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Efficacy and Safety of Short-Term Dual Antiplatelet Therapy in East Asians: A Systematic Review and a Meta-Analysis of Randomized Clinical Trials

Ying Ma, MD, Peng-Yu Zhong, MD,* Yao-Sheng Shang, MD,* Nan Bai, MD,* Ying Niu, MD,* and Zhi-Lu Wang, MD†*

Abstract: The optimal duration of dual antiplatelet therapy (DAPT) for patients implanted with new-generation drug-eluting stents in East Asians is currently still controversial. The purpose of this meta-analysis was to investigate the efficacy and safety of short-term DAPT in patients with those. In this study, randomized controlled trials from PubMed, EMBASE, and Cochrane Library were searched to compare the efficacy and safety of short-term DAPT (6 months or less) with long-term DAPT (12 months or more) in patients implanted with new-generation drug-eluting stents in East Asian from inception to September 2020. The primary efficacy outcome was all-cause death, the primary safety outcome was major bleeding, and the secondary outcomes included cardiovascular death, myocardial infarction, definite or possible stent thrombosis, and stroke. A total of 6 randomized controlled trials with 15,688 patients met inclusion criteria; there were no significant differences in the incidence of all-cause death [risk ratio (RR), 1.03; 0.76–1.39; P = 0.856)], cardiovascular death (RR, 0.83; 0.55–1.24; P = 0.361), myocardial infarction (RR, 0.97; 0.72–1.31; P = 0.853), definite or possible stent thrombosis (RR, 1.52; 0.83–2.78; P = 0.170), and stroke (RR, 0.90; 0.61–1.31; P = 0.574) between short-term and long-term DAPTs. However, there was a significant difference in the risk of major bleeding (RR, 0.64; 0.49–0.85; P = 0.002) between the 2 groups. Compared with long-term DAPT, the short-term DAPT can reduce the risk of major bleeding without increasing the risk of death or ischemia for East Asians (Registered by PROSPERO, CRD42020213266).

Key Words: dual antiplatelet therapy, acute coronary syndrome, percutaneous coronary intervention, new-generation drug-eluting stents, meta-analysis

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INTRODUCTION

Dual antiplatelet therapy (DAPT) drugs include aspirin and $P2Y_{12}$ receptor inhibitors, which can reduce stent thrombosis by inhibiting platelet aggregation, and have become the cornerstone of treatment for the acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI). In 2001, the PCI-CURE trial first explored the efficacy and safety of the DAPT strategy in patients after PCI. It included 2658 patients with non-ST segment elevation ACS after PCI. The results showed that the DAPT could significantly reduce adverse cardiovascular events at 30 days after PCI by 30% without increasing bleeding complications compared with aspirin alone.[1] Based on this study, the American College of Cardiology/American Heart Association guideline for the management of patients with unstable angina and non–ST segment elevation myocardial infarction recommend that patients with non-ST segment elevation ACS should take clopidogrel for at least 1 month, and they may continue to take it for 9 months, if they are not at high risk of bleeding and are planning selective PCI.[2] The CREDO trial published in 2002 extended the duration of DAPT to 12 months for patients undergoing PCI, the results showed that 12-month DAPT significantly reduced the composite outcomes of death, myocardial infarction, and stroke by 26.9% but did not significantly increase the risk of major bleeding.[3] Therefore, the 2007 American College of Cardiology/American Heart Association unstable angina and non–ST segment elevation myocardial infarction guidelines recommend that patients undergoing drug-eluting stents (DES) implantation should use clopidogrel for at least 12 months.[4] Meanwhile, the DAPT has become a standardized treatment strategy for patients undergoing PCI. However, the optimal duration of the DAPT after PCI remains unclear. The subsequent clinical trials showed that the efficacy of short-term DAPT was not inferior to long-term DAPT for patients undergoing DES implantation.[5–8] Consequently, the guidelines gradually recommend shortening the optimal DAPT duration.[9,10]

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From the *The First Clinical Medical College of Lanzhou University, Lanzhou, China; and †Department of Cardiology, the First Hospital of Lanzhou University, Lanzhou, China.

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Correspondence: Zhi-Lu Wang, MD, Department of Cardiology, the First Hospital of Lanzhou University, No. 1, Donggang West Rd, Chengguan District, Lanzhou, Gansu 730000, China (e-mail: wangzhl@lzu.edu.cn).

The new-generation DES not only has thinner stent beams but also can realize the synchronization of drug release and polymer carrier degradation, effectively inhibit intimal hyperplasia, and significantly reduces the risk of restenosis, in-stent thrombosis, and death after PCI.[11–13] The PLATINUM China trial confirmed that the everolimus-eluting stent platinum chromium has lower late lumen loss compared with the first-generation paclitaxel-eluting stent.[14] The development of these stents also makes short-term DAPT strategy possible. The CHARISMA study showed that there were significant differences in cardiovascular outcomes and bleeding complications among different ethnic groups of patients. Non-white patients, especially Asians, are more likely to have bleeding complications than white patients.[15] The higher risk of bleeding in East Asian patients may be related to their lower weight, genetic background, and disease pattern.[16] The consensus on antiplatelet therapy for patients with ACS or PCI in East Asians in 2018 recommends that DAPT can be extended to more than 12 months to prevent recurrent ischemic events in high-risk patients, the duration of DAPT should be shortened in patients with high-risk of bleeding or intolerance long-term DAPT in East Asians.[17] However, it is unclear whether the short-term DAPT is not inferior to long-term DAPT in patients with new-generation DES in East Asians.

