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ORIGINAL ARTICLE

Efficacy of Short-term Dual Antiplatelet Therapy after Implantation of Second-generation Drug-eluting Stents: A Meta-analysis and Systematic Review

Peisen Huang^{1#}, Yuan Yu^{2#}, Xikun Han¹, and Yuejin Yang^{1*}

¹State Key Laboratory of Cardiovascular Disease, ²National Clinical
Research Center of Cardiovascular Diseases, Fuwai Hospital,
National Center for Cardiovascular Diseases, Chinese Academy of
Medical Sciences & Peking Union Medical
College, Beijing 100037, China

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percutaneous coronary intervention; efficacy

Objective The benefit of short-term dual antiplatelet therapy (DAPT) following second-generation drug-eluting stents implantation has not been systematically evaluated. To bridge the knowledge gap, we did a meta-analysis to assess the efficacy of ≤ 6 months *versus* ≥ 12 months DAPT among patients with second-generation drug-eluting stents.

Methods We searched online databases and identified randomized controlled trials that assess the clinical impact of short-term DAPT (≤ 6 months) published before March 3, 2016. The efficacy endpoints included the incidence of all-cause death, myocardial infarction, cerebrovascular accidents, and definite or probable stent thrombosis. Safety endpoint defined as major bleeding was also evaluated and discussed.

Results We included 5 trials that randomized 9473 participants (49.8%, short-term DAPT duration *vs.* 50.2%, standard duration). A total of 9445 (99.7%) patients reported the efficacy endpoints, and the safety endpoint was available from 4 studies ($n=8457$). There was no significant difference in efficacy endpoints between short-term and standard DAPT duration (≥ 12 months) [risk ratio (RR) 0.96; 95% confidence intervals (CI), 0.80-1.15]. Short-term DAPT duration did not significantly increase the individual risk of all-cause death, myocardial infarction, cerebrovascular accidents, or definite or probable stent thrombosis. Although short-term DAPT obviously reduced risk of major bleeding compared with standard DAPT (RR 0.53; 95% CI, 0.29-0.96), significant publication bias was found when accessing the safety endpoint of the 4 studies (Egger's test, $P=0.009$).

Conclusions The efficacy of short-term DAPT was comparable with that of standard duration DAPT.

DAPT less than 6 months may be appropriate for patients receiving second-generation drug-eluting stents implantation.

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DUAL antiplatelet therapy (DAPT) has been the cornerstone in secondary prevention after percutaneous coronary intervention (PCI) procedures. At first, extended DAPT was considered to be associated with a significant reduction in late and very late stent thrombosis in patients undergoing PCI with the first-generation drug-eluting stent (DES) implantation. However, prolonged DAPT could lead to a significant increase in bleeding events, which may offset the potential benefit.¹ In the second-generation DESs' era, with superior safety due to improved vascular healing and stent strut intimal coverage properties,²⁻⁴ the new DESs raise the possibility to shorten DAPT duration while maintaining the efficacy.⁵ Current European Society of Cardiology (ESC) and American Heart Association/American College of Cardiology (AHA/ACC) guidelines recommend a minimum duration of DAPT of 6 to 12 months and 12 months respectively,⁶⁻⁷ for such circumstance. While neither of them provided specific recommendation of the DAPT for the second-generation DESs, despite they account for the vast majority of stents used nowadays.

In recent years, several randomized trials evaluated the outcome of short-term DAPT in patients undergoing PCI with the second-generation DESs, including zotarolimus-eluting stent (ZES) and everolimus-eluting stent (EES). Due to the rarity of ischemic and bleeding events, each trial had limited statistical power to conclude the noninferiority on shorter duration of DAPT. One newly published meta-analysis concluded it was safe with DAPT no more than 6 months in patients receiving second-generation DESs.⁸ While it actually did not exclude randomized controlled trials enrolling patients undergoing bare metal stents (BMS) and the first-generation DESs. So far, barely systematic evidences particularly based on the second-generation DESs are available in the current cardiology practice.

