer antiplatelet agents ticagrelor and prasugrel have faster and stronger platelet inhibition in comparison to the commonly used clopidogrel [5] following coronary angioplasty and hence the European guidelines now recommend both antiplatelet drugs as first-line choice for the post-interventional treatment of patients with ACS [6].

Recently, a few meta-analyses based on the general population comparing the efficacy and safety of ticagrelor versus prasugrel were published. However, controversial issues were observed. For example, a head-to-head comparison by Bundhun et al. showed comparable outcomes between ticagrelor and prasugrel for the treatment of patients with ACS [7]. Bleeding events were also similarly observed. Nevertheless, another head-to-head comparison by Sakurai et al. showed prasugrel to be associated with lower risk of bleeding events in comparison to ticagrelor [8].

Patients with type 2 diabetes mellitus (T2DM) are at higher risk of thrombosis due to platelet dysfunctions [9]. Clopidogrel hyporesponsiveness was also observed in this subgroup of patients following PCI [10]. However, those newer potent antiplatelet agents were not systematically compared in a subgroup of patients with T2DM.

In this analysis, we aimed to systematically compare the post-interventional clinical outcomes and bleeding events observed with ticagrelor versus prasugrel in patients with T2DM.

METHODS

Search Strategies (Data Sources, Search Terms, Inclusion and Exclusion Criteria)

The database of EMBASE (www.sciencedirect.com), MEDLINE including its subset PubMed, the Cochrane Central Register of Controlled Trials, and www.ClinicalTrials.gov were carefully searched for publications comparing the post-coronary interventional outcomes following ticagrelor versus prasugrel use in patients with T2DM. Articles which were published in English were considered relevant to this analysis.

"Ticagrelor, prasugrel and percutaneous coronary intervention", "ticagrelor, prasugrel, percutaneous coronary intervention and diabetes mellitus", "ticagrelor, prasugrel, diabetes mellitus", "ticagrelor, prasugrel, coronary artery diseases", "prasugrel, ticagrelor, acute coronary syndrome", "ticagrelor, prasugrel, coronary angioplasty", "prasugrel, ticagrelor, myocardial infarction" were the search terms which were used.

The inclusion criteria were:

(a) Randomized or non-randomized trials comparing the post-interventional clinical outcomes and bleeding events in T2DM patients following treatment with ticagrelor versus prasugrel
(b) Studies which involved data that could be used to carry out this analysis

The exclusion criteria were:

(a) Meta-analyses, literature reviews, and letters to editors
(b) Studies which did not report the corresponding endpoints
(c) Studies only reporting platelet aggregation without considering the post-interventional endpoints or bleeding events
(d) Studies that included data which could not be used in the analysis
(e) Duplicated studies

Types of Participants and Outcomes Reported

All the participants were T2DM patients with coronary artery disease of different degree (ST and non-ST segment elevated myocardial infarction, ACS) who recently underwent PCI and who were treated with either ticagrelor or prasugrel.

The outcomes reported in each study and the corresponding follow-up time periods are listed in Table 1.

The following endpoints were assessed in this analysis:

- Mortality
- Myocardial infarction (MI)
- Major adverse cardiac events (MACEs) consisting of mortality, MI, and revascularization
- Stroke
- Total bleeding events including all bleeding events which were reported
- Thrombolysis in Myocardial Infarction (TIMI) [11] defined minor bleeding
- TIMI defined major bleeding [11]
- Minor bleeding defined according to the Bleeding Academic Research Consortium (BARC 1 and 2) [12]
- Major bleeding defined according to the Bleeding Academic Research Consortium (BARC > 2) [12]
- Minimal bleeding (any type of minimal bleeding)

Data Extraction and Quality Assessment

Relevant data including the number of participants with T2DM, the total number of T2DM participants assigned to the ticagrelor group, the total number of T2DM participants assigned to the prasugrel group, the baseline features of the participants, the total number of events associated with mortality, MI, MACEs, stroke, and bleeding outcomes were carefully extracted by four reviewers.

Data were cross-checked by all the reviewers. Any disagreements which followed were resolved by discussion.

The methodological quality of the trials was assessed with reference to the recommendations of the Cochrane Collaboration [13].

Statistical Analysis

Statistical analysis was carried out by the Revman software (version 5.3). Odds ratios (OR) and 95% confidence intervals (CI) were used to represent the data during subgroup analysis.

Heterogeneity was assessed by the Q statistic test. A result reporting a P value less or equal to 0.05 was considered statistically significant whereas any P value greater than 0.05 was considered statistically insignificant.

Heterogeneity was also assessed by the I^2 statistic test. Heterogeneity was considered to be high if the I^2 value was high. A low heterogeneity was represented by a lower I^2 value.