Therefore, the purpose of this systematic review and meta-analysis aims to verify the efficacy and safety of short-term DAPT in patients with new-generation DES in East Asians. The results showed that the application of short-term DAPT in patients with new-generation DES is effective and safer in East Asians.

METHODS

Data Source and Quality Assessment

This systematic review and meta-analysis based on randomized controlled trials were performed following the Preferred Reporting Items for Systematic Review and Meta-Analysis guideline.[18] PubMed, EMBASE, and Cochrane Library databases were formally searched from inception to September 2020. The keywords used are as follows: "drug eluting stent" OR "DES" OR "percutaneous coronary intervention" OR "percutaneous coronary interventions" OR "percutaneous coronary revascularization" OR "percutaneous coronary revascularizations" OR "PCI" AND "Dual Anti Platelet Therapy" OR "Dual Anti-Platelet Therapies" OR "DAPT". There was no language restriction, an update reminder for PubMed was created to keep up with the latest research, the search strategy is shown in the Supplemental appendix (see **Table 1–3**, **Supplemental Digital Content 1**, http://links.lww.com/JCVP/A732). The inclusion criterion of the study met the following requirements: (1) the East Asian patients, (2) compared short-term DAPT (6 months or less) with long-term DAPT (12 months or more), (3) the included trials should include the outcomes of interest to us, (4) randomized controlled trials, (5) the new-generation DES was applied to the patients, and (6) follow-up duration of ≥12 months. The exclusion criteria are as follows: (1) less than 90% of patients had follow-up data, (2) ongoing research or unrecoverable data, and (3) comments. New-generation DES in this meta-analysis included the newer second-generation DES and the next-generation DES. The details are as follows: (1) the Xience prime everolimus-eluting stent with wider U-shaped connecting links, (2) the PROMUS element everolimus-eluting stent on a platinum chromium platform, (3) the resolute endeavor zotarolimus stent with a new biocompatible polymer, and (4) the Nobori biolimus-eluting stent with a bioresorbable polymer. Old-generation DES is defined as bare-metal stents, first-generation DES, and second-generation DES. Repetitive articles published by the same author were excluded to avoid data duplication caused by multiple reports. Two investigators (Y.M. and P.-Y.Z.) independently screened all titles, abstracts, and full texts, then the trial eligibility was assessed according to the inclusion and exclusion criteria, and all differences shall be settled by a third party (Y.-S.S., N.B., and Y.N.). The risk of bias for each randomized controlled trial was evaluated according to the Cochrane tool of Collaboration.[19] The quality of evidence for each outcome was assessed by the Grades of Recommendations Assessment, Development and Evaluation (GRADE).[20] Because our analyses were based on previously published studies, there was no requirement for local ethics and informed consent of patients. This protocol of meta-analysis was registered in PROSPERO (CRD42020213266).

Data Acquisition and Clinical Outcome

Two investigators (Y.M. and P.-Y.Z.) independently extracted the baseline characteristics of patients and trials. When the data is incomplete or unclear, they will negotiate with a third party (Z.-L.W.). The primary effective outcome was all-cause death, and the primary safety outcome was major bleeding; the definition of major bleeding in all trials was accepted. The secondary outcomes included cardiovascular death, myocardial infarction, definite or possible stent thrombosis, and stroke.

Statistical Analysis

Review manager 5.4 and Stata 14.1 were used for statistical analysis of the systematic review and meta-analysis. Mantel–Haenszel method was performed to calculate the risk ratio (RR) and 95% confidence interval (CI) of each outcome. All results adopted 2-tailed P values, and statistical significance was set as $P < 0.05$. The Cochrane Q statistic with Pearson's χ^2 test and the Higgins I^2 test were applied to evaluate heterogeneity. Labbe and Galbraith plots were used to test the heterogeneity when heterogeneity exists ($I^2 \geq 50\%$). Meanwhile, sensitivity analysis and subgroup analysis were used to further seek the source of heterogeneity. In addition, the sensitivity analysis was also used to detect the impact of any single trial on the overall result. The subgroup analyses were performed according to the difference of study design, $P2Y_{12}$ receptor inhibitors, age, ethnicity of patients, and sample size. Trial Sequential Analysis version 0.9.5.10 software (Copenhagen Trial Unit) was exploited to calculate the sample size and assess the results. The Egger's and

Begg's test, as well as visual inspection of funnel plots, were hired to assess publication bias.