Therefore, we sought to assess the efficacy of short-term DAPT (≤ 6 months) compared with that of standard DAPT (≥ 12 months) by doing a comprehensive meta-analysis of randomized controlled trials among patients undergoing the second-generation DESs implantation.

MATERIALS AND METHODS

Database search

The literature searches were performed in Medline (with the

Ovid interface), EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and China National Knowledge Internet (CNKI) database to identify relevant randomized clinical trials published up to March 3, 2016. We also screened the ClinicalTrials.gov. The following search terms were used: "randomized controlled trial", "random", "placebo", "random allocation", "single-blind", "double-blind", "triple-blind", "DES", "drug-eluting stent", "DAPT", "dual antiplatelet therapy", "aspirin", "ASA", "acetylsalicylic acid", "clopidogrel", "Plavix", "prasugrel", "Effient", "ticagrelor", "Brilinta", "thienopyridine", "short term", "short duration", "3-month", and "6-month". Manually searching for additional relevant studies was done until no further citations were available. Searches were restricted to trials of human participants with full text published in English or Chinese.

Inclusion and exclusion criteria

We selected all randomized controlled trials that analyzed the efficacy of ≤ 6 months DAPT vs. ≥ 12 months after implantation of second-generation DESs. Two investigators (Peisen Huang and Yuan Yu) independently assessed all potentially relevant studies to identify studies that satisfied the following criteria: 1) human subjects underwent implantation of the second-generation DESs to treat coronary artery disease, 2) participants were randomly assigned to receive either short-term DAPT, defined as management with aspirin and a P2Y₁₂ receptor inhibitor (clopidogrel, prasugrel, or ticagrelor) for no more than 6 months, or standard duration DAPT, defined as DAPT treatment given for at least 12 months after index PCI, and 3) follow up for at least 12 months. Exclusion criteria were: 1) a non-randomized controlled design, editorial comments, reviews, and conference abstracts, 2) a repeated report on the same study population or duplicated data. Discrepancies between the two reviewers in study selection were resolved by a third independent investigator.

Data collection and assessment of risk of bias

Two investigators (Peisen Huang and Yuan Yu) independently reviewed the full text of included trials and did the data collection. Efficacy endpoint (all-cause death, myocardial infarction, cerebrovascular accidents, and definite or probable stent thrombosis) and safety endpoint (major bleeding) were analyzed. In trials where participants were

randomly divided to implant the first- or second-generation stents, we only extracted subjects' data referred to the second-generation DES.

Risk of bias was evaluated by the same two authors, in accordance with the Cochrane Collaboration's method based on the following methodological items: adequacy of random sequence generation, allocation concealment, blinding (at participants or outcome assessors level), incomplete outcome data reporting, selective outcome depiction, adequate description of sample size calculation, detailed funding sources disclosure and other important bias.⁹

Statistical analysis

Data were analyzed with RevMan version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark). The summary risk ratio (*RR*) and 95% confidence intervals (*CI*s) were estimated using fixed effects method (Mantel-Haenszel) for dichotomous outcomes. Breslow-Day χ^2 test ($P < 0.1$) and I^2 statistic were used to assay the heterogeneity among the trials: I^2 values $< 25\%$ indicating low, 25% - 50% indicating moderate, and $> 50\%$ indicating high heterogeneity.¹⁰ Funnel plot asymmetry was visually inspected to address for possible small study effects, together with Egger's and Begg's test to access publication bias, over and above any subjective evaluation.¹¹ A P value of < 0.05 was

considered as statistically significant. Meta-regression was done according to difference in DAPT duration and proportion of patients with acute coronary syndrome (ACS) between study arms. The sensitivity analysis was performed to investigate the robustness of our results by repeated data analysis omitting one study at a time to assess whether any of the included studies had a dominated effect on the results. The study was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.

RESULTS

Description of studies

We screened the title, abstract and/or full text of 180 eligible publications (Fig. 1). Of these, 175 studies were excluded and only 5 trials (9473 participants) met the inclusion criteria for this analysis.¹²⁻¹⁶ All studies were multicenter with relatively low bias (Table 1).