A fixed statistical model was used if I^2 was less than 50% whereas a random statistical model was used if I^2 was greater than 50%.

Sensitivity analysis was carried out by an exclusion method. Each study was excluded one by one and a new analysis was carried out each time to observe for any significant change in the main results.

Publication bias was visually assessed by observing funnel plots.

Compliance with Ethical Guidelines

Ethical approval was not required for this study since it did not involve experiments with animals or humans performed by any of the authors.

Table 1 Types of participants, outcomes reported, and follow-up time periods

Studies	Types of PCI participants	Outcomes reported	Follow-up time period
Alexopoulos 2012 [15]	T2DM patients with STEMI	Mortality, minor or minimal bleeding event	5 days
Alexopoulos 2013 [16]	T2DM patients with ACS	Major bleeding, MACEs, BARC 1 bleeding	15 days
Alexopoulos 2012B [17]	T2DM patients with non-STEMI	Major bleeding, MACEs, BARC 1 and 2 bleeding	15 days
Bonello 2015 [18]	T2DM patients with ACS	Cardiovascular death, MACEs, BARC > 2 bleeding events, stroke	30 days
Conrotto 2018 [19]	T2DM patients with ACS	Mortality, MI, MACEs, stroke, BARC 2–5 bleeding	19 months
Dimitroulis 2018 [20]	T2DM patients with STEMI	MACCEs, all-cause mortality, cardiovascular death, MI, stroke, TIMI major and TIMI minor bleeding	12 months
Franchi 2016 [21]	T2DM patients with CAD	BARC 1–5 bleeding, dyspnea	7 days
Hochholzer 2017 [22]	T2DM patients with CAD	Death, MI, TIMI major and minor bleeding, BARC 3–5	30 days
Laine 2014 [23]	T2DM patients with ACS	Death, MACEs	In-hospital
Motovska 2016 [24]	T2DM patients with AMI	TIMI major, TIMI minor, TIMI minimal bleeding, BARC 1–5, MACEs, MI, stroke, death	30 days
Parodi 2013 [25]	T2DM patients with STEMI	Death, MI, stroke, TIMI major, minor, minimal bleeding, dyspnea	In-hospital
Perl 2014 [26]	T2DM patients with AMI	Bleeding events	30 days
Song 2017 [27]	T2DM patients with ACS	Mortality	365 days

PCI percutaneous coronary intervention, *T2DM* type 2 diabetes mellitus, *STEMI* ST segment elevated myocardial infarction, *ACS* acute coronary syndrome, *CAD* coronary artery disease, *AMI* acute myocardial infarction, *MACEs* major adverse cardiac events, *MACCEs* major adverse cardiovascular and cerebrovascular events, *BARC* bleeding defined according to the Bleeding Academic Research Consortium, *TIMI* Thrombolysis in Myocardial Infarction, *MI* myocardial infarction

RESULTS

Search Outcomes

Searched outcomes (Preferred Reporting Items for Systematic reviews and Meta-Analyses: PRISMA guideline) [14] resulted in a total of 745 articles. Following a careful assessment of the titles and abstracts, 698 articles were eliminated. Forty-seven (47) full-text articles were assessed for eligibility. Further eliminations were carried out for the following reasons: meta-analyses (3), letters of correspondence (3), reported only platelet outcomes (11), reported