RESULTS

Search Results and Study Characteristics

The process of literature screening and trial selection is shown (Fig. 1). A total of 906 articles were searched from medical databases and online meetings; of which, 595 articles were identified by reading the title and abstract, and 35 articles were defined by reading the full text. Six randomized controlled trials with a total of 15,688 patients were finally included.[21–26] Among them, the TWILIGHT-China trial was a subgroup analysis of the TWILIGHT trial. In addition, 7829 patients received short-term DAPT, and 7859 patients received long-term DAPT.

The baseline characteristics of included trials are shown (Table 1). Three trials compared 3-month with 12-month DAPT, whereas the other 3 trials, respectively, compared the efficacy and safety between 1-month and 12-month DAPTs, 6-month and 12-month DAPTs, 6-month and 18-month DAPTs. In terms of ethnicity, the patients in 2 trials were Chinese, the 2 trials were Korean, and the rest were Japanese. One trial included patients with ACS, and the remaining trials recruited patients with ACS and stable coronary artery disease. Antiplatelet agents for DAPT strategy were aspirin combined with clopidogrel or prasugrel or ticagrelor. In 5 trials, patients also used novel $P2Y_{12}$ receptor inhibitors (prasugrel or ticagrelor). The follow-up period ranged from 12 to 18 months.

The baseline characteristics of included patients are shown (Table 2). The average age of the patients was between 60 and 69.1 years old. Male patients accounted for 67.2%–80.1%, the patients with ACS 55.8% approximately, patients with diabetes 34.0%, patients with hypertension 64.3%, and patients with a history of smoking 37.4%. Different types of new-generation DES were used in the trials included, including 1 or more of the following stents were used, such as cobalt chromium everolimus-eluting stent, platinum chromium everolimus-eluting stent, bioresorbable polymer sirolimus-eluting stent, and locally approved DES.

The Primary Efficacy Outcomes

The incidence of all-cause death was reported in all 6 trials. Of the 15,688 patients, 170 patients died during the follow-up period. There is no significant difference in the incidence of all-cause death between short-term DAPT and long-term DAPT groups, with only moderate heterogeneity (1.09% vs. 1.06%; RR, 1.03; 0.76–1.39; $P = 0.856$; $I^2 = 27.6\%$; $P_{\text{Heterogeneity}} = 0.227$) (Fig. 2A). The NIPPON trial–produced heterogeneity was determined by sensitivity analysis.[25] The heterogeneity of all-cause death was reduced after excluding the results of this trial, and there is no

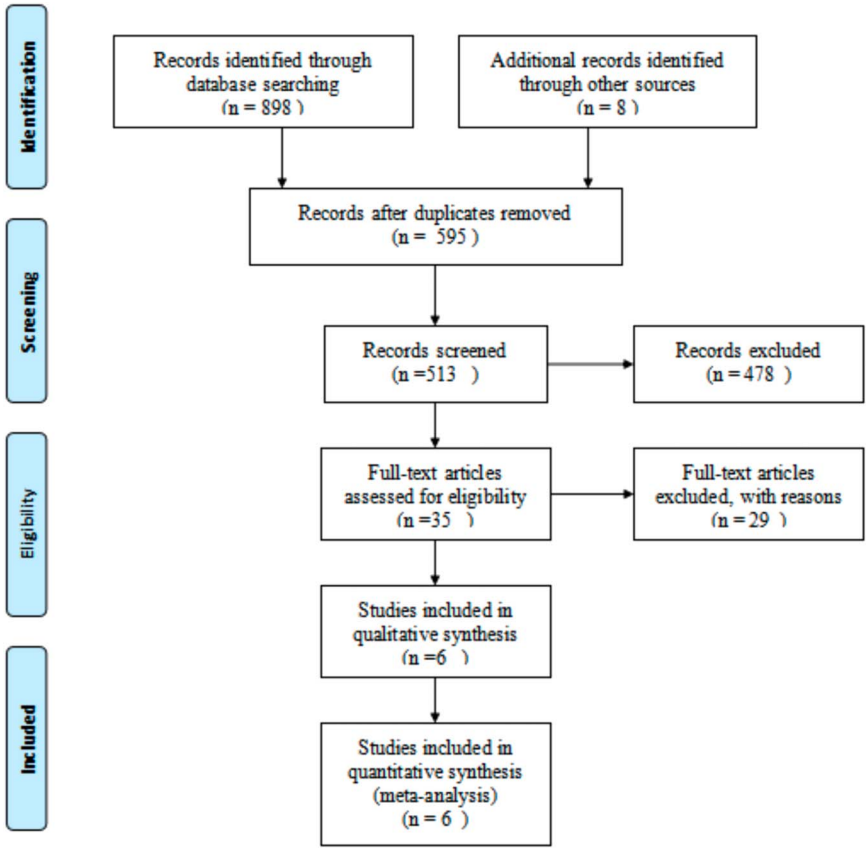

FIGURE 1. Flow diagram of literature search.

