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REVIEW ARTICLE

Maintained $P2Y_{12}$ inhibitor monotherapy after shorter-duration of dual antiplatelet therapy in patients undergoing coronary drug-eluting stents implantation: An updated meta-analysis of randomized trials

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Abstract

What is known and Objective: It is well known that high in-stent thrombotic risk due to the superimposition of a platelet-rich thrombus was considered as the main origin of major adverse cardiac events after stent implantation. The clinical management of antiplatelet therapy strategy after percutaneous coronary intervention (PCI) remains controversial. This study is sought to explore the efficacy and safety of a maintained $P2Y_{12}$ inhibitor monotherapy after shorter-duration of dual antiplatelet therapy (DAPT) in these patients.

Methods: Medline, Google Scholar, Web of Science, and the Cochrane Controlled Trials Registry were searched online for retrieving eligible citations. A composite of all-cause death, myocardial infarction (MI) and stroke was defined as major adverse cardio- and cerebro-vascular events (MACCE), which is analysed as the primary efficacy endpoint. The risk of bleeding events was chosen as safety endpoint.

Results: Five randomized clinical trials (RCT) with 32,143 patients were finally analysed. A maintained $P2Y_{12}$ inhibitor monotherapy after shorter-duration of DAPT cloud not only reduce the incidence of MACCE [odds ratios (OR): 0.89, 95% confidence intervals (CI): 0.79–0.99, $p = 0.037$], but also the bleeding risk (OR 0.61, 95% CI: 0.44–0.85, $p = 0.003$). No higher incidence of any ischaemic events, including MI, stroke or definite stent thrombosis (ST) was observed with respect to this new antiplatelet therapy option.

Conclusions: A maintained $P2Y_{12}$ inhibitor monotherapy after shorter-duration of DAPT was suggested as a more preferable antiplatelet therapy option in patients undergoing coronary drug-eluting stents (DES) placement. Larger and more powerful randomized trials with precise sub-analyses are still necessary for further confirming these relevant benefits.

KEYWORDS
drug-eluting stents implantation, dual antiplatelet therapy, $P2Y_{12}$ inhibitor monotherapy, shorter-duration

1 | WHAT IS KNOWN AND OBJECTIVE

Coronary artery disease (CAD) has been widespread of the world, in which the acute coronary syndrome (ACS) may be more dangerous for leading to higher mortality.[1] Either US or European guidelines strongly recommend percutaneous coronary intervention (PCI) with drug-eluting stent (DES) for these high-risk patients.[2,3] Hereafter, a standard dual antiplatelet therapy (DAPT) consisting of aspirin and a $P2Y_{12}$ inhibitor (clopidogrel, ticagrelor or prasugrel) should be well accepted for preventing ischaemic events, which is recommended for at least 12 months in ACS and for at least 6 months in stable coronary artery disease (SCAD).[4,5] Although markable benefits have been demonstrated in decreasing the risk of thrombus with respect to this routine regimen, the simultaneously increased bleedings were also observed, which might be considered as a main origin of higher mortality.[6–8] Therefore, another one approach via shortening the duration of DAPT followed by a mandatory aspirin monotherapy was raised and showed feasibility in low-risk patients but underpowered for preventing ischaemic events.[9] Besides, the prolonged mandatory aspirin monotherapy after short-duration of DAPT in these patients may enhance gastrointestinal haemorrhage and thus can also limit the usage of this option. Regarding the management of antiplatelet therapy strategy after PCI is still a debate.

Recently, a new alternative antiplatelet therapy opinion has been suggested by several large randomized trials (RCT), among which indicated that shorter-duration of DAPT followed by a $P2Y_{12}$ inhibitor monotherapy is associated with lower risk of bleedings but not at the expense of increased incidence of ischaemic events in these patients undergoing PCI.[10,11] Conversely, another 1 large randomized clinical trial (RCT)[12] reported negative results, showing this new option was not superior to standard DAPT in prevention of all-cause mortality or new Q-wave myocardial infarction after PCI. These conflicting data will easily confuse the clinical decision-making in selection of antiplatelet strategy for these patients and restrict the benefits of this new alternative antiplatelet therapy regimen being well established. On the contrary, the TICO trial[13] is being published, which is the latest RCT focusing on this topic may provide more quantitative assessment of evidence for this option. Therefore, we conducted this meta-analysis to ulteriorly evaluate the efficacy and safety of the new alternative antiplatelet therapy regimen.

2 | METHODS

2.1 | Literature search

To identify eligible citations, several electronic databases (including Medline, Google Scholar, Web of Science and the Cochrane Controlled Trials Registry) were searched online (the latest search was at December 2021). Potential eligible trials were also screened from any other Internet sources, as well as these listed in recently published review articles or meta-analyses. To make sure all relevant articles were finally enrolled, a combination of these key words were used: 'Clopidogrel or Ticagrelor or Prasugrel', 'monotherapy', 'dual antiplatelet therapy or DAPT', 'coronary artery disease or CAD', 'acute coronary syndrome or ACS', 'acute myocardial infarction or AMI', 'percutaneous coronary intervention or PCI or drug-eluting stent or DES'.

