

Shorter- versus Longer-duration Dual Antiplatelet Therapy in Patients with Diabetes Mellitus Undergoing Drug-eluting Stents Implantation: A Meta-analysis of Randomized Controlled Trials

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Abstract

Background: Patients with diabetes mellitus (DM) have a higher risk of thromboembolic events; however, the optimal duration of dual antiplatelet therapy (DAPT) remains unclear. The goal of this study was to assess the efficacy and safety of various DAPT durations in patients with DM undergoing drug-eluting stent implantation.

Methods: We conducted a literature search for randomized controlled trials (RCTs). We searched databases including EMBASE, PubMed, Cochrane Library, and Scopus up to June 2016. Investigators extracted data independently, including outcomes, characteristics, and study quality. A random-effect model was used to pool odds ratios (ORs) with 95% confidence intervals (CIs) of the clinical outcomes.

Results: Six RCTs totaling 6040 patients with DM were included in the study. Shorter-duration DAPT resulted in an increased rate of stent thrombosis (ST) (OR, 1.83, 95% CI: 1.03–3.26, $P = 0.04$), but did not increase the risk of myocardial infarction (OR, 1.33, 95% CI: 0.71–2.47, $P = 0.37$), stroke (OR, 0.96, 95% CI: 0.52–1.77, $P = 0.90$), target vessel revascularization (OR, 1.19, 95% CI: 0.46–3.07, $P = 0.71$), all-cause death (OR: 0.72, 95% CI: 0.48–1.09, $P = 0.12$), or cardiac death (OR, 0.82, 95% CI: 0.49–1.36, $P = 0.44$) significantly. Shorter-duration DAPT was associated with a decreased risk of major bleeding (OR, 0.60, 95% CI: 0.38–0.94, $P = 0.02$).

Conclusion: In patients with DM, longer-duration DAPT had a lower risk of ST, but was associated with an increased bleeding risk.

Key words: Diabetes Mellitus; Dual Antiplatelet Therapy; Meta-analysis; Stent Thrombosis

INTRODUCTION

Patients with diabetes mellitus (DM) have a higher risk of thromboembolic events, and DM is a strong and independent predictor of stent thrombosis (ST) after drug-eluting stent (DES) implantation.^[1,2] Current clinical practice guidelines recommend 6–12-month dual antiplatelet therapy (DAPT) following DES implantation;^[3,4] however, the optimal DAPT duration in patients with DM has not yet been defined. Recently, large-scale trials, such as the SECURITY and DAPT trials, published conflicting results of the DM subgroup;^[5,6] therefore, we performed the meta-analysis to assess the optimal DAPT duration in this special population.

METHODS

Search strategy and eligibility criteria

We conducted a systematic search to compare shorter- and longer-duration DAPT in patients with DM after DES implantation from databases including PubMed, Cochrane

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Library, EMBASE, and Scopus for randomized controlled trials (RCTs) up to June 2016. We also searched ClinicalTrials.gov databases and checked references of reviews to locate other eligible studies. Our search also included conference abstracts and did not restrict language or publication dates. Search terms included “dual antiplatelet”, “stent”, and “diabetes mellitus”. The specific search strategies for each database are listed in Supplementary Table 1.

The eligibility criteria included: (1) RCTs; (2) patients with DM who received DAPT after coronary DES implantation; (3) shorter-duration DAPT with standard therapy (12-month DAPT) or standard therapy with prolonged DAPT; (4) any of the following endpoints: ST, myocardial infarction (MI), stroke, target vessel revascularization (TVR), all-cause death, cardiac death, and major bleeding; and (5) at least 12-month follow-up. Exclusion criteria included: bare-metal stent implantation, biodegradable polymer-based DES, and discontinuation or interruption (but not duration) of DAPT.

Study selection, data abstraction, and quality assessment

Two reviewers reviewed titles and abstracts independently to exclude irrelevant records and then obtained full-text records of potentially suitable articles. The third reviewer identified discrepancies. After full agreement on the included studies, two reviewers first extracted the data independently and assessed the risk of each study and then cross-examined these results. The quality of the RCTs was assessed with the Cochrane collaboration’s risk-of-bias tool.^[7]

Outcome variables

Major bleeding was defined differently across RCTs according to major thrombolysis in myocardial infarction bleeding in the EXCELLENT, REAL/ZEST-LATE, and RESET trials, while Bleeding Academic Research Consortium Type 3 or 5 was used in the SECURITY and DAPT trials.