TABLE 1. Characteristics of Randomized Controlled Trials Included

	SMART-CHOICE	STOPDAPT-2	TWILIGHT-China	TICO	I-LOVE-IT 2	NIPPON
Publication	2019	2019	2020	2020	2016	2017
Design	Open-label noniferiority	Open-label noniferiority	Double-blind noniferiority	Open-label superiority	Double-blind noninferiority	Double-blind noninferiority
Type	Multicenter, RCT	Multicenter, RCT	Multicenter, RCT	Multicenter, RCT	Multicenter, RCT	Multicenter, RCT
Authors	Joo-Yong Hahn	Hirotoshi Watanabe	Yaling Han	Jang Y	Yaling Han	Masato Nakamura
Patients, n	2993	3009	1028*	3056	1829	3773
Intervention (n)	1495	1500	512*	1527	909	1886
Comparator (n)	1498	1509	516*	1529	920	1887
Region	Korea	Japan	China*	Korea	China	Japan
Study cohort	ACS + stable CAD	ACS + stable CAD	ACS + stable CAD*	ACS	ACS + stable CAD	ACS + stable CAD
ACS cohort size	1741	1148	—	3056	1496	549
Intervention DAPT strategy	ASA + Clopidogrel or prasugrel or ticagrelor	ASA + clopidogrel or prasugrel	ASA + ticagrelor*	Aspirin + ticagrelor	ASA + clopidogrel	ASA + clopidogrel or ticlopidine
Intervention DAPT duration (mo)	3	1	3*	3	6	6
Comparator DAPT strategy	ASA+Clopidogrel or ticagrelor	ASA + clopidogrel or prasugrel	ASA + ticagrelor*	Aspirin + ticagrelor	ASA + clopidogrel	ASA + clopidogrel or ticlopidine
Comparator DAPT duration (mo)	12	12	12*	12	12	18
Stent type	CoCr-EES PtCr-EES BP-SES	CoCr-EES	Locally approved* DES	BP-SES	BP-SES	Nobori DES
Follow-up (mo)	12	12	12*	12	12	18
Time to randomization	At 3 mo	At the index procedure	At 3 mo*	At the index procedure	At the index procedure	At the index procedure

*Subgroup analysis of Chinese patients from TWILIGHT trial.

ASA, aspirin; BP-SES, bioresorbable polymer sirolimus-eluting stent; CAD, coronary artery disease; CoCr-EES, cobalt chromium everolimus-eluting stent; PtCr, EES platinum chromium everolimus-eluting stent; RCT, randomized controlled trial.

significant difference between the 2 groups (1.18% vs. 1.22%; RR, 0.91; 0.66–1.26; P = 0.581; I^2 =0.0%; $P_{\text{Heterogeneity}}$ = 0.498) (see **Figure 1A**, **Supplemental Digital Content 1**, http://links.lww.com/JCVP/A732). In most subgroups, there is no significant difference in the incidence of all-cause death between the 2 groups (see **Figure 2A**, **Supplemental Digital Content 1**, http://links.lww.com/JCVP/A732).

The Primary Safety Outcomes

The risk of major bleeding was shown in all 6 trials. A total of 15,688 patients were followed up, including 205 patients who experienced major bleeding. There is significant difference in the risk of major bleeding between short-term DAPT and long-term DAPT groups (1.02% vs. 1.59%; RR, 0.64; 0.49–0.85; P =0.002; I^2 = 50.1%; $P_{\text{Heterogeneity}}$ =0.058) (Fig. 2B). However, there was severe heterogeneity in the trial included. Labbe and Galbraith plots indicate that the I-LOVE-IT 2 trial was more likely to produce heterogeneity (see **Figures 3 and 4**, **Supplemental Digital Content 1**, http://links.lww.com/JCVP/A732); the trial-produced heterogeneity was also identified by sensitivity analysis.[24] After excluding the results of the trial, the heterogeneity of major bleeding was reduced, and there is a significant difference between the 2 groups (RR, 0.58; 0.43–0.78; P = 0.000; I^2 = 26.5%; $P_{\text{Heterogeneity}}$ =0.245) (see Figure 1B, **Supplemental Digital Content 1**, http://links.lww.com/JCVP/A732). The subgroup analysis further shows that reduction in the risk for major bleeding in the short-term DAPT was related to several subgroups, including patients with novel $P2Y_{12}$ receptor inhibitors (RR, 0.58; 0.43–0.78; P = 0.000), the sample size of ≥3000 (RR, 0.54; 0.36–0.79; P = 0.001), and the differences between countries (see **Figure 2B**, **Supplemental Digital Content 1**, http://links.lww.com/JCVP/A732).