2.2 | Inclusion and exclusion criteria

For eligible studies, the followed inclusion criteria should be fulfilled: (1) original full-text randomized articles; (2) enrolling adult patients undergoing coronary DES implantation successfully (age from 18 to 90 years); (3) comparing shorter-duration of DAPT (≤3 months) followed by a maintained $P2Y_{12}$ inhibitor monotherapy versus standard DAPT as secondary prevention after PCI; (4) performing ≥1-year follow-up and (5) reported relevant adverse clinical events. Studies should be excluded if (1) enrolling patients with cardiogenic shock or receiving oral anticoagulants (e.g. warfarin, dabigatran and rivaroxaban); (2) duplicated studies or different studies using the same samples; (3) non-English language or non-human population studies and (4) review articles or meta-analyses.

2.3 | Data extraction, synthesis and quality assessment

All relevant citations were assessed for eligibility by two independent investigators (Fan and Tian) with standardized data-abstraction forms. A third assessor (Zhang) was arranged for resolving disagreements. The data of name or first author of the trial, baseline demographics, characteristics of medical histories, type of implanted DES and reported clinical events during the follow-up were extracted and synthesized. Risk of bias in each included study was assessed according to the Cochrane Collaboration's tool.[14]

2.4 | Study endpoints

The primary efficacy endpoint of this study was a composite of major adverse cardio- and cerebrovascular events (MACCE), including all-cause death, myocardial infarction (MI) and stroke. The risk of definite stent stenosis (ST) defined by the Academic Research Consortium[15] was evaluated as the secondary efficacy endpoint. Bleeding events classified across Bleeding Academic Research Consortium (BARC)[16] were chosen as the safety endpoints. All relevant data were recorded according to the standard definitions and there only slight difference regarding definitions of clinical endpoints in each included trial.

2.5 | Statistical analysis

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement[17] was followed when performing this

meta-analysis. Pooled odds ratios (OR) with 95% confidence intervals (CI) were calculated for estimates of efficacy and safety endpoints (recorded as dichotomous variables). Entire statistical analysis was conducted using the STATA 12.0 (Stata Corp LP), and all *p*-values were two-tailed. Statistical significance would be considered if a p-value was less than 0.05. Significant heterogeneity was indicated if the p-value of Cochrane's Q test was <0.10 and/or the I^2 statistic was ≥50%, a random-effect model should be subsequently selected. Otherwise, the fixed-effect model with the Mantel–Haenszel method would be used. Publication bias were assessed using Egger's test, and significant asymmetry should be considered if the *p*-value was <0.1.[18] Sensitivity analyses was performed to approve the stability of the treatment effects.

3 | RESULTS

3.1 | Characteristics of the selected studies

After screening 4725 initial records through the electronic databases and another six articles from several other Internet sources, a total of 5 RCTs[10–13,19] with 32,143 patients were finally enrolled in this meta-analysis (Figure 1). Among these trials, participants from 3 RCTs[11–13] were administered ticagrelor as maintained monotherapy after shorter-duration of DAPT, while 1 RCT[19] replaced that with clopidogrel instead. Patients from another 1 RCT[10] received either clopidogrel, ticagrelor or prasugrel as maintained monotherapy appropriately. The outcomes of primary efficacy endpoint (a composite of all-cause death, myocardial infarction and stroke) and safety endpoint were reported in all included trials except for TICO trial,[13] among which the data of a composite of all-cause death, MI, stroke, ST and target vessel revascularization were analysed as MACCE instead. The secondary efficacy endpoint (risk of definite stent thrombosis) was analysed using definite or probable stent thrombosis instead in 2 RCTs[11,13] due to absence from the relevant data. The main characteristics of selected citations are summarized in Tables 1 and 2. Assessment for qualities of included trials were described in Table 3.

3.2 | Efficacy outcomes

Dramatically, a maintained $P2Y_{12}$ inhibitor monotherapy after shorter-duration of DAPT was associated with lower risk of MACCE (OR 0.89, 95% CI: 0.79–0.99, $p = 0.037$; $I^2 = 0.5\%$, $p = 0.403$,