The main characteristics of the studies included are reported in Table 2. Briefly, the subjects enrolled in the trials were PCI suitable and underwent the second-generation DESs (ZES or EES) implantation. In the Real Safety and Efficacy of 3-month Dual Antiplatelet Therapy Following Endeavor Zotarolimus-eluting Stent Implantation (RESET) study, 16.1% of eligible patients randomly allocated

Figure 1. PRISMA flow chart for the trial selection process.

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT: randomized controlled trial; DES: drug-eluting stent.

Table 1. Results of bias risk assessment of the 5 included studies

Methodological items	ITALIC ¹²	OPTIMIZE ¹⁴	RPRODIFY ¹⁵	RESET ¹⁶	SECURITY ¹³
Random sequence generation	Yes (Web-based)	Yes	Yes (Computer-generated)	Yes (Web-based)	Yes
Allocation concealment	Yes (Centralized randomization)	Unclear	Yes (Sealed envelopes)	Unclear	Unclear
Blinding of participants*	Yes	Yes	Yes	Yes	Yes
Blinding of outcome assessment	Yes	Yes	Yes	Yes	Yes
Incomplete outcome data	Yes	Yes	Yes	Yes	Yes
Selective outcome reporting	Yes	Yes	Yes	Yes	Yes
Sample size calculation	Yes	Yes	Yes	Yes	Yes
		(Non-inferiority design)		(Non-inferiority design)	(Non inferiority design)
Funding sources disclosure	Yes (Industry-funded)	Yes (Industry-funded)	Yes (Investigator-driven)	Yes (Public Health- and Industry-funded)	Yes (Public Health-funded)
Other bias	Yes (Prematurely terminative)	No	No	No	Yes (Prematurely terminative)

ITALIC: Is There a Life for DES after Discontinuation of Clopidogrel; OPTIMIZE: Optimized Duration of Clopidogrel Therapy Following Treatment with the Zotarolimus-Eluting Stent in Real-World Clinical Practice; PRODIFY: Prolonging Dual Antiplatelet treatment after Grading Stent-induced Intimal Hyperplasia Study; RESET: Real Safety and Efficacy of a 3-month Dual Antiplatelet Therapy Following Endeavor Zotarolimus-eluting Stents Implantation; SECURITY: Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-month Dual Antiplatelet Therapy.

*Open-label studies may possess low risk of bias if outcome assessment was blinded and/or if lack of blinding is unlikely to influence outcome.

to Sirolimus-eluting stent were also included.¹⁶ The percentage of patients with stable coronary artery disease ranged from 25.2% to 59.2%, and acute coronary syndrome from 23.5% to 74.8%. All trials compared dual antiplatelet therapy with aspirin alone. DAPT in all trials consisted of aspirin and thienopyridine, which is dominantly clopidogrel, with only 1.8% and 0.1% of patients receiving prasugrel or ticagrelor in the Is There a Life for DES after Discontinuation of Clopidogrel (ITALIC)¹² and Second Generation Drug-eluting Stent Implantation Followed by Six- Versus Twelve-month Dual Antiplatelet Therapy (SECURITY)¹³ studies, respectively. In 3 studies, the randomization to DAPT regimens took place at the time of index PCI,^{13-14, 16} and in 1 month after the index procedure in another trial¹⁵ and 6 months after the index procedure in the remaining trial.¹² The duration of DAPT therapy was 3 or 6 months in short-term DAPT group. All trials assessed 12-month DAPT therapy as the standard group, apart from the Prolonging Dual Antiplatelet Treatment after Grading Stent-induced Intimal Hyperplasia study (PRODIFY),¹⁵ in which patients received 24 months of DAPT therapy.