The Secondary Outcomes

The incidence of cardiovascular death was reported in all 6 trials, which is similar between the 2 groups (0.54% vs. 0.65%; RR, 0.83; 0.55–1.24; P = 0.361; I^2 = 0.0%; $P_{\text{Heterogeneity}}$ =0.583) (Fig. 3A). Six randomized controlled trials also provided data on the incidence of myocardial infarction, and the short-term DAPT group does not increase the incidence of myocardial infarction compared with long-term DAPT group (1.05% vs. 1.08%; RR, 0.97; 0.72–1.31; P = 0.853; I^2 = 0.3%; $P_{\text{Heterogeneity}}$ =0.414) (Fig. 3B). There is also no significant difference in the incidence of definite or possible stent thrombosis between the 2 groups in the 6 studies (0.33% vs. 0.22%; RR, 1.52; 0.83–2.78; P = 0.170; I^2 = 0.0%; $P_{\text{Heterogeneity}}$ =0.773) (Fig. 3C). In addition, there is no significant difference in the risk of stroke between the 2

TABLE 2. Clinical Features of Patients Included

	SMART-CHOICE	STOPDAPT-2	TWILIGHT-China	TICO	I-LOVE-IT 2	NIPPON
Patients (n)	1495/1498	1500/1509	512/516*	1527/1529	909/920	1886/1887
Age (mean)	64.6/64.4	68.1/69.1	63.6/63.8*	61/61	60.4/60.0	67.2/67.4
Male (%)	72.7/74.2	78.9/76.5	72.5/71.5*	78.8/80.1	67.2/68.7	79.4/78.8
Smokers (%)	28.4/24.5	26.6/20.6	27.7/32.0*	36.3/38.4	36.6/38.3	60.3/58.0
Hypertension (%)	61.6/61.3	73.7/74.0	61.7/58.7*	49.8/51.1	61.0/64.8	73.1/71.2
Diabetes (%)	38.2/36.8	39.0/38.0	35.2/37.0*	27.4/27.3	23.2/22.1	38.4/37.4
Dyslipidemia (%)	45.1/45.5	74.4/74.8	—	—	61.0/64.8	68.5/68.3
Previous MI (%)	4.1/4.3	13.8/13.2	19.1/19.4*	4.2/3.2	17.2/15.8	11.8/12.2
Previous PCI (%)	11.5/11.8	33.5/35.1	30.1/29.3*	8.8/8.3	8.5/6.5	26.1/25.0
Previous CABG (%)	—	1.1/2.8	0.6/1.2*	0.52/0.65	0.4/0.4	1.8/1.3
LVEF (%)	60.0/59.9	59.8/59.7	—	—	60.8/60.3	—
STEMI (%)	11.0/10.0	19.4/17.9	—	35.6/36.4	13.4/13.7	11.9/12.0
NSTEMI (%)	16.0/15.4	5.4/6.6	—	35.3/31.9	11.3/10.7	1.6/2.0
Unstable angina (%)	31.2/32.8	12.9/14.2	—	29.1/31.7	58.0/56.5	20.0/17.9
Stable angina (%)	—	—	—	0/0	14.3/15.1	44.4/48.7
ACS	58.2/58.2	37.7/38.7	—	—	82.7/80.9	33.5/31.9

*Subgroup analysis of Chinese patients from TWILIGHT trial.

CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non–ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

groups, and no heterogeneity in the 6 studies (0.63% vs. 0.70%; RR, 0.90; 0.61–1.31; $P = 0.574$; $I^2 = 1.1\%$; $P_{\text{Heterogeneity}} = 0.409$) (Fig. 3D). In the subgroup analysis, there is no significant difference in the incidence of secondary outcomes (see **Figure 2C–F**, **Supplemental Digital Content 1**, http://links.lww.com/JCVP/A732).

Trial Sequential Analysis, Assessment of Quality, and Publication Bias

Trial sequential analysis is performed for each outcome (see Figure 5, **Supplemental Digital Content 1**, http://links.lww.com/JCVP/A732). The curves of all-cause death, cardiovascular death, myocardial infarction, and definite or probable stent thrombosis outcomes were under the conventional boundary, which showed that the sample size of the above outcome was not consistent with the expectation. In addition, the curve of major bleeding exceeded the conventional boundary, which showed that the sample size of major bleeding met the expectation. Meanwhile, the curve of major bleeding also transcended the trial sequential analysis boundary, which indicated that there was no false-positive in the result. However, the sample size of stroke outcome was too small, the generation of graph fails. The risk of bias assessment shows that the risk of bias for attrition, selection, and reporting was low in all trials, and the risk of bias for performance and detection was high in 2 of 6 trials (see **Figure 6**,**Supplemental Digital Content 1**, http://links.lww.com/JCVP/A732). The quality of evidence for each outcome is demonstrated (see **Table 4**, **Supplemental Digital Content 1**, http://links.lww.com/JCVP/A732), which showed that the quality of evidence for all-cause death, cardiovascular death, myocardial infarction, clear or possible stent thrombosis, and stroke outcomes were high, whereas the quality of evidence for major bleeding outcomes was moderate. There was no publication bias in all outcomes. All the outcomes are symmetrically distributed in the funnel plot, and the P value of Begg's and Egger's are both more than 0.05 in all outcomes (see **Figure 7**, **Supplemental Digital Content 1**, http://links.lww.com/JCVP/A732).

DISCUSSION

This meta-analysis is the first study to investigate the efficacy and safety of short-term DAPT in patients with new-generation DES implantation in East Asians. It demonstrates that the short-term DAPT was not associated with a high incidence of all-cause death, cardiovascular death, myocardial infarction, definite or possible stent thrombosis, and stroke. However, the short-term DAPT can significantly reduce the risk of major bleeding, and this benefit was consistent with patients who received novel $P2Y_{12}$ receptor inhibitors or those with a sample size of major bleeding of $\geq$3000. Meanwhile, this benefit was consistent with patients from Korea or Japan. In addition, the GRADE evidence levels of major bleeding and other outcomes were moderate and high, respectively.