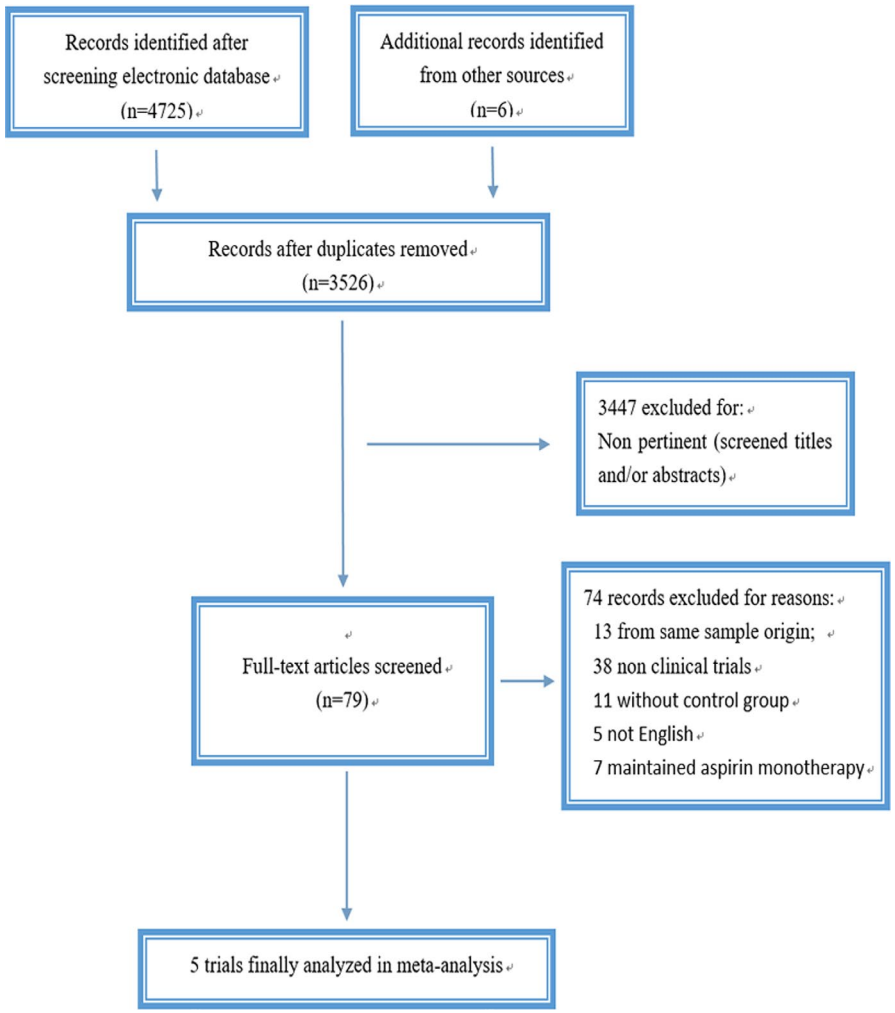

FIGURE 1 Flow chart of depicting the selection of the studies included in this meta-analysis

TABLE 1 Baseline characteristics of the included randomized trials

Study	Population	Dosing regimen of $P2Y_{12}$ inhibitors monotherapy	Dosing regimen of standard DAPT	Type of DES	Follow-up	Bleeding classification
GLOBAL LEADERS (2018)	SCAD or ACS	Aspirin (75–100 mg/d) plus ticagrelor 90 mg twice daily for 1 month, followed by 90 mg ticagrelor twice daily for 23 months.	Aspirin (75–100 mg/d) plus either clopidogrel (75 mg/d, for SCAD) or 90 mg ticagrelor twice daily (for ACS), followed by aspirin (75–100 mg/d) for 12 months.	Biodegradable polymer-based biolimus A9-eluting stents	24 months	BARC
STOPDAPT-2 (2019)	SCAD or ACS	Aspirin (81–200 mg/d) plus clopidogrel (75mg/d) or prasugrel (3.75 mg/d) for 1 month, followed by clopidogrel (75 mg/d) monotherapy for up to 5 years.	Aspirin (81–200 mg/d) plus clopidogrel (75 mg/d) for up to 12 months, then switched to aspirin monotherapy for up to 5 years.	CoCr-EES	12 months	TIMI/BARC
SMART-CHOICE (2019)	SCAD or ACS	Aspirin (100 mg/d) plus a $P2Y_{12}$ inhibitor [clopidogrel (75 mg/d) or prasugrel (10 mg/d) or ticagrelor 90 mg twice daily] for 3 months, followed by a $P2Y_{12}$ inhibitor for at least 12 months.	Aspirin (100 mg/d) plus a $P2Y_{12}$ inhibitor [clopidogrel (75 mg/d) or prasugrel (10 mg/d) or ticagrelor 90 mg twice daily] for at least 12 months.	Everolimus or Sirolimus-eluting stents	12 months	BARC
TWILIGHT (2019)	SCAD or ACS	Aspirin (81–200 mg/d) plus ticagrelor 90 mg twice daily for 3 month, followed by ticagrelor 90 mg twice daily monotherapy for an additional 12 months.	Aspirin (81–200 mg/d) plus ticagrelor 90 mg twice daily for 15 months.	NA	15 months	BARC/GUSTO/TIMI
TICO (2020)	ACS	Aspirin (100 mg/d) plus ticagrelor 90 mg twice daily for 3 month, followed by ticagrelor 90 mg twice daily monotherapy for an additional 12 months.	Aspirin (100 mg/d) plus ticagrelor 90 mg twice daily for 12 months.	Bioresorbable polymer sirolimus-eluting stents	15 months	TIMI

Abbreviations: ACS, acute coronary syndrome; BARC, Bleeding Academic Research Consortium; CoCr-EES, cobalt-chromium everolimus-eluting stent; d, day; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; mg, milligram; NA, not available; RCT, randomized controlled trials; SCAD, stable coronary artery disease; TIMI, Thrombolysis in Myocardial Infarction.

TABLE 2 Characteristics of the patients' past medical histories among the included randomized trials

	$P2Y_{12}$ inhibitor monotherapy/standard DAPT								
Study	Patients, *n*	Age, y	Male, %	Hypertension, %	Diabetes, %	Dyslipidemia, %	CRD, %	Prior stroke, %	Prior bleeding events, %
GLOBAL LEADERS (2018)	7980/7988	76.6/76.9	64.5/64.6	74.0/73.3	25.7/24.9	69.3/70.0	13.9/13.5	2.6/2.6	0.6/0.7
STOPDAPT-2 (2019)	1500/1509	78.9/76.5	68.1/69.1	73.7/74.0	39.0/38.0	74.4/74.8	5.5/5.6	5.4/7.0	1.3/1.9
SMART-CHOICE (2019)	1495/1498	72.7/74.2	64.6/64.4	61.6/61.3	38.2/36.8	45.1/45.5	2.9/3.5	6.6/6.8	NA
TWILIGHT (2019)	3555/3564	76.2/76.1	65.2/65.1	72.6/72.2	37.1/36.5	60.7/60.2	16.8/16.7	NA	0.9/0.9
TICO (2020)	1527/1529	61/61	79/80	50/51	27/27	NA	19/22	4/4	NA

Abbreviations: CRD, chronic renal disease; DAPT, dual antiplatelet therapy; *n*, number; NA, not available; y, years.