Efficacy and safety endpoints

All 5 trials consisted of 9445 (99.7%) patients, reporting

the efficacy endpoints. We found no significant heterogeneity among trials as assessed by $\chi^2=4.64$ ($P=0.33$), and I^2 value was 14% (Fig. 2). In a Mantel-Haenszel fixed-effects model, no significant difference in terms of efficacy was found between short-term and standard DAPT duration (RR 0.96; 95% CI , 0.80-1.15; Fig. 2).

Short-term DAPT was not associated with all-cause death when compared with standard duration treatment (RR 0.91; 95% CI , 0.69-1.21; $I^2=0$; Fig. 3A). Similarly no significantly increased risk of myocardial infarction (RR 1.06; 95% CI , 0.78-1.43; $I^2=0$; Fig. 3B), definite or probable stent thrombosis (RR 0.96; 95% CI , 0.53-1.73; $I^2=0$; Fig. 3C) or cerebrovascular accidents (RR 0.81; 95% CI , 0.46-1.45; $I^2=34\%$; Fig. 3D) was observed in short-term DAPT. The safety endpoint was available from 4 studies ($n=8457$).^{12-14,16} In a Mantel-Haenszel fixed-effects meta-analysis, patients with short-term DAPT were at significantly reduced risk of major bleeding compared with ones with standard DAPT (RR 0.53; 95% CI , 0.29-0.96; $I^2=0$; Fig. 4).

Bias risk

Funnel plots and the Egger's test assessing the efficacy endpoints suggested no evidence of publication bias (Figs. 5A-E). In the subanalysis, short-term DAPT did not increase

Table 2. Main characteristics of the 5 included trials

Items	ITALIC ¹²	SECURITY ¹³	OPTIMIZE ¹⁴	PRODIGY ^{15*}	RESET ¹⁶
Patients (n)	1850	1399	3119	988	2117
Age (yrs)	61.6	65.2	61.6	67.7	62.4
Male (%)	80	77.2	63.3	78.7	63.6
BMI (kg/m ²)	27	NA	NA	27.5	25
Current smoker (%)	51.8	22.2	17.9	23.9	24
Previous PCI (%)	23.3	17.7	20.0	NA	3.3
Comorbidities					
Diabetes (%)	37.0	30.7	35.4	23.3	29.3
Dyslipidaemia (%)	67.1	63	61.1	60.0	58.8
Hypertension (%)	65.0	72.8	87.2	69.6	61.9
Severity of illness					
Ejection fraction (%)	NA	56.5	NA	50.8	64.1
Silent ischemia (%)	20.2	-	8.9	-	-
Stable CAD (%)	41.3	50.7	59.2	25.2	45.4
ACS (%)	23.5	31.6	31.9	74.8	54.6
Procedural characteristics					
Multivessel disease (%)	NA	42.3	25.9	71.4	22.7
LAD treated (%)	72.8	43.5	47.2	58.9	53.2
Lesion length (mm)	NA	19	18.4	13.45	19.8
Stent/lesion	NA	NA	1.2	1.2	1.0
Type of DES used	EES	ZES, EES	ZES	ZES, EES	EES, SES, ZES
Thienopyridine category	Clopidogrel (98.2%), prasugrel Clopidogrel (99.9%), prasugrel Clopidogrel (100%) and ticagrelor (1.8%)	Clopidogrel (99.9%), prasugrel Clopidogrel (100%) and ticagrelor (0.1%)	Clopidogrel (100%)	clopidogrel (100%)	Clopidogrel (100%)
Main inclusion criteria	EES ≥18 years; PCI suitability; Xience V DES implantation; all or patients with documented silent ischemia; second-generation not acute MI (<30 days); clinical situations excluding silent ischemia; DES implantation <24 hours; ≥1 lesion; ≥50% DS; RVD treatment of the left main artery	Stable angina or unstable angina with documented unstable angina, recent (but not acute) MI (<30 days); RVD chronic stable coronary artery disease or ACS (NSTEMI/STEMI)	Stable angina, silent ischemia, recent (but not acute) MI (<30 days); RVD chronic stable coronary artery disease or ACS (NSTEMI/STEMI)	≥18 years; ≥1 coronary artery lesion; ≥50% DS; PCI suitability; RVD ≥2.25 mm; chronic stable coronary artery disease or ACS (NSTEMI/STEMI)	≥20 years; ≥50% DS; RVD 2.5 to 4.0 mm; elective PCI; stable angina, unstable angina, or acute MI