Statistical analysis

All statistical analyses were conducted by Review Manager 5.3 (The Cochrane Collaboration, Copenhagen, Denmark). A random-effect model was used to pool odds ratios (ORs). Heterogeneity across studies was checked by Chi-square test and I^2 statistic, with $P < 0.10$ or $I^2 > 50\%$ representing a significant heterogeneity. All reported P values were two-sided, with $P < 0.05$ considered statistically significant. We did not test for publication bias because of the limited number of studies. Sensitivity analyses were performed by excluding sequentially one study at a time to test the robustness of the results.

RESULTS

Study selection and quality assessment

The process of study selection is listed in Figure 1. Finally, six RCTs totaling 6040 patients with DM were included in the analysis.^[5,6,8-11] The main features of the included RCTs are reported in Table 1. The baseline clinical, angiographic, and procedural characteristics of

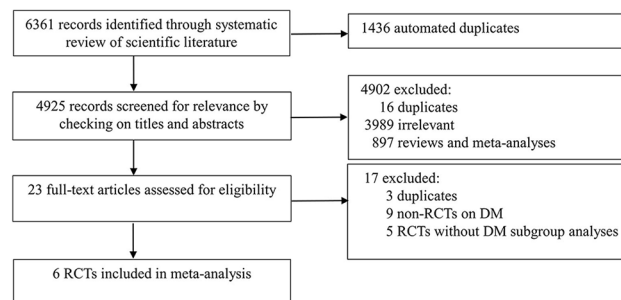


Figure 1: Search flow diagram of the studies included in the meta-analysis. DM: Diabetes mellitus; RCT: Randomized controlled trial.

patients are listed in Supplementary Table 2. The quality of the RCTs is shown in Supplementary Table 3. In the subgroup of shorter versus 12-month DAPT, the definition of short- and long-duration DAPT was 3–6 months for short duration and 12 months for long duration. In the subgroup of 12-month versus longer DAPT, the definition of short- and long-duration DAPT was 12 months for the shorter duration and 24–30 months for the longer duration.^[12,13] Two RCTs compared 3-month versus 12-month DAPT (the OPTIMIZE and RESET trials); two compared 6-month versus 12-month DAPT (the EXCELLENT and SECURITY trial), and the others compared 12-month versus >12-month DAPT (the DAPT study and REAL/ZEST-LATE trial). Second-generation DESs were used in two RCTs, and the others mixed the first- and second-generation DESs together in analyses. Overall, 63.9% of the patients received second-generation DESs; 18.8% received prasugrel, and the rest were treated with clopidogrel. Three RCTs provided outcomes at 12 months after DES implantation, two at 24 months, and one at 33 months. Three trials were carried out in Korea, one in Brazil, and two internationally.

Primary endpoints

The definitions of the primary endpoints in each record are listed in Supplementary Table 4. There was no significant difference for the primary endpoints between shorter- and longer-duration DAPT [OR , 1.04, 95% confidence interval [CI]: 0.65–1.65, $P = 0.88$; $I^2 = 60\%$; Supplementary Figure 1]. The results were consistent between abbreviated-term and prolonged-term DAPT studies (P for interaction = 0.42).

Definite/probable stent thrombosis

Definite or probable ST occurred in 34 patients (1.06%) with shorter-duration DAPT and 18 patients (0.55%) with longer-duration DAPT. Compared with longer-duration DAPT, shorter-duration DAPT had an increased risk of ST [OR , 1.83, 95% CI : 1.03–3.26, $P = 0.04$; $I^2 = 0\%$; Figure 2a]. The results were consistent between abbreviated-term and prolonged-term DAPT studies (P for interaction = 0.76).

Myocardial infarction

MI occurred in 96 patients (3.63%) with shorter-duration DAPT and 73 patients (2.68%) with longer-duration DAPT. No significant difference was found between shorter- and

Table 1: Characteristics of the included RCTs

Study, year	Setting	Definition of shorter and longer durations	Total number	Type of DES	P2Y12 inhibitor	Follow-up (months)
Shorter versus 12-month DAPT						
SECURITY, 2016	International	Shorter: 6 months Longer: 12 months	429	2G	Clopidogrel Prasugrel	24
OPTIMIZE, 2014	Brazil	Shorter: 3 months Longer: 12 months	1103	2G	Clopidogrel	12
RESET, 2012	Korea	Shorter: 3 months Longer: 12 months	292	1G 2G	Clopidogrel	12
EXCELLENT, 2012	Korea	Shorter: 6 months Longer: 12 months	550	1G 2G	Clopidogrel	12
12-month versus prolonged DAPT						
REAL/ZEST-LATE, 2010	Korea	Shorter: 12 months Longer: 24 months	704	1G 2G	Clopidogrel	24
DAPT, 2014	11 countries	Shorter: 12 months Longer: 30 months	3391	1G 2G	Clopidogrel Prasugrel	33

1G: First-generation; 2G: Second-generation; DES: Drug-eluting stent; RCTs: Randomized controlled trials; DAPT: Dual antiplatelet therapy.

longer-duration DAPT [*OR*, 1.33, 95% *CI*: 0.71–2.47, *P* = 0.37; *I*² = 32%; Figure 2b]. The results were consistent between abbreviated-term and prolonged-term DAPT studies (*P* for interaction = 0.66).