TABLE 3 Assessment for the risk of bias according to Cochrane Collaboration's Tool

	SELECTION BIAS					
Study	Random sequence generation	Allocation concealment	Blinding of participants, personnel	Blinding of outcome assessors	Complete outcome data	Free of selective outcome reporting
GLOBAL LEADERS (2018)	Yes	Yes	No	Yes	Yes	Yes
STOPDAPT–2 (2019)	Yes	Yes	No	Yes	Yes	Yes
SMART-CHOICE (2019)	Yes	Yes	No	Yes	Yes	No
TWILIGHT (2019)	Yes	Yes	Yes	Yes	Yes	Yes
TICO (2020)	Yes	Yes	No	Yes	Yes	Unclear

Note: 'Yes' for low risk of bias; 'No' for high risk of bias.

fixed-effect model; Figure 2) and did not increase either the incidence of all-cause death (OR 0.88, 95% CI: 0.76–1.03, $p = 0.114$; $I^2 = 0.0\%$, $p = 0.633$, fixed-effect model; Figure 3A), MI (OR 0.97, 95% CI: 0.84–1.12, $p = 0.701$; $I^2 = 0.0\%$, $p = 0.601$, fixed-effect model; Figure 3B), stroke (OR 1.01, 95% CI: 0.79–1.30, $p = 0.938$; $I^2 = 48.6\%$, $p = 0.100$, fixed-effect model; Figure 3C) and cardiovascular death (OR 0.73, 95% CI: 0.51–1.04, $p = 0.077$; $I^2 = 0.0\%$, $p = 0.930$, fixed-effect model; Figure 3D). Besides, the new alternative antiplatelet therapy regimen was not inferior to standard DAPT in reducing the risk of definite ST (OR 0.98, 95% CI: 0.73–1.31, $p = 0.889$; $I^2 = 0.0\%$, $p = 0.854$, fixed-effect model; Figure 4A).

3.3 | Safety endpoints

Shorter-duration of DAPT followed by a maintained $P2Y_{12}$ inhibitor monotherapy significantly decreased the risk of bleeding events (OR 0.61, 95% CI: 0.44–0.85, $p = 0.003$; $I^2 = 79.0\%$, $p = 0.001$, random-effect model; Figure 4B), regardless of major (OR 0.60, 95% CI: 0.47–0.78, $p < 0.001$; $I^2 = 4.6\%$, $p = 0.381$, fixed-effect model; Figure 4C) or minor bleedings (OR 0.62, 95% CI: 0.44–0.87, $p = 0.006$; $I^2 = 73.8\%$, $p = 0.004$, random-effect model; Figure 4D).

3.4 | Sensitivity analysis and publication bias

Sensitivity analysis demonstrated the stability of these treatment effects (Figures SS1–SS9) and Egger's test indicated no publication bias (Figures SP1–SP9).

4 | DISCUSSION

The major finding in this present meta-analysis indicated that shorter-duration of DAPT followed by a maintained $P2Y_{12}$ inhibitor monotherapy could not only reduce the risk of bleeding events, but also the incidence of MACCE in patients undergoing coronary DES placement successfully. Non-inferior effects in decreasing the risk of all-cause death, stroke, MI, definite ST and cardiovascular death were also observed when compared versus standard DAPT.

Among these patients receiving coronary DES implantation, high in-stent thrombotic risk due to the superimposition of a platelet-rich thrombus was considered as the main origin of major adverse cardiac events.[20] To prevent these secondary ischaemic complications, longer duration of DAPT, high maintenance of clopidogrel or replacing clopidogrel by another potent $P2Y_{12}$ inhibitors (ticagrelor or prasugrel) was recommended as appropriate.,[21–23] Instead when patients were at high bleeding risk, de-escalation of DAPT intensity was cautiously tried for above-mentioned reasons. In prior meta-analyses, longer DAPT was reported to result in higher risk for bleedings, making these patients get free from lower rates of death.[8,24] As a result, another one alternative approach via shortening the duration of DAPT was tried and had shown non-inferiority in preventing ischaemic events.[9,25] Unfortunately, another two meta-analyses indicated a significant increase of MI and stent thrombosis associated with this approach when the most of enrolled patient populations were with high-risk ACS.[6,26] Besides, the given increased risk of gastrointestinal haemorrhage regarding prolonged mandatory aspirin monotherapy because of early withdraw of DAPT in these patients could not be ignored yet. Based on these data, reconciling balance between thrombotic and bleeding risk for these patients was still seemed to be difficult.