Items	ITALIC ¹²	SECURITY ¹³	OPTIMIZE ¹⁴	PRODIGY ^{15*}	RESET ¹⁶
Main exclusion criteria	Aspirin resistance; prior DES Patients treated for saphenous STEMI presenting for primary Elective surgery planned <24 Cerebral/peripheral implantation <1 year; bleeding vein graft and in-stent restenosis; or rescue PCI; BMS implantation months after index PCI (unless atherosclerotic arterial disease, diathesis or active bleeding; <48 hours STEMI; <6 months <6 months; previous treatment DAPT could be maintained thro- thromboembolic disease or ST DAPT contraindications; major NSTEMI; LVEF <30%; DAPT with any DES; elective surgery ughout the peri-surgical period); history; LVEF <40%; restenotic surgery <6 weeks; severe liver contraindications; creatinine planned <12 months; DAPT bleeding diathesis; major surgery lesion; CTO; LM disease requi- failure; elective surgery planned >177 µmol/L; bleeding diathesis contraindications; saphenous <15 days; active bleeding or ring intervention; cardiogenic <1 year; life expectancy <2 or active bleeding; life expectancy vein graft lesion previous stroke <6 months; shock; STEMI<48 hours years <2 years concomitant or foreseeable need for anticoagulants				
Primary endpoint	Composite of all-cause death, Composite of cardiac death, MI, NACCE (composite of all-cause Composite of all-cause death, Composite of cardiac death, MI, MI, repeat emergency TVR, stroke, ST, or BARC type 3 or 5 death, MI, stroke, or major MI or CVAs ST, ID-TVR and TIMI major or stroke, or major bleeding bleeding) minor bleeding				
Secondary endpoint	All-cause death, MI, repeat Cardiac death, MI, stroke, ST, ST; ID-TVR; MACE (composite All-cause death; MI; CVAs; Composite of all-cause death; emergency TVR, stroke; minor or BARC type 2, 3, or 5 of all-cause death, MI and any cardiac death; ST MI; ST and minimal bleeding bleeding; CI of the individual revascularization); bleeding components of the primary endpoint; ID-TVR; all-cause mortality				
Time to randomization	6 months after index PCI	At index PCI	At index PCI	1 month after index PCI	At index PCI
DAPT duration(mon)					
Short-term DAPT group	6	3	6	3	
Standard DAPT group	12	12	24	12	
Year of publication	2015	2014	2013	2012	
Registration number	NCT01476020	NCT00944333	NCT01113372	NCT00611286	NCT01145079

BMI: body mass index; PCI: percutaneous coronary intervention; CAD: coronary artery disease; ACS: acute coronary syndrome; LAD: left anterior descending artery; DES: drug-eluting stents; EES: everolimus-eluting stent; ZES: zotarolimus-eluting stent; SES: sirolimus-eluting stent; MI: myocardial infarction; DS: diameter stenosis; BMS: bare metal stents; RVD: reference vessel diameter; NSTEMI/STEMI: non-ST-elevation/ST-elevation myocardial infarction; DAPT: dual antiplatelet therapy; LVEF: left ventricular ejection fraction; ST: stent thrombosis; CTO: chronic total occlusion; LM: left main; TVR: target vessel revascularization; ID-TVR: ischaemia-driven TVR; CVAs: cerebrovascular accidents; BARC: Bleeding Academic Research Consortium; NACCE: net adverse clinical and cerebral events; TIMI: thrombolysis in myocardial infarction; CI: confidence interval; NA, not available; -: no data.

*Only the data of the second-generation DES subgroup was extracted.

†Only the 12-month follow-up data were available despite the designed follow-up was 24 months.

Figure 2. Comparison of total efficacy of short-term dual antiplatelet therapy (DAPT) vs. standard DAPT.