Stroke

Stroke occurred in 21 patients (0.84%) with shorter-duration DAPT and 23 patients (0.89%) with longer-duration DAPT. No significant difference was observed between shorter- and longer-duration DAPT [*OR*, 0.96, 95% *CI*: 0.52–1.77, *P* = 0.90; *I*² = 0%; Figure 2c]. The results were consistent between abbreviated-term and prolonged-term DAPT studies (*P* for interaction = 0.63).

Target vessel revascularization

TVR occurred in 25 patients (2.53%) with shorter-duration DAPT and 20 patients (2.03%) with longer-duration DAPT. No significant difference was observed between shorter- and longer-duration DAPT [*OR*, 1.19, 95% *CI*: 0.46–3.07, *P* = 0.71; *I*² = 46%; Figure 2d]. The results were consistent between abbreviated-term and prolonged-term DAPT studies (*P* for interaction = 0.05).

All-cause death and cardiac death

All-cause death occurred in 40 patients (1.60%) with shorter-duration treatment and 58 patients (2.25%) with longer-duration treatment. No significant difference was found between shorter- and longer-duration DAPT [*OR*, 0.72, 95% *CI*: 0.48–1.09, *P* = 0.12; *I*² = 0%; Figure 3a]. The results were consistent between abbreviated-term and prolonged-term DAPT studies (*P* for interaction = 0.96). Similar results were observed for cardiac death [*OR*, 0.82, 95% *CI*: 0.49–1.36, *P* = 0.44; *I*² = 0%; *P* for interaction = 0.90; Figure 3b].

Major bleeding

Major bleeding occurred in 30 patients (1.27%) with shorter-duration DAPT and 53 patients (2.17%) with longer-duration DAPT. Shorter-duration DAPT was associated with a decreased risk of major bleeding

[*OR*, 0.60, 95% *CI*: 0.38–0.94, *P* = 0.02; *I*² = 0%; Figure 4]. The results were consistent between abbreviated-term and prolonged-term DAPT studies (*P* for interaction = 0.97).

DISCUSSION

In this meta-analysis involving 6040 patients with DM, we found that longer-duration DAPT was associated with a lower risk of ST, but with an increased risk of bleeding.

The optimal DAPT duration following DESs implantation has been assessed by many previous meta-analyses.^[12,13] DM took more than 25% of patients undergoing percutaneous coronary intervention,^[14] and it is an independent predictor of thrombotic events after coronary stenting.^[1,2,15] Endothelial dysfunction, increased monocyte activation, altered smooth muscle cell migration in DM—which were caused by the effects of hyperglycemia—insulin resistance, and altered free fatty acids may account for the increased risk of thromboembolic events.^[16] In this way, patients with DM may benefit from longer-duration DAPT. We found that longer-duration DAPT decreased the risk of ST significantly. As the patients involved in our meta-analysis were at a low risk of cardiac events (26.7% patients were presented with low-risk acute coronary syndrome, 20.7% with prior MI, 4.5% with heart failure, 6.1% with renal insufficiency, and 4.3% with prior stroke), our findings might underestimate the benefit of longer-duration DAPT for DM. The observational studies also indicate that patients with DM who received prolonged DAPT had a lower risk of death or MI.^[17,18]

Different types of DESs used in patients with DM may make a difference. New-generation DESs might attenuate the benefit of longer-duration DAPT. Two RCTs included in our analyses indicated that patients with DM who received second-generation DESs did not experience any additional benefit from prolonged DAPT.^[5,11] The CREATE study also found that in patients with DM who received biodegradable polymer-based DESs, longer DAPT (>6 months) was