Accordingly, the efficacy and safety of a new alternative antiplatelet therapy option (shorter-duration of DAPT followed by a maintained $P2Y_{12}$ inhibitor monotherapy) was initially explored in the GLOBAL LEADERS trial, in which a total of 15,968 patients were included and then randomly divided into two groups at 1:1 ratio. The participants in experimental group received 1 month of DAPT followed by ticagrelor monotherapy for up to 24 months while whom in control group received standard 12 months of DAPT followed by aspirin monotherapy for up to 24 months

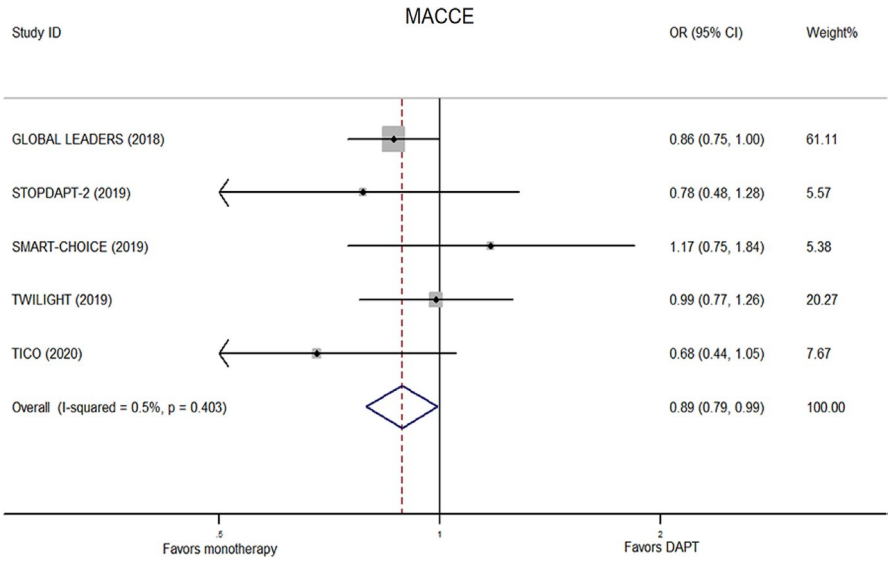

FIGURE 2 Forest plots of the primary efficacy endpoints of the included trials. The odds ratios of MACCE with regarding to shorter-duration of DAPT followed by a $P2Y_{12}$ inhibitor monotherapy versus standard DAPT

(7980 vs. 7988). The overall result indicated no better effects of experimental regimen in regardless of preventing the primary endpoint (all-cause mortality or new Q-wave MI) 2 years after PCI or decreasing bleeding events, but the post hoc analysis within 12 months demonstrated the superiority of this antiplatelet therapy option in preventing the risk of all-cause death and new Q-wave MI.[12] In contrast, the STOPDAPT-2 trial indicated that 1 month of DAPT (aspirin plus clopidogrel) followed by clopidogrel monotherapy could significantly decrease the composite of cardiac death, MI and stroke (1.96% vs. 2.51%, $p = 0.005$), as well as the risk of bleeding events (BRAC 3 or 5: 0.54% vs. 1.81%, $p = 0.003$) when compared with 12 months of DAPT.[19] In general, ticagrelor was well-known as a potent oral $P2Y_{12}$ inhibitor for its faster and greater inhibiting effects on platelet aggregation than clopidogrel.[27] Thus, there might be several interfering factors involved to sway the final results. The most possible explanations were mainly due to these participants from this trial were with stable CAD and the implanted DES were with higher thromboresistance to reduce stent thrombosis.[28] The DAPT score had been developed as predict for both ischaemic and bleeding risk in order to guide clinical decision-making in the duration of DAPT,[29] but a sub-analysis from GLOBAL LEADERS trial indicated the score did not provide additional value for selection of antiplatelet strategy beyond the first year in a contemporary PCI population.[30] The negative results would partly limit the further usage of the bleeding risk score in clinic. In fact, the exploration for efficacy and safety regarding this new option seemed to be more powerful was performed in SMART-CHOICE trial[10] because the participants were administered clopidogrel, ticagrelor or prasugrel as maintained monotherapy appropriately, which indicated significant superiority of this new option in reducing the risk of bleeding events (2.0% vs. 3.4%, $p = 0.02$) and did not increase ischaemic risk either.

In this present meta-analysis, a ~32% reduction in the risk of bleeding events was associated with shorter-duration of DAPT followed by a maintained $P2Y_{12}$ inhibitor monotherapy after coronary DES implantation, regardless of major or minor bleedings. The positive results were in line with that from the TWILIGHT trial, which is the most powerful RCT focusing on this topic in high-risk ACS patients. After analysing the data of 7,119 participants, a 40% reduction in the risk of bleeding events (classified as BRAC 2, 3 or 5) was found with respect to this new alternative antiplatelet therapy strategy and no higher risk of death, MI, or stroke observed when compared to standard DAPT.[11] Furthermore, this current