All studies included in this meta-analysis were randomized controlled trials, and the risk of bias was also assessed by the Cochrane tool of Collaboration. The results showed that the risk of selection bias, attrition bias, and reporting bias was low, whereas the risk of performance bias and detection bias was high; 4 of 6 trials did not blind participants and personnel. Although the short-term and long-term DAPT strategies have similar efficacy in East Asians, the short-term DAPT strategy reduces the risk of major bleeding by 36%. All 6 trials consistently showed a reduced risk of major bleeding, and no dose–response relationship was found in each trial. In addition, trial sequential analysis was

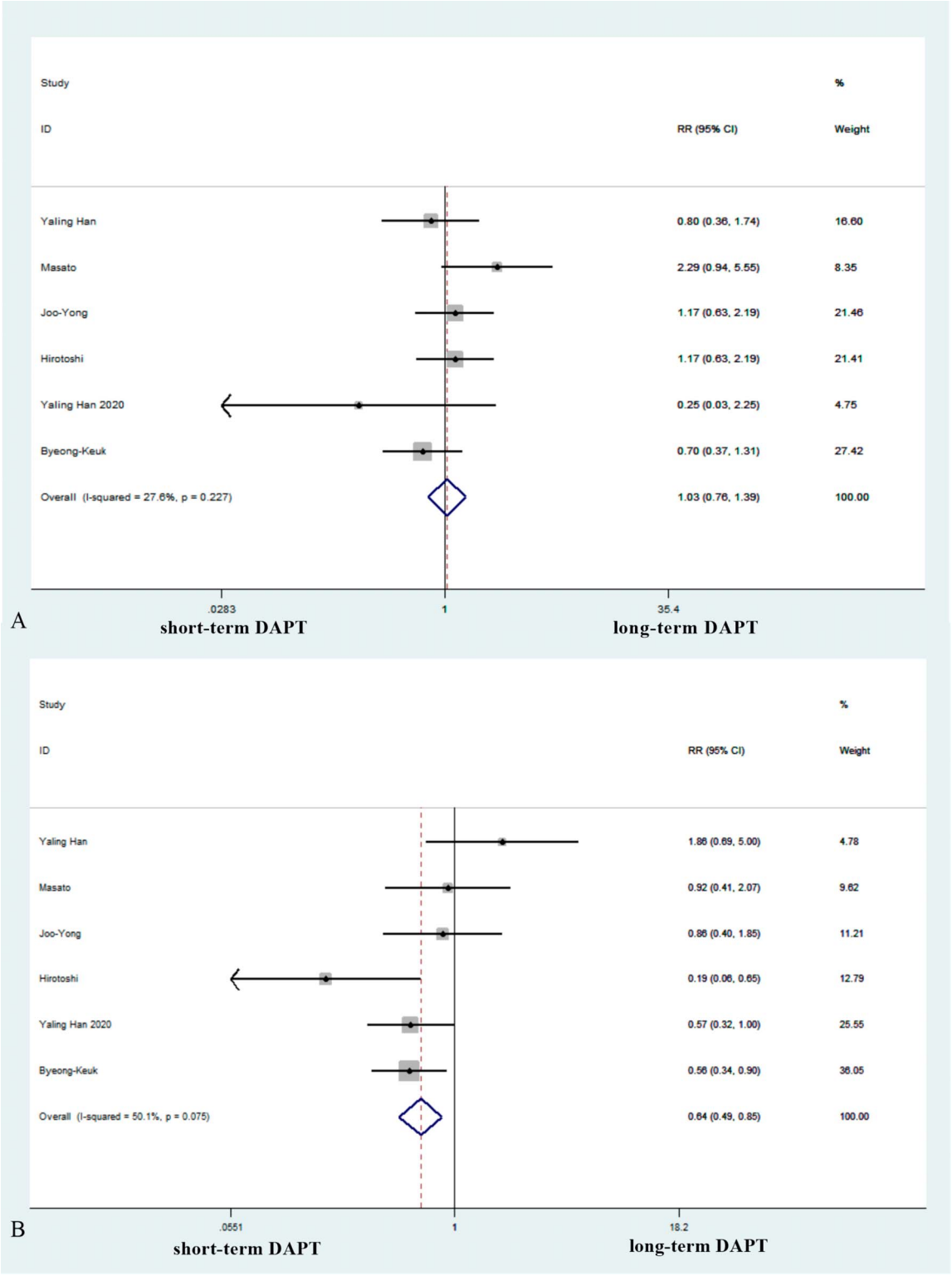

FIGURE 2. Comparison of primary outcomes between short-term DAPT and long-term DAPT. A, All-cause death. (B) Major bleeding.