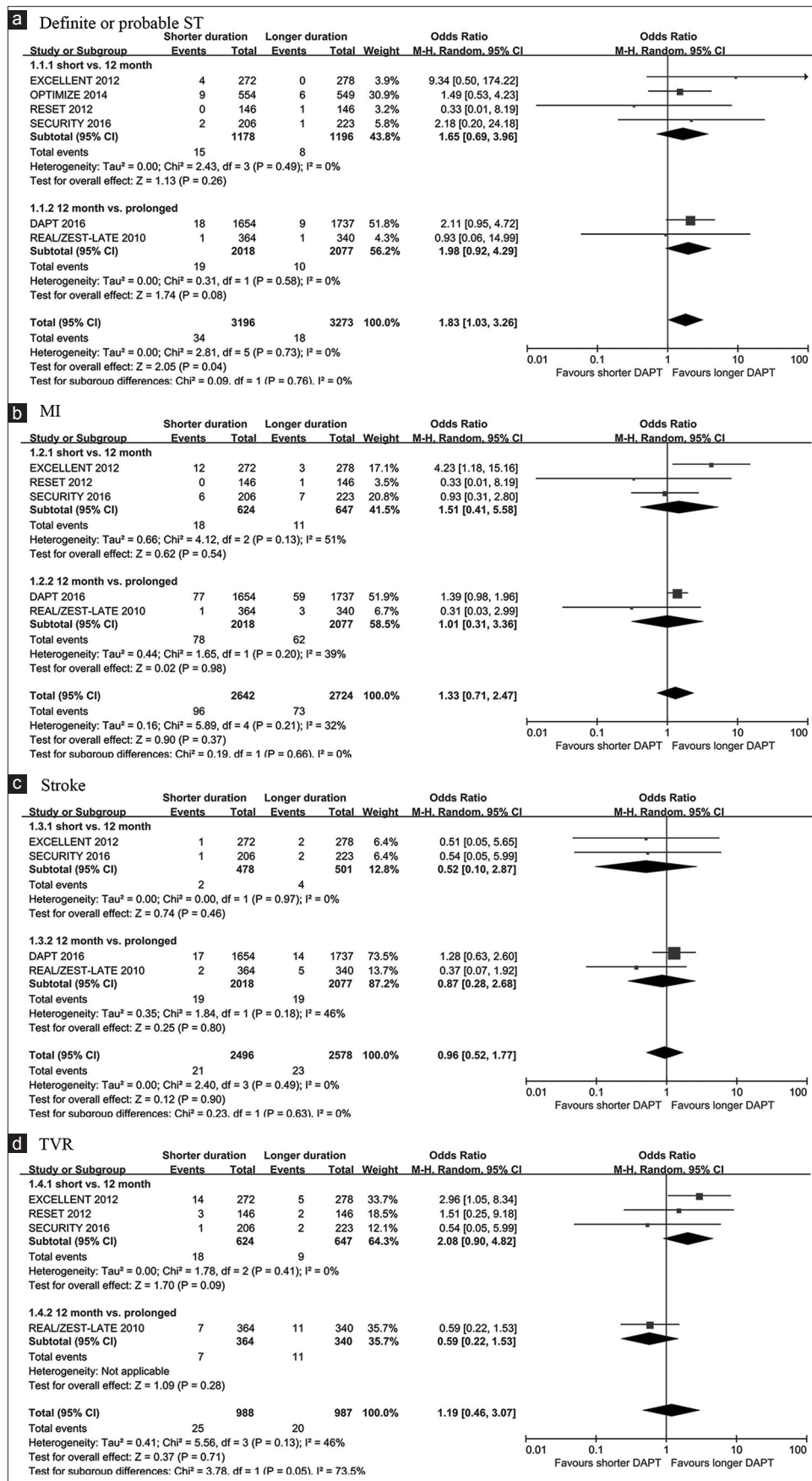


Figure 2: Risk estimates of definite or probable ST (a), MI (b), stroke (c), and TVR (d) with shorter and longer DAPT durations in patients with DM. DAPT: Dual antiplatelet therapy; ST: Stent thrombosis; MI: Myocardial infarction; TVR: Target vessel revascularization; DM: Diabetes mellitus.