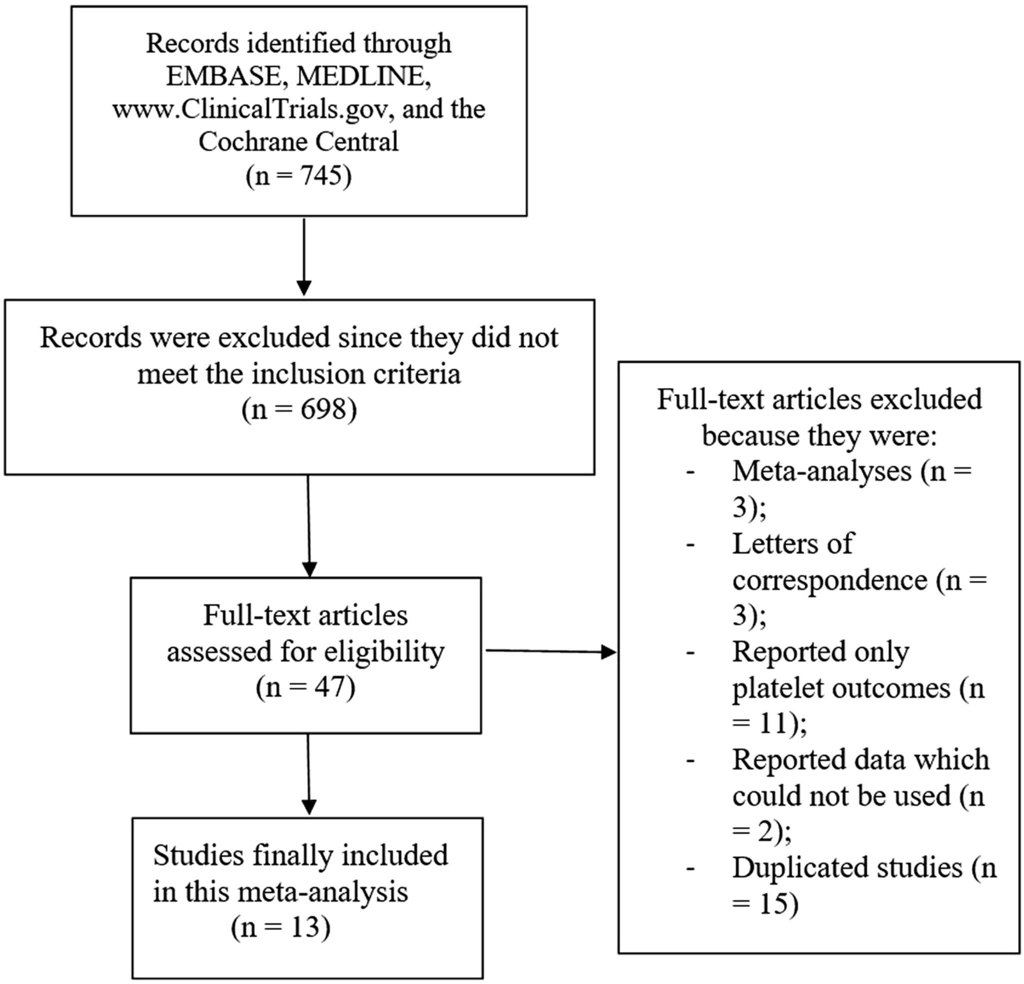

Fig. 1 Flow diagram representing the flow of study selection

data which could not be used in this analysis (2), duplicated studies (15). Finally, 13 articles [15–27] were selected for this analysis as shown in Fig. 1.

Main and Baseline Features of the Studies and Participants

A total of 2004 participants with T2DM were included in this analysis; of these, 996 T2DM participants were assigned to ticagrelor whereas 1008 T2DM participants were assigned to prasugrel. The enrollment period was between years 2012 and 2016 as shown in Table 2. Table 2 lists the number of T2DM participants extracted from each study.

Table 3 lists the baseline features of the T2DM participants. The mean age of the patients varied from 55.8 to 71.8 years. The majority of participants were male. The percentages of participants with hypertension, dyslipidemia, and a smoking history are reported in Table 3.

Post-Interventional Clinical Outcomes and Bleeding Events Observed with Ticagrelor Versus Prasugrel in Patients with Type 2 Diabetes Mellitus

Following PCI, when the adverse clinical outcomes were assessed in T2DM patients who were assigned to ticagrelor versus prasugrel,

Table 2 General features of the studies

Studies	Type of study	Participants' enrollment period	No. of T2DM participants assigned to ticagrelor group (*n*)	No. of T2DM participants assigned to prasugrel group (*n*)
Alexopoulos 2012	NRT	–	3	2
Alexopoulos 2013	NRT	2012	15	15
Alexopoulos 2012B	RT	2012	6	4
Bonello 2015	RT	2014	31	44
Conrotto 2018	NRT	2012–2016	386	386
Dimitroulis 2018	NRT	2012–2015	30	32
Franchi 2016	RT	2013–2015	24	26
Hochholzer 2017	RT	2016	10	9
Laine 2014	RT	2012–2013	50	50
Motovska 2016	RT	2013–2016	124	127
Parodi 2013	RT	2012	3	6
Perl 2014	NRT	–	19	17
Song 2017	NRT	2013–2014	295	290
Total no. of participants (*n*)			996	1008

NRT non-randomized trial, *RT* randomized trial, *T2DM* type 2 diabetes mellitus

mortality (OR 1.00, 95% CI 0.57–1.76; $P = 0.99$, $I^2 = 19\%$), MI (OR 0.86, 95% CI 0.42–1.75; $P = 0.67$, $I^2 = 0\%$), MACEs (OR 0.73, 95% CI 0.42–1.27; $P = 0.27$, $I^2 = 0\%$), and stroke (OR 0.72, 95% CI 0.20–2.59; $P = 0.61$, $I^2 = 0\%$) were not significantly different between the two different groups of antiplatelet agents as shown in Fig. 2.