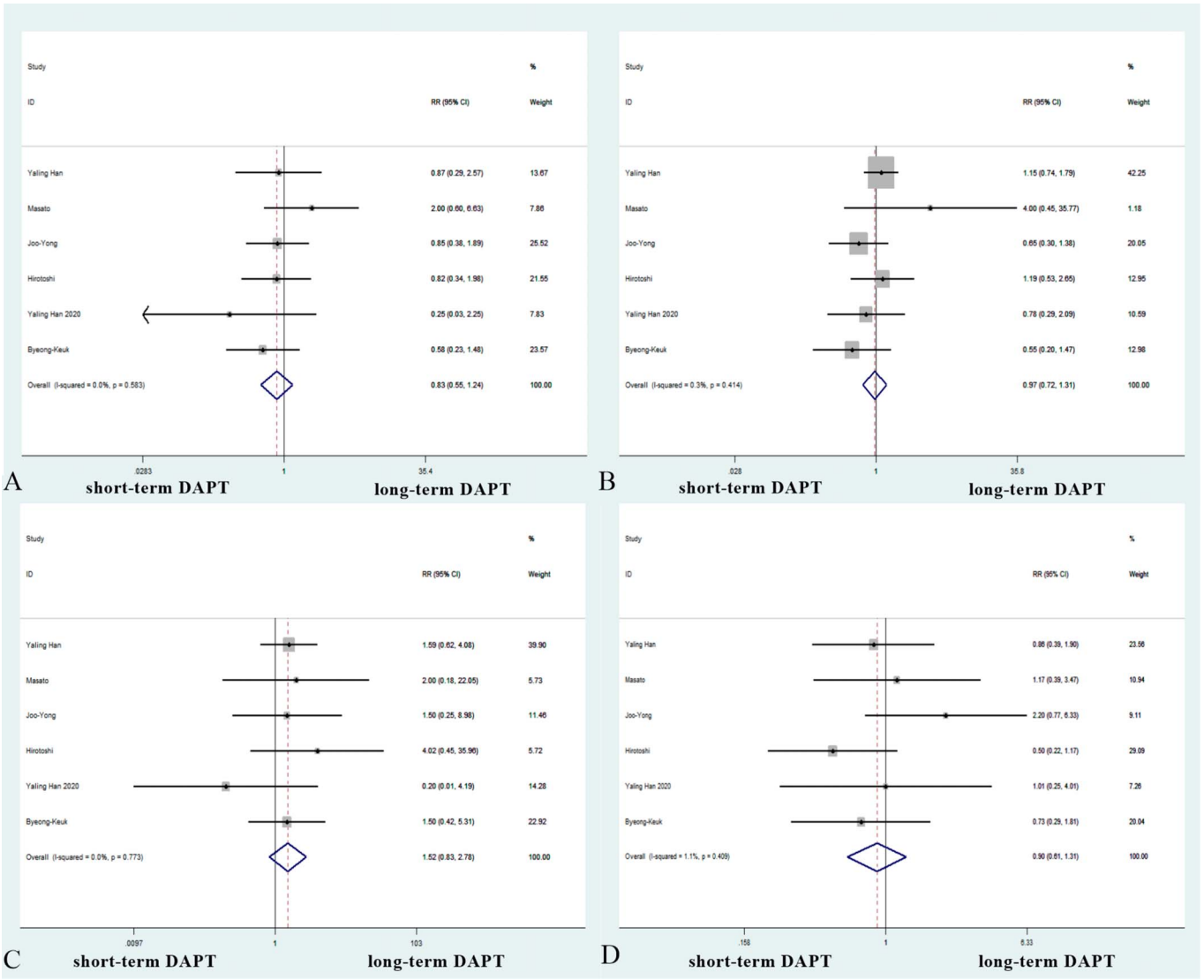

FIGURE 3. Comparison of secondary outcomes between short-term DAPT and long-term DAPT. A, Cardiovascular death. (B) Myocardial infarction. (C) Definite or probable stent thrombosis. (D) Stroke.

conducted in this study to decrease the risk of random errors induced by repeated significance tests. The results showed that the curve of major bleeding exceeded the conventional boundary and met the expected sample size. Therefore, the conclusion that short-term DAPT can reduce the risk of major bleeding in East Asian patients undergoing new-generation DES should be considered as a true positive result. Meanwhile, the conclusions of this meta-analysis are similar to those of the 2018 updated expert consensus statement on antiplatelet therapy for patients with ACS or undergoing PCI in East Asians,[17] which suggested that 6-month DAPT should be recommended for East Asian patients with stable coronary artery disease after DES implantation, whereas 12-month DAPT is reasonable for East Asian patients with ACS after stent implantation. Prolonging DAPT for more than 12 months is useful in high-risk patients to prevent recurrent ischemic events. For patients with a high risk of bleeding or who cannot tolerate long-term DAPT treatment, shortening the duration of DAPT can also be considered. Furthermore, PubMed, EMBASE, and Cochrane Library database(databases) were searched in this study with no language restrictions. Meanwhile, we provide a detailed search strategy as a supplement. The selection and inclusion of trials are reproducible. No publication bias was found by the funnel plot and the *P* value of Begg's and Egger's test.