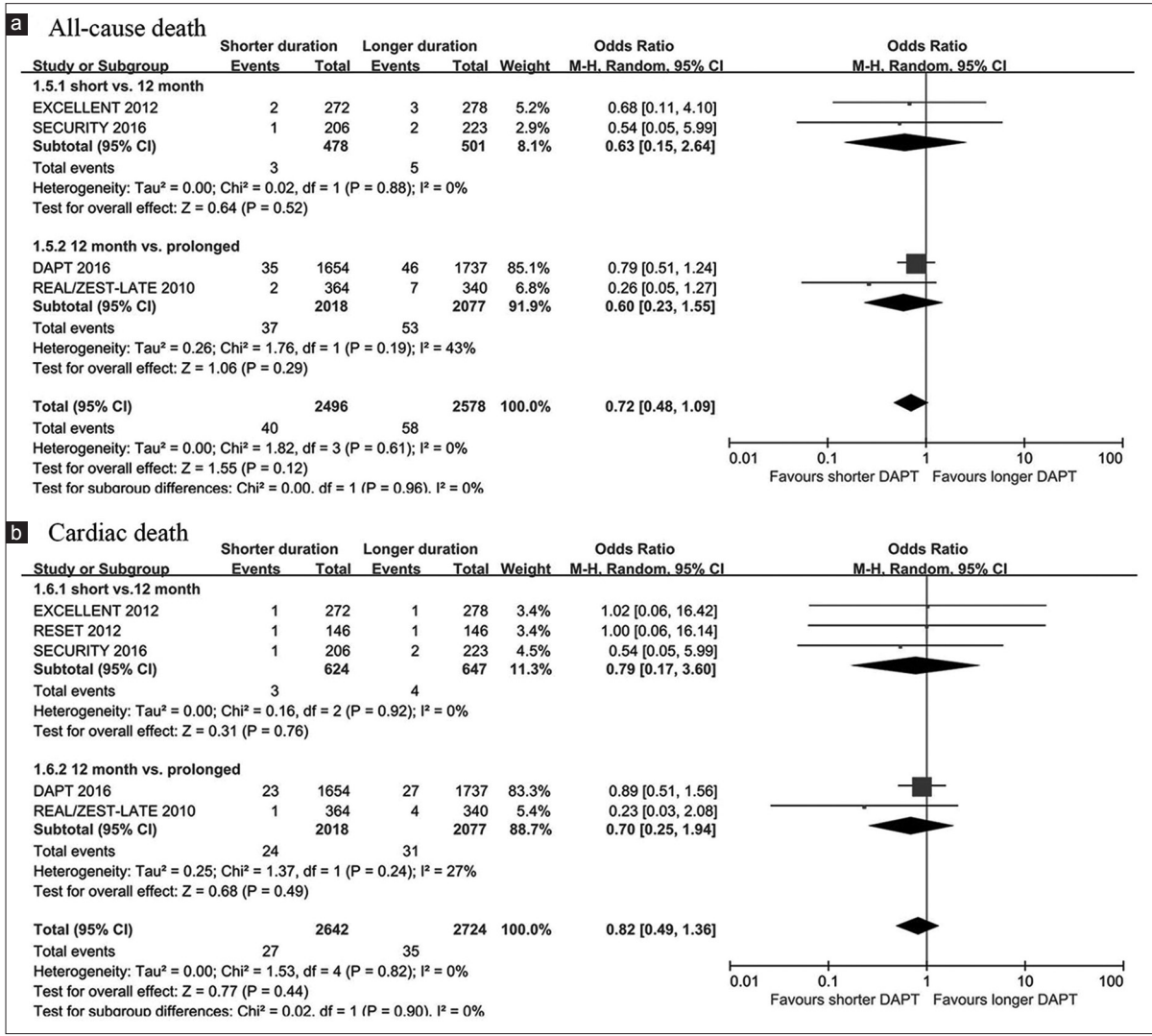


Figure 3: Risk estimates of all-cause death (a) and cardiac death (b) with shorter and longer DAPT duration in patients with DM. DAPT: Dual antiplatelet therapy; DM: Diabetes mellitus.