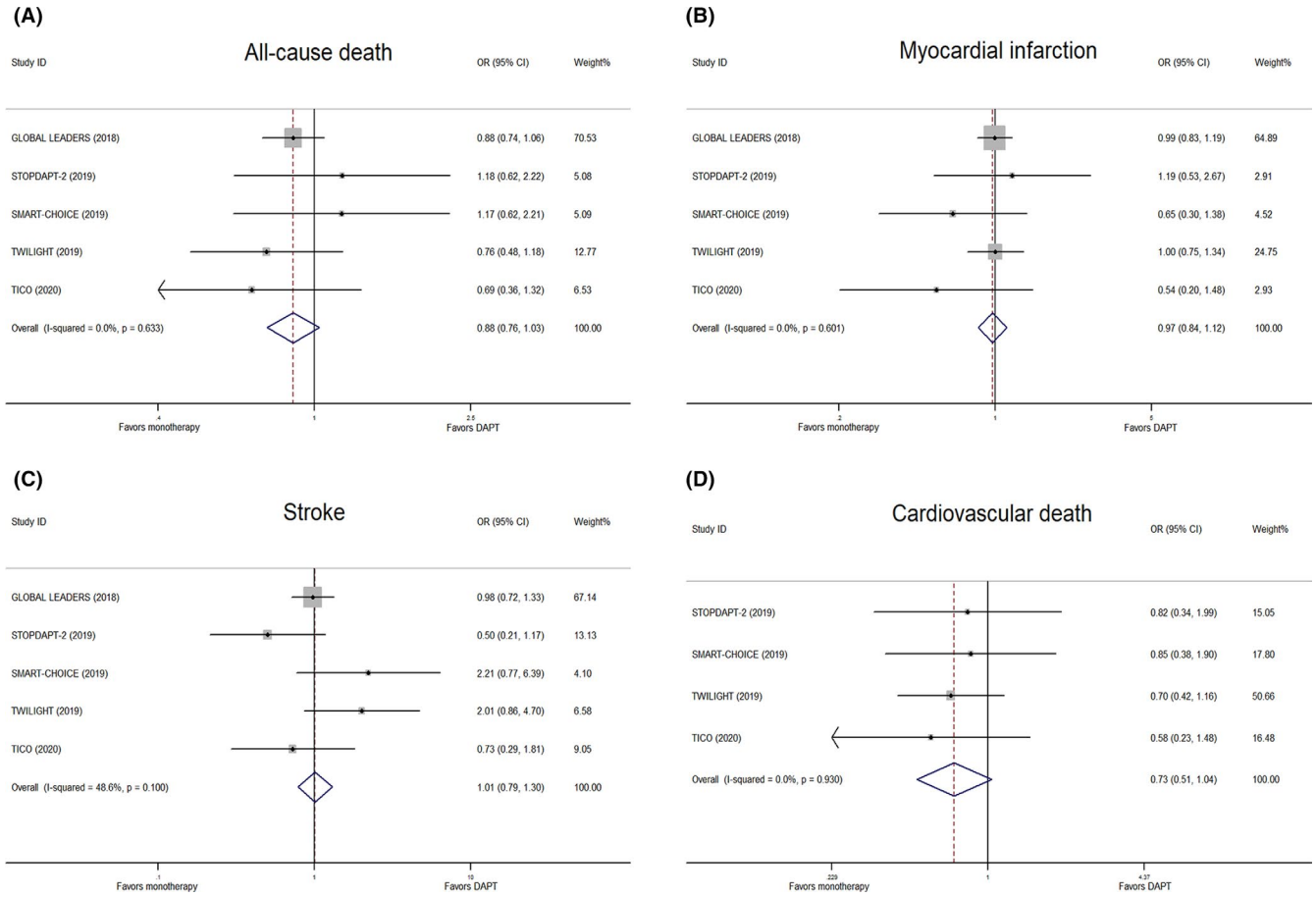

FIGURE 3 Forest plots of other efficacy and safety endpoints of the included trials. (A) The odds ratios of all-cause death, (B) myocardial infarction, (C) stroke, (D) cardiovascular death