Several previous randomized controlled trials have shown that the short-term DAPT after PCI is not inferior to long-term DAPT in efficacy and safety.[27–30] A systematic review and meta-analysis by Khaled M et al compared efficacy and safety of short-term DAPT (6-month or less) with long-term DAPT (12- month or more) in patients undergoing PCI.[31] The results showed that there was no significant difference in mortality, cardiovascular death, and risk of myocardial infarction, definite or probable stent thrombosis, and

stroke between the 2 groups. However, shortening DAPT was associated with a reduced risk of major bleeding. Monica Verdoia et al[32] published a systematic review and meta-analysis in 2020, which compared 3-month with 6-month DAPT strategies after the implantation of new-generation DES. The results showed that very short DAPT can significantly reduce the risk of major bleeding without increasing the risk of major ischemic events and comparable survival rates. This conclusion is similar to our meta-analysis. However, there were some differences in the population included. This study included the controversial East Asian patients. Meanwhile, a new-generation DES was adopted. A systematic review and meta-analysis by Khaled M et al compared the efficacy and safety of long-term and short-term DAPT between Asians and non-Asian people in 2020.[33] The results showed that long-term DAPT significantly reduced ischemic outcomes only in non–East Asian compared with short-term DAPT, whereas short-term DAPT reduced the bleeding events in both ethnic groups. In terms of race, the results were similar to our meta-analysis. Sun et al published a meta-analysis in 2021, which evaluated the efficacy and safety of short-term ($\leq$6 months) and long-term ($\geq$12 months) DAPT in East Asians undergoing PCI. As in our article, the results also showed that short-term DAPT can significantly reduce the incidence of major bleeding compared with long-term DAPT.[34] The differences were that we performed subgroup analyses according to the study design, $P2Y_{12}$ receptor inhibitor, age, ethnicity of patients, and sample size. Meanwhile, the GRADE and TSA were exploited, respectively, to assess the quality of evidence for each outcome and calculate the sample size in our meta-analysis.

The results of this study need to be applied to clinical practice carefully. First, in terms of stents, the PLATINUM trial shows that novel platinum chromium everolimus-eluting stent was not inferior to the cobalt chromium everolimus-eluting stent in terms of safety and efficacy for patients undergoing PCI.[14] However, the meta-analysis by Lou et al demonstrates that the new-generation DES does not bring more benefits than the second-generation DES.[35] Whether new-generation DES can bring more clinical benefit than the second-generation DES is still controversial. The new-generation DES was applied to all trials included. Therefore, the conclusions of this study are only applicable to patients undergoing new-generation DES. Second, patients included in this meta-analysis were from East Asians. A series of short-term DAPT strategies recommended by international guidelines should be considered for patients with DES. However, due to differences in biology and cultural backgrounds, the conclusions of the trials in East Asian patients seem to be inconsistent with those in Europe and the United States. The East Asian Paradox hypothesis revealed this characteristic of patients with East Asians and proposed the duration of DAPT in patients with East Asians should be different from that of patients with Europeans and Americans.[36] Therefore, it should not apply to other patients. Finally, patients with ACS accounted for 55.8% in this meta-analysis. Traditionally, patients with ACS may have a higher risk of thrombosis than those with the chronic coronary syndrome. These patients are suitable for prolonging the duration of DAPT. However, the risk of thrombosis in East Asian patients is very low. Whether the short-term DAPT can be used for patients with ACS in East Asians is unclear. In this meta-analysis, patients with ACS were included in the TICO trial, but the results were similar to other trials. The duration of DAPT in patients after PCI depends on the overall measurement of the risk of ischemia and bleeding. Therefore, this result cannot be generalized to all patients with ACS.

Limitation

This meta-analysis may have some limitations. First of all, there are some differences in the design of the trials included, half of which are double-blind design, the other half are open-label design. Second, patients have taken different types of $P2Y_{12}$ receptor inhibitors, which may be related to heterogeneity. Patients receiving novel $P2Y_{12}$ receptor inhibitors may be more suitable for the short-term DAPT. However, it is unclear whether there is a difference between clopidogrel and ticagrelor in antiplatelet therapy in East Asian patients. Therefore, more randomized controlled trials are needed to explain the differences between clopidogrel and novel $P2Y_{12}$ receptor inhibitors in East Asian patients. Finally, only the curve of major bleeding exceeded the trial sequential analysis boundary and achieved the expected sample size. Therefore, false-negative results may occur, and more randomized controlled trials are needed to meet the expected sample size.

CONCLUSIONS

According to this systematic review and meta-analysis, the short-term DAPT was not associated with an increased incidence of all-cause death, cardiovascular death, myocardial infarction, definite or probable stent thrombosis, and stroke. However, compared with long-term DAPT, the short-term DAPT reduced the risk of major bleeding by 36%. Clinically, the short-term DAPT strategy in 175 patients can prevent 1 patient from the risk of major bleeding. In conclusion, the short-term DAPT strategy was associated with a reduced risk of major bleeding.

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