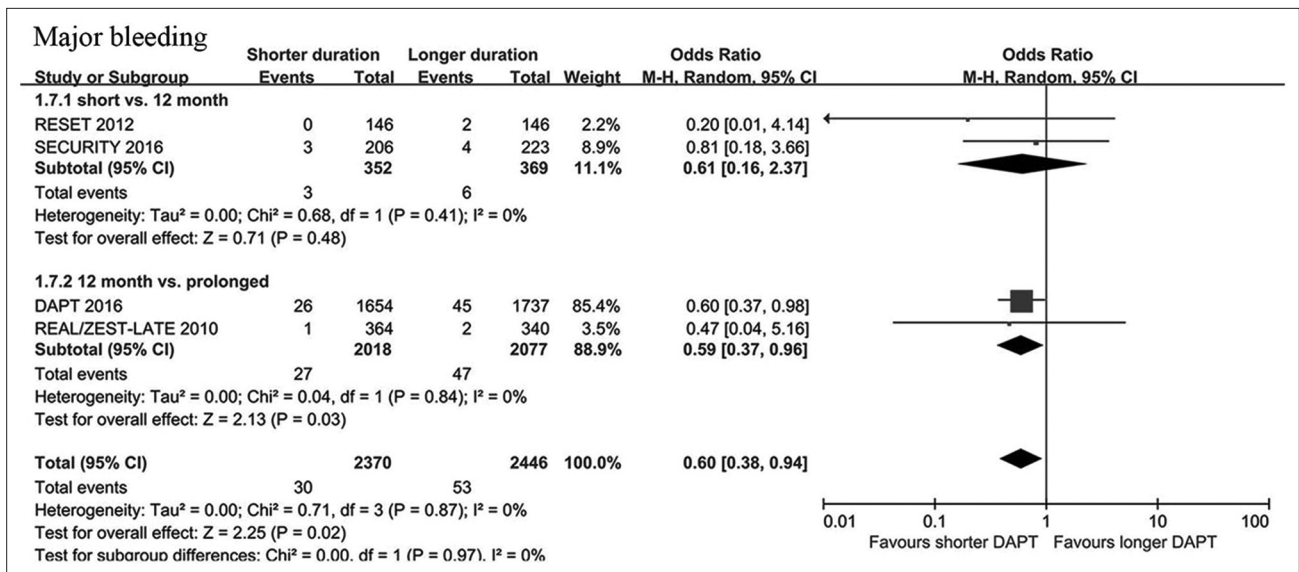


Figure 4: Risk estimates of major bleeding with shorter and longer DAPT duration in patients with DM. DAPT: Dual antiplatelet therapy; DM: Diabetes mellitus.

not beneficial in reducing major adverse cardiovascular events (4.1% vs. 4.9%, $P = 0.76$).^[19]

Registries and clinical trials have found consistently that patients with DM are at higher risk of bleeding compared to patients without DM.^[20-23] We also found that longer-duration DAPT carried an increased risk of bleeding. As patients with DM had activated platelets and increased atherothrombosis and had poor response to clopidogrel,^[24-26] newer antiplatelet agents were recommended. Recent trials have indicated that patients with DM who received prasugrel or ticagrelor had a greater reduction in ischemic events, without increasing bleeding risk compared to clopidogrel.^[27,28]

The DAPT and TL-PAS trials found longer duration of the more intensive DAPT (prasugrel and aspirin), significantly reduced MI, and ST risk with an increased bleeding rate,^[29,30] but the subgroup analyses of patients with DM were lacking. Overall, although patients with DM are a high-risk group, with a stronger indication for more intensive DAPT, the optimal duration for DM remains unknown. More trials are needed to determine whether shorter-duration DAPT is enough for patients with DM who receive more intensive DAPT.

Our meta-analysis had several potential limitations. First, the included subgroup analyses were a preset group of large-scale RCTs, and the data regarding DM were not sufficiently reported. For these reasons, we could not explore the impact of the types or the severity or duration of DM on the optimal DAPT duration. Those requiring insulin therapy had high frequencies of chronic kidney disease, heart failure, and previous MI, and were at an increased risk of adverse cardiovascular events compared to noninsulin-dependent DM.^[31-34] Such a high-risk subgroup might require longer-duration DAPT, and further studies are needed for insulin-dependent DM. Second, as literature is scant concerning DAPT durations for DM, the current meta-analysis was hindered in determining the impact of second-generation DESs or new-generation P2Y12 inhibitors on the optimal DAPT duration. Future studies on this topic are needed. Third, as the included patients were at a low risk of thromboembolic events, our finding could not be generalized to high-risk populations.

In conclusion, the current meta-analysis demonstrates that for patients with DM, longer-duration DAPT has a lower risk of ST after DES implantation, but with an increased risk of bleeding. Our results need to be confirmed in RCTs designed specifically for patients with DM.

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Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

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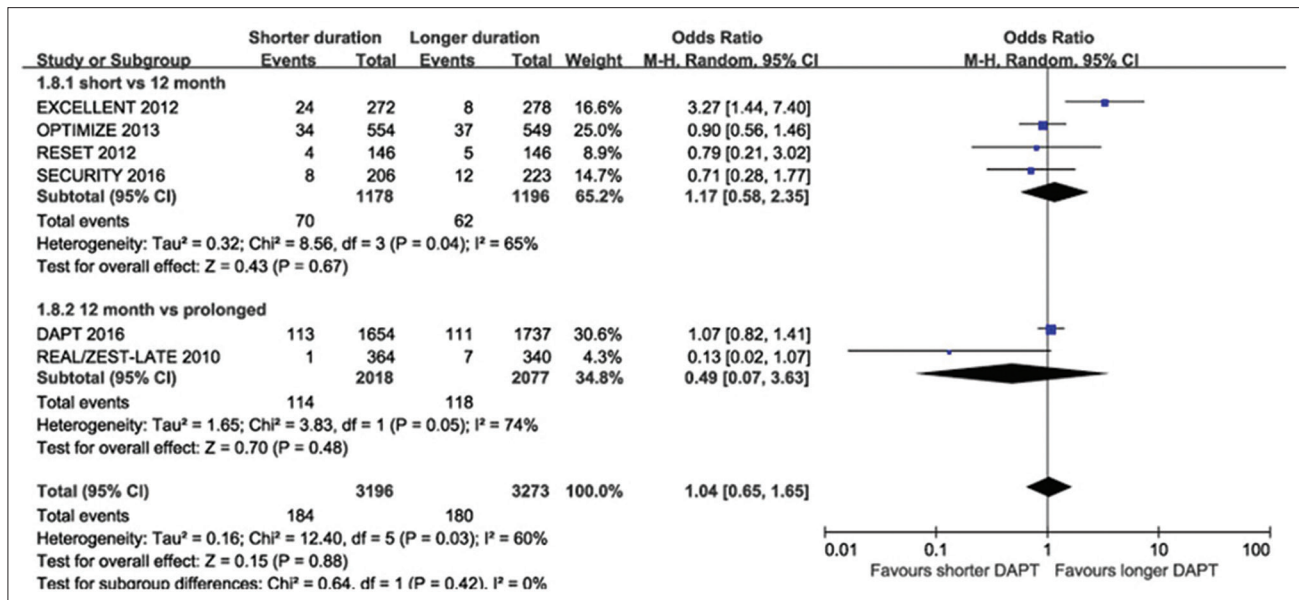
Conflicts of interest