The post-interventional bleeding events were also assessed following ticagrelor or prasugrel use in these patients with T2DM. Total bleeding events (OR 0.87, 95% CI 0.55–1.40; $P = 0.58$, $I^2 = 6\%$), TIMI defined minor bleeding (OR 2.39, 95% CI 0.58–9.91; $P = 0.23$, $I^2 = 0\%$), TIMI defined major bleeding (OR 1.42, 95% CI 0.27–7.45; $P = 0.68$, $I^2 = 0\%$), BARC major bleeding (OR 0.55, 95% CI 0.22–1.36; $P = 0.20$, $I^2 = 0\%$), BARC minor bleeding (OR 1.44, 95% CI 0.52–3.99; $P = 0.48$, $I^2 = 0\%$), and total minimal bleeding (OR 3.12, 95% CI 0.55–17.59; $P = 0.20$, $I^2 = 0\%$) were not significantly different as shown in Fig. 3.

The results are summarized in Table 4.

Sensitivity Analysis and Publication Bias

When each study was excluded one by one and a new analysis was carried out, consistent results were obtained throughout. Publication bias was visually assessed through funnel plots. Based on this assessment, a low evidence of publication bias was observed across all the studies that assessed the post-interventional clinical outcomes and bleeding events observed with ticagrelor versus prasugrel in these patients with T2DM as shown in Figs. 4 and 5.

DISCUSSION

The post-interventional clinical outcomes and bleeding events observed with ticagrelor versus prasugrel were compared in patients with T2DM. Findings of this analysis showed no

Table 3 Baseline features of the participants

Studies	Age (years) Tica/Prasu	Male (%) Tica/Prasu	HBP (%) Tica/Prasu	DSL (%) Tica/Prasu	CS (%) Tica/Prasu
Alexopoulos 2012	58.0/61.0	86.0/74.0	43.0/44.0	46.0/59.0	64.0/48.0
Alexopoulos 2013	60.9/65.4	93.3/93.3	73.3/66.7	46.7/53.3	33.3/40.0
Alexopoulos 2012B	55.8/57.4	92.9/82.1	57.1/53.6	67.9/42.9	64.3/42.9
Bonello 2015	61.5/60.0	69.8/79.8	52.8/57.9	53.3/45.3	48.0/36.8
Conrotto 2018	62.6/62.9	79.5/80.8	67.6/68.4	63.0/65.3	43.8/40.2
Dimitroulis 2018	63.0/57.0	76.0/81.0	65.0/53.0	24.0/22.0	49.0/58.0
Franchi 2016	59.0/59.0	72.0/72.0	93.0/93.0	87.0/87.0	24.0/24.0
Hochholzer 2017	69.0/70.0	78.0/82.0	80.0/84.0	96.0/84.0	–
Laine 2014	64.8/62.8	66.0/86.0	80.0/70.0	56.0/62.0	28.0/28.0
Motovska 2016	61.8/61.8	73.7/77.1	51.2/51.4	35.4/33.4	65.8/64.0
Parodi 2013	67.0/67.0	76.0/80.0	72.0/60.0	40.0/20.0	36.0/36.0
Perl 2014	63.2/57.5	80.8/79.0	63.5/43.5	63.5/59.7	34.6/51.6
Song 2017	71.8/71.7	64.6/65.3	86.6/87.0	82.1/81.7	16.5/16.5

HBP hypertension, *DSL* dyslipidemia, *CS* current smoker, *Tica* ticagrelor group, *Prasu* prasugrel group

significant difference in mortality, MI, MACEs, stroke, total bleeding events, TIMI defined major and minor bleedings, BARC major and minor bleedings as well as no significant difference in minimal bleeding events.

Recently, the Prasugrel versus Ticagrelor in Patients with Acute Myocardial Infarction Treated with Primary Percutaneous Coronary Intervention (PRAGUE-18) Trial which compared these two newer potent antiplatelets with clopidogrel showed that the latter was inferior in terms of efficacy [28]. However, bleeding risk was increased with ticagrelor and prasugrel in comparison with clopidogrel. In the PRAGUE-18 trial, ticagrelor and prasugrel were compared with clopidogrel. But in this analysis, ticagrelor was compared with prasugrel and the results showed no significant difference in patients with T2DM.

A subgroup analysis of a randomized, open-label, crossover study conducted in different US centers and which included 21 patients with T2DM showed that even with stable coronary artery disease, ticagrelor could achieve a faster onset and a greater magnitude of platelet inhibition in comparison to clopidogrel [29], which would be an advantage for patients with T2DM who were more prone to platelet hyperactivity [9]. It should be noted that hyperactive platelets in patients with T2DM were due to the increased expression of the platelet surface adhesion receptors and molecules, and due to enhanced production of thromboxane as well as thrombin, resulting in easy and rigorous aggregation of platelets. Increased prostaglandin synthetase activity, increased arachiodonic acid metabolism, and decreased antioxidant levels have also been linked to the mechanisms involved in hyperactive platelets in patients with T2DM [30]. Other explanations for platelet dysfunctions were related to the production of immature, larger platelets by the bone marrow, and activation of platelets due to repeated vascular damage in these patients with T2DM [31].