The squares and the horizontal lines indicate the risk ratio and the (95% CI) for each trial included; the size of each square is proportional to the statistical weight of a trial in the meta-analysis; diamond indicates the effect estimate derived from meta-analysis, with the center indicating the point estimate and the left and the right ends of the (95% CI).

the all-cause death, myocardial infarction, stent thrombosis, and cerebrovascular accidents, which was consistent with the overall results. Moreover, meta-regression showed neither the difference in DAPT duration (Figs. 6A-E) nor proportion of patients with ACS (Figs. 7A-E) had significant effects on both overall efficacy results and individual indicator. However, there was significant publication bias when accessing safety endpoints of the 4 studies (Fig. 5F). Egger's test ($P=0.0094$) could validate the bias due to small study effects. Meta-regression analysis showed there was interaction between efficacy and ACS component ($p^{int}=0.04$), but not DAPT duration ($p^{int}=0.06$).

DISCUSSION

This is a meta-analysis specifically focusing on patients receiving the second-generation DESs to evaluate the benefit of short-term (≤ 6 months) DAPT compared with standard (≥ 12 months) DAPT. It included 5 RCTs of more than 9400 participants. We did not detect a significant difference in the overall efficacy endpoint, as well as individual risk of all-cause death, myocardial infarction, stent thrombosis and cerebrovascular events between the two groups. The meta-analysis findings were not sensitive to the exclusion of any trial, and no substantial heterogeneity was observed in trial results with respect to the efficacy endpoints.

It is well recognized that DAPT plays an important role in patients undergoing PCI procedure.¹⁷ However, benefit from shorter or longer duration of DAPT remains a matter of considerable controversy. Previous observational studies favored DAPT beyond 1 year,¹⁸⁻²⁰ for prolonged dual antiplatelet regimen can reduce the occurrence of very late stent thrombosis after PCI.²¹ However, prolonged duration of DAPT accompanied with higher risk of bleeding.^{1, 22-24}

The expected benefit with prolonged DAPT was offset by an increased risk in major bleeding and a significantly higher non-cardiovascular mortality in the recently completed, large DAPT trial, which changed the perspective on extended thienopyridine use.¹ If true, the increase in death associated with prolonged DAPT among the diverse population of cardiovascular patients could have profound consequences on public health. A previous systematic analysis of 32 135 participants after implantation of various DESs showed that the increased risk of short-term DAPT on stent thrombosis was attenuated with the use of second-generation DESs.²⁵ This indicated a better performance in preventing stent thrombosis when compared with the first-generation counterparts. Therefore, with second-generation DES dominantly used in contemporary practice, a short-term of DAPT strategy of less than 6 months seems to be more acceptable when evaluating the trade-off between ischemic and bleeding risk.

Currently, neither guidelines nor published meta-analysis specifically focused on the duration of DAPT after second-generation DESs implantation. There were several trials evaluated the safety and efficacy of interrupted DAPT at 3 or 6 months compared with long-term DAPT at 12 or 24 months, and were particularly enrolling patients undergoing second-generation DESs implantation.¹²⁻¹⁶ However, the wide confidence intervals and low rate of events accrued in each of RCT made it underpowered to detect clinically-meaningful differences in hard endpoints such as stent thrombosis and MI.²⁶ Although a recent analysis reported by Ziada *et al*⁸ claimed that abbreviated-duration of DAPT (≤ 6 months) following second-generation DESs associated with a significant reduction in major bleeding complications compared with standard-duration DAPT. The subgroup analyses which excluded studies that first-generation DES use $\geq 25\%$ still contained a certain part of patients undergoing BMS or first-generation DES. Thus, a

Figure 3. Comparison of individual safety indicator of short-term DAPT vs. standard DAPT.

A. Odds ratio with (95% CI) for all-cause death; B. myocardial infarction; C. definite or probable stent thrombosis; D. cerebrovascular accidents.

systematic examination of the short-term DAPT on efficacy and safety after second-generation DES implantation was still in a great need for the evolving DESs' era.