There are no conflicts of interest.

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Supplementary Figure 1: Primary endpoints for shorter versus longer DAPT duration in patients with DM. DAPT: Dual antiplatelet therapy; DM: Diabetes mellitus.

Supplementary Table 1: Study search strategy

Database	Search strategy	Records
Scopus	TITLE-ABS-KEY (antiplatelet OR clopidogrel OR ticagrelor OR prasugrel) AND TITLE-ABS-KEY (stent OR stents) AND diabetes	4156
PubMed	((antiplatelet [Title/Abstract] OR clopidogrel [Title/Abstract] OR ticagrelor [Title/Abstract] OR prasugrel[Title/Abstract])) AND stent [Title/Abstract] AND diabetes	472
Cochrane	There are 158 results from 907144 records for your search on 'antiplatelet OR clopidogrel OR ticagrelor OR prasugrel in title, abstract, keywords and stent in title, abstract, keywords and diabetes in trials'	188
Embase	antiplatelet:ab, ti OR clopidogrel:ab, ti OR ticagrelor:ab, ti OR prasugrel:ab, ti AND stent:ab, ti AND diabetes	1545

Supplementary Table 2: Baseline clinical, angiographic, and procedural characteristics of patients enrolled among trials included in the meta-analysis

Characteristics	REAL/ZEST-LATE [‡]		RESET [‡]		OPTIMIZE [‡]		DAPT		EXCELLENT [‡]		SECURITY	
	Shorter	Longer	Shorter	Longer	Shorter	Longer	Shorter	Longer	Shorter	Longer	Shorter	Longer
Age (years)	61.9	62.0	62.4	62.4	61.3	61.9	62.8	62.5	63.0	62.4	65.5	66.7
Female (%)	30.6	30.0	35.1	37.1	36.5	36.9	29.2	31.0	34.9	36.1	28.2	26.0
DM (%)	27.1 [‡]	25.1 [‡]	30.1 [‡]	28.8	35.4 [‡]	35.3 [‡]	100.0	100.0	37.7 [‡]	38.6 [‡]	100	100
Type 1 (%)	–	–	–	–	10.2	10.4	28.1	29.3	–	–	21.4	19.7
Type 2 (%)	–	–	–	–	25.2	24.9	71.9	70.9	–	–	78.6	80.3
Hypertension (%)	56.9	57.1	62.6	61.4	86.4	88.2	88.6	87.2	72.7	73.8	82.5	80.3
Dyslipidemia (%)	43.5	43.2	58.2	59.9	63.2	63.7	–	–	75.2	76.3	69.4	70.9
Current smoking (%)	32.1	29.8	25.0	22.8	18.6	17.3	21.4	20.1	27.4	25.8	18.9	20.2
Prior MI (%)	3.3	3.8	1.8	1.6	34.6	34.8	24.8	23.2	6.5	3.7	23.8	17.1
Prior PCI (%)	11.8	13.0	3.7	3.0	20.9	19.1	34.1	35.6	9.3	8.6	22.8	17.0
Prior CABG (%)	–	–	0.2	0.6	7.1	8.2	16.4	15.2	1.5	1.0	5.8	7.2
Prior stroke (%)	3.3	4.3	0.0	0.0	2.5	2.5	4.2	5.3	6.5	6.7	–	–
Peripheral arterial disease (%)	–	–	0.0	0.0	2.8	3.0	8.6	8.6	–	–	–	–
Heart failure (%)	–	–	10.0	11.8	4.3	4.2	8.2	7.5	0.6	0.7	–	–
Renal insufficiency (%)	–	–	– [§]	– [§]	7.4	5.8	7.2	6.2	0.8	1.2	– [§]	– [§]
LVEF (%)	59.7	59.2	64.3	63.9	–	–	–	–	61.0	61.4	55.8	55.7
ACS (%)	21.2	22.1	14.6	13.8	31.6 [*]	32.3 [*]	21.4	22.3	51.1 [†]	52.0 [†]	35.9	32.3
Therapy at discharge												
Aspirin + clopidogrel	99.9	99.7	100.0	100.0	100.0	100.0	64.6	68.3	100.0	100.0	99.0	98.7
Aspirin + prasugrel	0.0	0.0	0.0	0.0	0.0	0.0	35.4	31.7	0.0	0.0	0.5	0.0
Multivessel disease	48.1	48.0	42.2	42.9	–	–	–	–	51.9	52.0	54.3	47.8
Bifurcation	12.5	12.1	0.0	0.0	14.7	14.9	–	–	10.2	11.4	10.7	12.1
Stents implanted												
Per patient	1.6	1.8	1.3	1.5	1.6	1.6	11.5	1.4	1.6	1.6	1.6	1.6
Per lesion	1.2	1.3	1.0	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.1	1.2
Stent length per lesion (mm)	30.9	31.8	22.7	22.9	20.4	20.4	19.2	18.1	27.8	28.3	19.2	19.3
Treated vessel												
Left main coronary	2.4	2.9	0.0	0.0	1.2	1.5	0.8	0.9	0.0	0.0	0.0	0.0
Left anterior descending	49.9	48.7	52.7	53.6	47.9	46.6	37.4	38.2	49.6	50.4	39.0	41.0
Left circumflex	18.1	19.9	21.3	19.2	23.4	24.3	24.3	24.1	22.0	21.7	19.0	18.0
Right coronary	29.6	28.5	67.6	69.2	27.6	27.7	33.0	33.2	28.3	27.9	32.0	28.0
Stent type												
First-generation	80.2	80.9	0.0	28.5	0.0	0	36.2	35.5	74.8	74.8	0.0	0.0
Second-generation	18.8	18.7	100.0	71.5	100.0	100.0	53.3	54.0	25.2	25.2	100.0	100.0