However, the controversy associated with these new potential antiplatelet agents does not appear to be reaching an end soon. Data from the large, multicenter, international Registry of New Antiplatelets in patients with Myocardial Infarction (RENAMI) having a longer follow-up

Study or Subgroup	Ticagrelor Events	Ticagrelor Total	Prasugrel Events	Prasugrel Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 Mortality						
Alexopoulos2012	1	3	1	2	1.0%	0.50 [0.01, 19.56]
Bonello2015	0	31	0	44		Not estimable
Conrotto2018	3	386	11	386	14.3%	0.27 [0.07, 0.96]
Dimitroulis2018	2	30	2	32	2.4%	1.07 [0.14, 8.13]
Hochholzer2017	1	10	0	9	0.6%	3.00 [0.11, 83.36]
Laine2014	0	50	1	50	1.9%	0.33 [0.01, 8.21]
Motovska2016	2	124	2	127	2.5%	1.02 [0.14, 7.39]
Parodi2013	1	3	0	6	0.3%	7.80 [0.23, 262.81]
Song2017	14	295	7	290	8.8%	2.01 [0.80, 5.07]
Subtotal (95% CI)		**932**		**946**	**31.9%**	**1.00 [0.57, 1.76]**
Total events	24		24			
Heterogeneity: Chi² = 8.61, df = 7 (P = 0.28); I² = 19%						
Test for overall effect: Z = 0.01 (P = 0.99)						
1.1.2 Myocardial Infarction						
Conrotto2018	8	386	10	386	12.8%	0.80 [0.31, 2.04]
Dimitroulis2018	3	30	3	32	3.4%	1.07 [0.20, 5.79]
Hochholzer2017	1	10	1	9	1.2%	0.89 [0.05, 16.66]
Motovska2016	2	124	2	127	2.5%	1.02 [0.14, 7.39]
Parodi2013	0	3	1	6	1.2%	0.52 [0.02, 16.83]
Subtotal (95% CI)		**553**		**560**	**21.3%**	**0.86 [0.42, 1.75]**
Total events	14		17			
Heterogeneity: Chi² = 0.20, df = 4 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.42 (P = 0.67)						
1.1.3 Major adverse cardiovascular events (MACEs)						
Alexopoulos2012B	0	6	0	4		Not estimable
Alexopoulos2013	0	15	0	15		Not estimable
Bonello2015	1	31	2	44	2.1%	0.70 [0.06, 8.08]
Conrotto2018	13	386	21	386	26.6%	0.61 [0.30, 1.23]
Dimitroulis2018	6	30	5	32	5.1%	1.35 [0.36, 4.99]
Laine2014	0	50	1	50	1.9%	0.33 [0.01, 8.21]
Motovska2016	3	124	3	127	3.8%	1.02 [0.20, 5.18]
Subtotal (95% CI)		**642**		**658**	**39.5%**	**0.73 [0.42, 1.27]**
Total events	23		32			
Heterogeneity: Chi² = 1.52, df = 4 (P = 0.82); I² = 0%						
Test for overall effect: Z = 1.11 (P = 0.27)						
1.1.4 Stroke						
Bonello2015	0	31	1	44	1.6%	0.46 [0.02, 11.67]
Conrotto2018	2	386	2	386	2.6%	1.00 [0.14, 7.14]
Dimitroulis2018	0	30	1	32	1.9%	0.34 [0.01, 8.78]
Motovska2016	1	124	1	127	1.3%	1.02 [0.06, 16.56]
Parodi2013	0	3	0	6		Not estimable
Subtotal (95% CI)		**574**		**595**	**7.4%**	**0.72 [0.20, 2.59]**
Total events	3		5			
Heterogeneity: Chi² = 0.44, df = 3 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.50 (P = 0.61)						
Total (95% CI)		**2701**		**2759**	**100.0%**	**0.84 [0.61, 1.18]**
Total events	64		78			
Heterogeneity: Chi² = 11.53, df = 21 (P = 0.95); I² = 0%						
Test for overall effect: Z = 1.00 (P = 0.32)						
Test for subgroup differences: Chi² = 0.67, df = 3 (P = 0.88), I² = 0%						