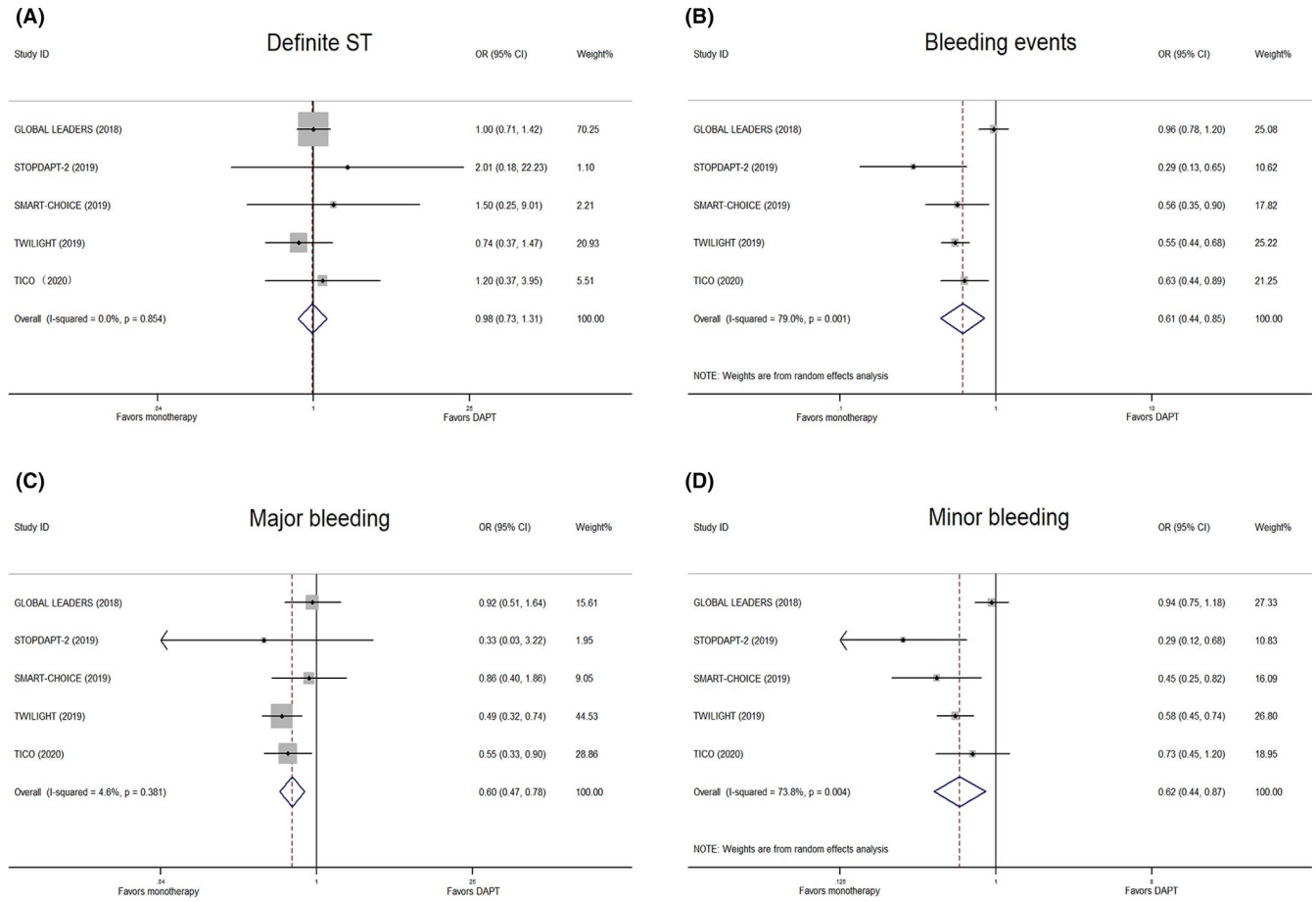

FIGURE 4 Forest plots of other efficacy and safety endpoints of the included trials. (A) Definite stent thrombosis, (B) bleeding events, (C) major bleeding, (D) minor bleeding, associated with shorter-duration of DAPT followed by a $P2Y_{12}$ inhibitor monotherapy versus standard DAPT

updated meta-analysis also indicated decreased risk of MACCE (OR 0.89, 95% CI: 0.79–0.99, $p = 0.037$), while the occurrence of any ischaemic events showed no significant difference between the two antiplatelet therapy regimens (MI: OR 0.97, 95% CI: 0.84–1.12, $p = 0.701$; Stroke: OR 1.01, 95% CI: 0.79–1.30, $p = 0.938$; definite ST: OR 0.98, 95% CI: 0.73–1.31, $p = 0.889$). Therefore, the significant reduction in MACCE was thought mainly resulted from the tendency towards decreased risk of bleeding-cause death, as the early withdraw of aspirin might reduce its gastrointestinal toxicity-related bleeding events.[31] In a recent systematic review, these authors also indicated that shorter-duration of DAPT (six months) was non-inferior to long-term DAPT (12 months) in preventing the secondary ischaemic events after DES implantation, and it could also significantly decrease the bleeding risk, leading to better clinical outcomes.[32] These positive results were also in line with that from the TICO trial, in which the significantly reduced risk of net adverse clinical events was also thought to be related with decreased major bleeding.[13] Of course, these positive results might suggest this new alternative option as a more preferable antiplatelet therapy regimen after coronary DES implantation, but larger and more powerful randomized trials are still warranted to guide clinical decision-making.

4.1 | Limitations

Several limitations should be acknowledged in the current meta-analysis. First, no individual patient data were analysed, especially for these with different stratification of ischaemic risk. Second, implanted DES were with no uniform types and the most were Biodegradable polymer-based DES, which had been reported with lower thrombotic risk. Other accurate details of PCI procedure might also have influence on final results. Third, no uniform shorter-duration of DAPT and period of follow-up, most of the included trials perform a 12-month follow-up which might restrict exploring the long-term benefits of this new antiplatelet therapy regimen. At last but not least, possible occurred drug adverse reactions (e.g. dyspnoea for ticagrelor) reduced adherence and then induced earlier discontinuation of DAPT would also sway the final results.

5 | WHAT IS NEW AND CONCLUSION

This comprehensive meta-analysis provides a clear demonstration that shorter-duration of DAPT followed by a maintained $P2Y_{12}$ inhibitor monotherapy could significantly decrease both the

incidence of MACCE and bleeding events in patients undergoing coronary DES placement with no increased risk of cardiovascular death, MI, stroke or definite ST. More powerful relevant randomized trials with precise sub-analyses are still warranted to guide its clinical decision-making.

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FZG and TNL were involved in the design, literature searching, assessment of study quality, and drafted the manuscript. Disagreements were resolved by HSH. FZG and TNL performed statistical analysis. HSH and MGS critically revised the manuscript. FZG constructed the maps. MGS and HSH critically revised original study design and the manuscript. All authors contributed to data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

CONFLICT OF INTEREST

There were no conflict of interest declared.

DATA AVAILABILITY STATEMENT

Some or all data, models used during the study are available from the corresponding author by request.