The results of the present meta-analysis, which included all of the randomized trials particularly evaluating optimal DAPT duration after PCI with second-generation DESs (The RESET trial¹⁶ is also included because only 16.1% of eligible patients randomly allocated to first-generation DESs), offered the first insight into the

efficacy and safety of short-term DAPT after second-generation DESs implantation. Despite a conventional association was found between DAPT cessation and an increased risk of ischemic events, we did not detect a significant increase or reduction in efficacy endpoints including all-cause mortality and risk of stent thrombosis. The specific inclusion of second-generation DESs in our meta-analysis may account for the relatively lower prevalence of such events.

Figure 4. Comparison of major bleeding risk of patients receiving short-term DAPT vs. standard DAPT.

The squares and the horizontal lines indicate the risk ratio and the (95% CI) for each trial included; the size of each square is proportional to the statistical weight of a trial in the meta-analysis; diamond indicates the effect estimate derived from meta-analysis, with the center indicating the point estimate and the left and the right ends of the (95% CI).

Figure 5. Funnel plots were done to access the probable publication bias.

A. Funnel plot for efficacy effect; B. all-cause death; C. myocardial infarction; D. definite or probable stent thrombosis; E. cerebrovascular accidents; F. safety effect.

RR: relative risk.

Previous studies showed that extended duration of DAPT increased the occurrence of bleeding events.^{1, 22-24} Here we observed that short-term DAPT was associated with a significant reduction in major bleeding complications, but there was significant publication bias when accessing the safety endpoint (Egger's test, $P=0.009$). Thus, there is still not enough evidence to support that short-term DAPT after second-generation DES implantation can further reduce the bleeding risk compared with standard DAPT.

Our study has important limitations. First, the total number of events remained relatively low despite pooling the data from 9445 patients, which would limit the strength to conclude on rare events such as cerebrovascular events,

stent thrombosis, or major bleeding. And two trials—the ITALIC¹² and SECURITY¹³ prematurely terminated (fulfilled 74.7% and 51.1%, respectively, of their designed sample size), decreasing the power of conclusion. Additionally, most of the trials reported the endpoints in 12-month follow-up, that we cannot exclude a significant difference may emerge in the long run. Whereas, the PRODIGY study successfully proved the non-inferiority of shorter duration of DAPT in 24-month observation.¹⁵ What's more, new thienopyridine, such as prasugrel and ticagrelor, which has been widely used in real-world treatment, while we barely include these prescriptions in current analysis. Although we cannot draw conclusions on them, novel thienopyridine with improve-

ment in safety and efficacy²⁷⁻²⁸ would not likely change the results. Finally, as none of these trials specialized on acute coronary syndrome and data on this subgroup was not available, we can only presume the efficacy of short-term DAPT on the high-risk patients from 3768 subjects with ACS.

In this meta-analysis of more than 9400 participants

receiving second-generation DESs implantation, short-term DAPT was associated with similar rates of efficacy endpoints compared with standard DAPT. These data suggest that a short-term DAPT strategy is appropriate for patients undergoing second-generation DESs implantation in the contemporary era. Future efforts focus on duration for new

Figure 6. Sensitivity analysis of all studies assessing association of difference in DAPT duration between study arms on meta-analysis results for overall efficacy endpoint and individual endpoints.

A. Meta-regression for efficacy effect; B. all-cause death; C. myocardial infarction; D. definite or probable stent thrombosis; E. cerebrovascular accidents.

RR: relative risk.

Figure 7. Sensitivity analysis of all studies assessing association of proportion of patients with acute coronary syndrome (ACS%) between study arms on meta-analysis results for overall efficacy endpoint and individual endpoints.

A. Meta-regression for efficacy effect; B. all-cause death; C. myocardial infarction; D. definite or probable stent thrombosis; E. cerebrovascular accidents.

antiplatelet drugs after DESs implanting with longer follow-up are needed, and the duration of DAPT among patients with acute coronary syndrome post-DESs should be defined.

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