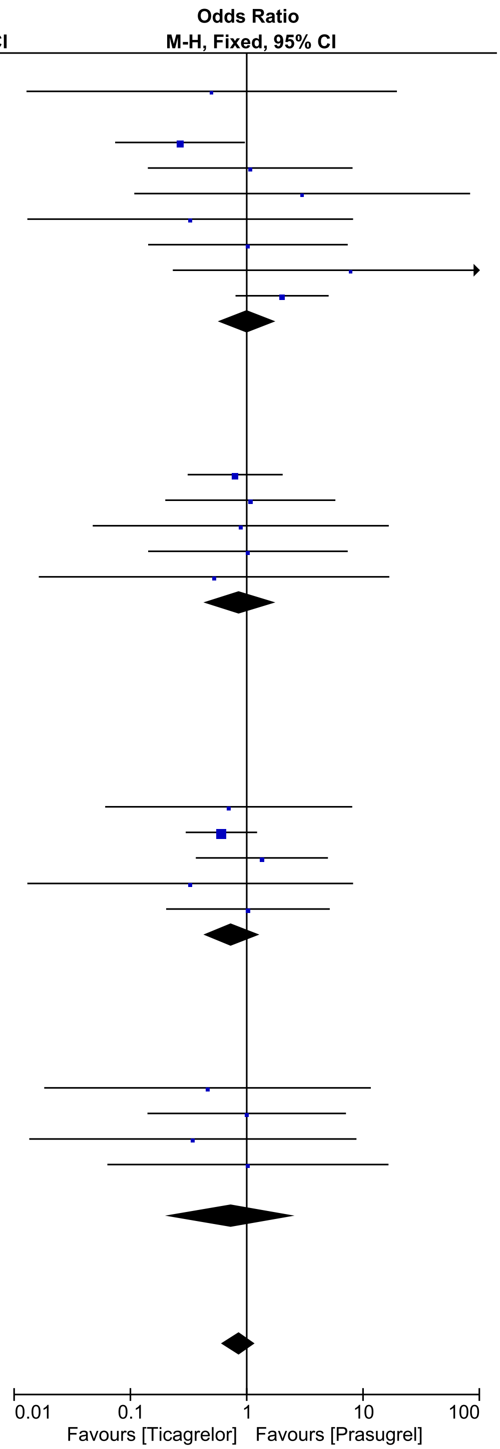

Fig. 2 Post-interventional clinical outcomes observed with ticagrelor versus prasugrel in patients with type 2 diabetes mellitus

Study or Subgroup	Ticagrelor Events	Ticagrelor Total	Prasugrel Events	Prasugrel Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.2.1 Total bleeding events						
Alexopoulos2012	1	3	0	2	0.6%	3.00 [0.08, 115.34]
Alexopoulos2012B	4	15	2	15	2.3%	2.36 [0.36, 15.45]
Alexopoulos2013	1	6	1	4	1.6%	0.60 [0.03, 13.58]
Bonello2015	2	31	4	44	4.9%	0.69 [0.12, 4.02]
Conrotto2018	10	386	23	386	35.3%	0.42 [0.20, 0.89]
Dimitroulis2018	3	30	1	32	1.4%	3.44 [0.34, 35.09]
Franchi2016	1	24	1	26	1.4%	1.09 [0.06, 18.40]
Hochholzer2017	1	10	1	9	1.5%	0.89 [0.05, 16.66]
Laine2014	0	50	0	50		Not estimable
Motovska2016	7	124	6	127	8.8%	1.21 [0.39, 3.70]
Parodi2013	2	3	0	6	0.2%	21.67 [0.64, 730.03]
Perl2014	1	19	0	17	0.8%	2.84 [0.11, 74.42]
Subtotal (95% CI)		**701**		**718**	**58.7%**	**0.87 [0.55, 1.40]**
Total events	33		39			
Heterogeneity: Chi² = 10.64, df = 10 (P = 0.39); I² = 6%						
Test for overall effect: Z = 0.56 (P = 0.58)						
1.2.2 TIMI defined minor bleeding						
Dimitroulis2018	2	30	1	32	1.4%	2.21 [0.19, 25.77]
Hochholzer2017	1	10	0	9	0.7%	3.00 [0.11, 83.36]
Motovska2016	1	124	1	127	1.5%	1.02 [0.06, 16.56]
Parodi2013	1	3	0	6	0.4%	7.80 [0.23, 262.81]
Subtotal (95% CI)		**167**		**174**	**4.0%**	**2.39 [0.58, 9.91]**
Total events	5		2			
Heterogeneity: Chi² = 0.81, df = 3 (P = 0.85); I² = 0%						
Test for overall effect: Z = 1.20 (P = 0.23)						
1.2.3 TIMI defined major bleeding						
Dimitroulis2018	1	30	1	32	1.5%	1.07 [0.06, 17.89]
Hochholzer2017	1	10	0	9	0.7%	3.00 [0.11, 83.36]
Motovska2016	1	124	1	127	1.5%	1.02 [0.06, 16.56]
Parodi2013	0	3	0	6		Not estimable
Subtotal (95% CI)		**167**		**174**	**3.7%**	**1.42 [0.27, 7.45]**
Total events	3		2			
Heterogeneity: Chi² = 0.29, df = 2 (P = 0.87); I² = 0%						
Test for overall effect: Z = 0.41 (P = 0.68)						
1.2.4 BARC major bleeding						
Bonello2015	2	31	4	44	4.9%	0.69 [0.12, 4.02]
Conrotto2018	3	386	9	386	14.1%	0.33 [0.09, 1.22]
Franchi2016	0	24	0	26		Not estimable
Hochholzer2017	1	10	0	9	0.7%	3.00 [0.11, 83.36]
Motovska2016	1	124	1	127	1.5%	1.02 [0.06, 16.56]
Subtotal (95% CI)		**575**		**592**	**21.2%**	**0.55 [0.22, 1.36]**
Total events	7		14			
Heterogeneity: Chi² = 1.85, df = 3 (P = 0.60); I² = 0%						
Test for overall effect: Z = 1.30 (P = 0.20)						
1.2.5 BARC minor bleeding						
Alexopoulos2012B	1	6	1	4	1.6%	0.60 [0.03, 13.58]
Alexopoulos2013	4	15	2	15	2.3%	2.36 [0.36, 15.45]
Franchi2016	1	24	1	26	1.4%	1.09 [0.06, 18.40]
Motovska2016	4	124	3	127	4.5%	1.38 [0.30, 6.29]
Subtotal (95% CI)		**169**		**172**	**9.9%**	**1.44 [0.52, 3.99]**
Total events	10		7			
Heterogeneity: Chi² = 0.61, df = 3 (P = 0.89); I² = 0%						
Test for overall effect: Z = 0.71 (P = 0.48)						
1.2.6 Total minimal bleeding						
Alexopoulos2012	1	3	0	2	0.6%	3.00 [0.08, 115.34]
Motovska2016	2	124	1	127	1.5%	2.07 [0.18, 23.07]
Parodi2013	1	3	0	6	0.4%	7.80 [0.23, 262.81]
Subtotal (95% CI)		**130**		**135**	**2.5%**	**3.12 [0.55, 17.59]**
Total events	4		1			
Heterogeneity: Chi² = 0.37, df = 2 (P = 0.83); I² = 0%						
Test for overall effect: Z = 1.29 (P = 0.20)						
Total (95% CI)		**1909**		**1965**	**100.0%**	**1.00 [0.71, 1.41]**
Total events	62		65			
Heterogeneity: Chi² = 20.02, df = 28 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.01 (P = 0.99)						
Test for subgroup differences: Chi² = 5.76, df = 5 (P = 0.33), I² = 13.2%						