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REFERENCES

1. Goldberg RJ, Spencer FA, Gore JM, Lessard D, Yarzebski J. Thirty-year trends (1975 to 2005) in the magnitude of, management of, and hospital death rates associated with cardiogenic shock in patients with acute myocardial infarction: a population-based perspective. *Circulation*. 2009;119(9):1211-1219. doi:10.1161/CIRCULATIONAHA.108.814947
2. Patel MR, Calhoon JH, Dehmer GJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate Use Criteria for Coronary Revascularization in Patients With Stable Ischemic Heart Disease: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2017;69(17):2212-2241. doi:10.1016/j.jacc.2017.02.001
3. Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *EuroIntervention*. 2019;14(14):1435-1534. doi:10.4244/EIJY19M01_01
4. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2016;68(10):1082-1115. doi:10.1016/j.jacc.2016.03.513
5. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2018;39(3):213-260. doi:10.1093/eurheartj/ehx419
6. Palmerini T, Benedetto U, Bacchi-Reggiani L, et al. Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials. *Lancet*. 2015;385(9985):2371-2382. doi:10.1016/S0140-6736(15)60263-X
7. Toyota T, Shiomi H, Morimoto T, Natsuaki M, Kimura T. Short versus prolonged dual antiplatelet therapy (DAPT) duration after coronary stent implantation: A comparison between the DAPT study and 9 other trials evaluating DAPT duration. *PLoS One*. 2017;12(9):e0174502. doi:10.1371/journal.pone.0174502
8. Palmerini T, Bacchi Reggiani L, Della Riva D, et al. Bleeding-related deaths in relation to the duration of dual-antiplatelet therapy after coronary stenting. *J Am Coll Cardiol*. 2017;69(16):2011-2022. doi:10.1016/j.jacc.2017.02.029
9. Feres F, Costa RA, Abizaid A, et al. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. *JAMA*. 2013;310(23):2510-2522. doi:10.1001/jama.2013.282183
10. 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):2428-2437. doi:10.1001/jama.2019.8146
11. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. *New Engl J Med*. 2019;381(21):2032-2042. doi:10.1056/NEJMoa1908419
12. Vranckx P, Valgimigli M, Jüni P, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet*. 2018;392(10151):940-949. doi:10.1016/S0140-6736(18)31858-0
13. Kim B-K, Hong S-J, Cho Y-H, et al. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome. *JAMA*. 2020;323(23):2407. doi:10.1001/jama.2020.7580
14. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. doi:10.1136/bmj.d5928
15. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *New Engl J Med*. 2007;356(10):1020-1029. doi:10.1056/NEJMoa067731
16. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123(23):2736-2747. doi:10.1161/CIRCULATIONAHA.110.009449
17. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700. doi:10.1136/bmj.b2700
18. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634. doi:10.1136/bmj.315.7109.629
19. Watanabe H, Domei T, Morimoto T, et al. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. *JAMA*. 2019;321(24):2414-2427. doi:10.1001/jama.2019.8145
20. Grove EL, Wurtz M, Thomas MR, Kristensen SD. Antiplatelet therapy in acute coronary syndromes. *Expert Opin Pharmacother*. 2015;16(14):2133-2147. doi:10.1517/14656566.2015.1079619

21. Ma W, Liang Y, Zhu J, Wang Y, Wang X. Meta-analysis appraising high maintenance dose clopidogrel in patients who underwent percutaneous coronary intervention with and without high on-clopidogrel platelet reactivity. *Am J Cardiol*. 2015;115(5):592-601. doi:10.1016/j.amjcard.2014.12.013
22. Singh S, Singh M, Grewal N, Khosla S. Comparative efficacy and safety of prasugrel, ticagrelor, and standard-dose and high-dose clopidogrel in patients undergoing percutaneous coronary intervention: a network meta-analysis. *Am J Ther*. 2016;23(1):e52-e62. doi:10.1097/MJT.0000000000000350
23. Fan ZG, Zhang WL, Xu B, Ji J, Tian NL, He SH. Comparisons between ticagrelor and clopidogrel following percutaneous coronary intervention in patients with acute coronary syndrome: a comprehensive meta-analysis. *Drug Design, Development Therapy*. 2019;13:719-730. doi:10.2147/DDDT.S196535
24. Giustino G, Baber U, Sartori S, et al. Duration of dual antiplatelet therapy after drug-eluting stent implantation: a systematic review and meta-analysis of randomized controlled trials. *J Am Coll Cardiol*. 2015;65(13):1298-1310. doi:10.1016/j.jacc.2015.01.039
25. Gwon H-C, Hahn J-Y, Park KW, et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. *Circulation*. 2012;125(3):505-513. doi:10.1161/CIRCULATIONAHA.111.059022
26. Palmerini T, Benedetto U, Biondi-Zoccai G, et al. Long-term safety of drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol*. 2015;65(23):2496-2507. doi:10.1016/j.jacc.2015.04.017
27. Storey RF, Husted S, Harrington RA, et al. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2007;50(19):1852-1856. doi:10.1016/j.jacc.2007.07.058
28. Otsuka F, Cheng Q, Yahagi K, et al. Acute Thrombogenicity of a durable polymer everolimus-eluting stent relative to contemporary drug-eluting stents with biodegradable polymer coatings assessed ex vivo in a swine shunt model. *JACC Cardiovasc Interv*. 2015;8(9):1248-1260. doi:10.1016/j.jcin.2015.03.029
29. Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA*. 2016;315(16):1735-1749. doi:10.1001/jama.2016.3775
30. Chichareon P, Modolo R, Kawashima H, et al. DAPT score and the impact of ticagrelor monotherapy during the second year after PCI. *JACC Cardiovasc Interv*. 2020;13(5):634-646. doi:10.1016/j.jcin.2019.12.018
31. Capodanno D, Mehran R, Valgimigli M, et al. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. *Nat Rev Cardiol*. 2018;15(8):480-496. doi:10.1038/s41569-018-0049-1
32. Aslam Zahid MB, Memon MS, Tappiti M, et al. Duration of dual antiplatelet therapy after stent implantation, still an enigma: a systematic review of randomized clinical trials. *Cureus*. 2021;13(11):e19549.

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