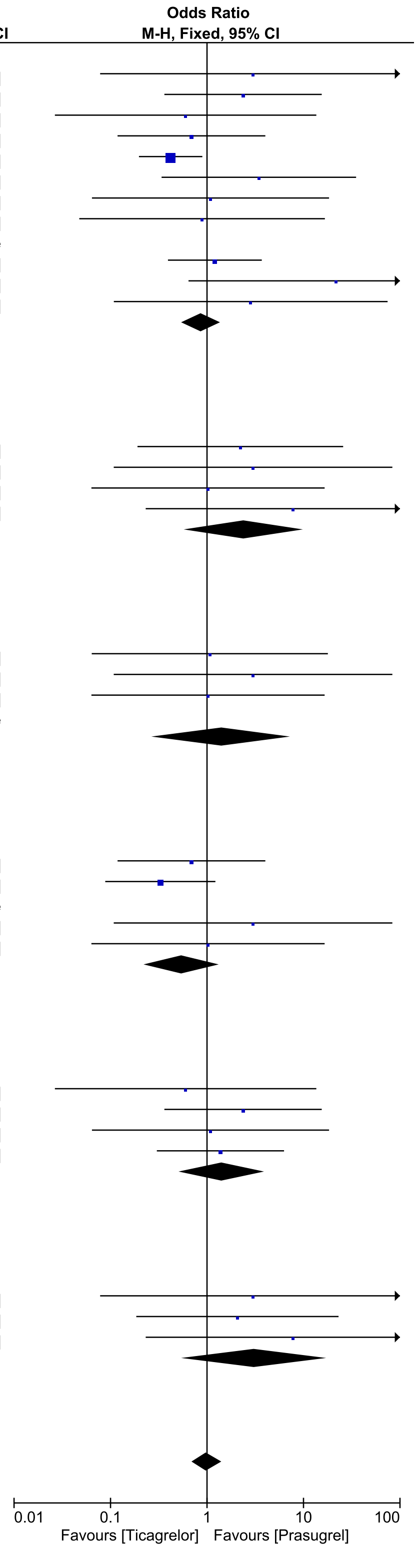

Fig. 3 Post-interventional bleeding events observed with ticagrelor versus prasugrel in patients with type 2 diabetes mellitus

Table 4 Summarized results of the analysis comparing the outcomes observed with ticagrelor versus prasugrel in patients with type 2 diabetes mellitus

Endpoints assessed	Total no. of studies (n)	OR with 95% CI	*P* value	I^2 value (%)
Mortality	9	1.00 (0.57–1.76)	0.99	19
Myocardial infarction	5	0.86 (0.42–1.75)	0.67	0
MACEs	7	0.73 (0.42–1.27)	0.27	0
Stroke	5	0.72 (0.20–2.59)	0.61	0
Total bleeding events	12	0.87 (0.55–1.40)	0.58	6
TIMI minor bleeding	4	2.39 (0.58–9.91)	0.23	0
TIMI major bleeding	4	1.42 (0.27–7.45)	0.68	0
BARC bleeding (minor)	4	1.44 (0.52–3.99)	0.48	0
BARC bleeding (major)	5	0.55 (0.22–1.36)	0.20	0
Minimal bleeding	3	3.12 (0.55–17.59)	0.20	0

OR odds ratios, *CI* confidence intervals, *TIMI* Thrombolysis in Myocardial Infarction, *BARC* bleeding defined by the Bleeding Academic Research Consortium, *MACEs* major adverse cardiac events

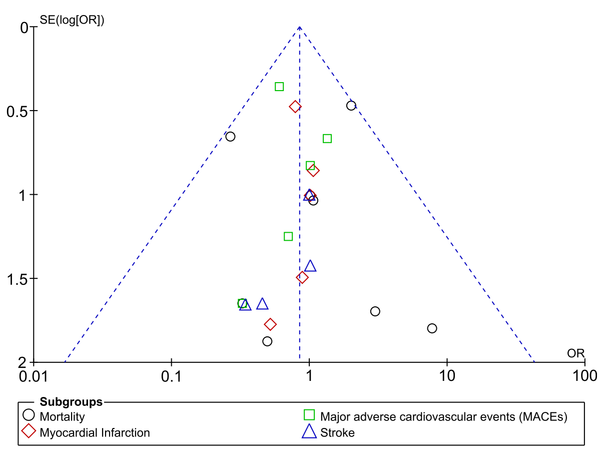

Fig. 4 Funnel plot representing publication bias

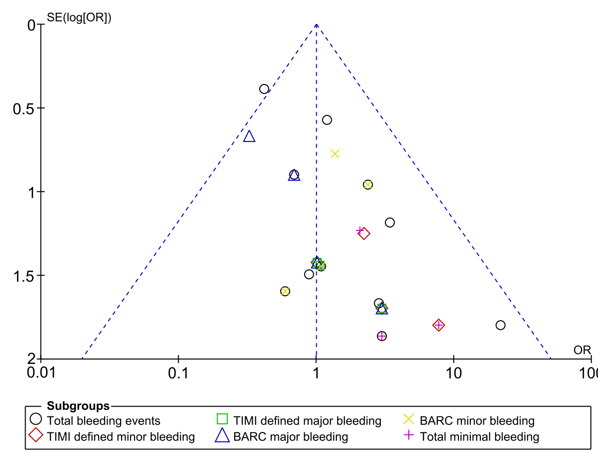

Fig. 5 Funnel plot representing publication bias

of the participants (19 months) showed major adverse cardiac events to be similar between ticagrelor and prasugrel in patients with T2DM [19]. However, ticagrelor was associated with a lower risk of both death and BARC bleeding [19]. Moreover, a review of literature based on clinical trials showed that ticagrelor and prasugrel significantly reduced ischemic events in comparison to clopidogrel, and ticagrelor and clopidogrel showed comparable bleeding risks [32]. However, prasugrel was associated with a significantly higher major bleeding risk. This effect was mainly observed in female and older patients [33]. Nevertheless, this current analysis, while directly comparing ticagrelor versus prasugrel in patients with T2DM, did not show any significant difference in bleeding events.

Limitations

This analysis has certain limitations. First of all, because of the small total number of participants, the results might have been affected. Secondly, the dosage of ticagrelor and prasugrel might have had an influence on the outcomes. Additionally, the use of other antiplatelet and other cardiac medications was ignored in this analysis. Also, a few studies reported a crossover from prasugrel to ticagrelor and vice versa. The follow-up time period was also not equivalent in the studies. Another limitation could be the fact that this analysis included data which were extracted from both randomized and non-randomized trials.

CONCLUSIONS

Ticagrelor and prasugrel were not associated with significantly different adverse clinical outcomes and bleeding events in these patients with T2DM. Therefore, both antiplatelet agents might safely be used in patients with T2DM following coronary intervention. However, this head-to-head comparison still remains a major challenge which should be resolved in larger clinical trials.

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Compliance with Ethical Guidelines. This meta-analysis is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. All data generated or analyzed during this study are included in this published article.

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