*Low-risk ACS (UA or MI <30 days); [†]Low-risk ACS (MI <72 h was excluded); [‡]The characteristics of patients were extracted from the overall population but not only diabetic patients; [§]Patients with serum creatinine >2.0 mg/dl were not included in the study. ACS: Acute coronary syndrome; CABG: Coronary artery bypass grafting; DES: Drug-eluting stent; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; –: Could not be calculated; DAPT: Dual antiplatelet therapy; DM: Diabetes mellitus; UA: Unstable angina.

Supplementary Table 3: Assessments of risk bias

Study, year	Randomization sequence generation	Allocation concealment	Blinding of participants, personnel	Blinding of outcomes assessment	Incomplete outcome data	Selective reporting	Other sources of bias
REAL/ZEST-LATE, 2010	Low risk: A preestablished, computer-generated randomization scheme	Unclear risk	High risk: Open-label study	Low risk	Low risk: 17 lost to follow-up (0.6%), but with an intention-to-treat analysis	Low risk	Low risk
RESET, 2012	Low risk: Web-based response system	Unclear risk	High risk: Open-label study	Low risk	Low risk: 31 lost to follow-up (1.5%), but with an intention-to-treat analysis	Low risk	Low risk
OPTIMIZE, 2013	Low risk: A dedicated web-based system and stratified by the presence of DM and institution	Unclear risk	High risk: Open-label study	Low risk	Low risk: 76 lost to follow-up (2.4%), but with an intention-to-treat analysis	Low risk	Low risk
DAPT, 2014	Low risk: A central interactive voice response system	Unclear risk	High risk: Open-label study	Low risk	Low risk: 571 lost to follow-up (5.7%), but with an intention-to-treat analysis	Low risk	Low risk
EXCELLENT, 2012	Low risk: A web-based online randomization system	Unclear risk	High risk: Open-label study	Low risk	Low risk: 15 lost to follow-up (1%), but with an intention-to-treat analysis	Low risk	Low risk
SECURITY, 2016	Low risk: By electronic case report, and balanced within center by blocks of 4	Unclear risk	High risk: Open-label study	Low risk	Low risk: 263 loss to follow-up (19%), but none excluded from the analysis	Low risk	Low risk

DAPT: Dual antiplatelet therapy; DM: Diabetes mellitus.

Supplementary Table 4: The definition of primary endpoint of RCTs

Study, year	The definition of primary endpoint
EXCELLENT, 2012	TVF: A composite of cardiac death, MI, or TVR
OPTIMIZE, 2013	NACCE: Composite of all-cause death, MI, stroke, or major bleeding
RESET, 2012	NACE: A composite of cardiac death, MI, ST, TVR, or bleeding
SECURITY, 2016	A composite of cardiac death, MI, stroke, definite or probable ST, or BARC Type 3 or 5 bleeding
DAPT, 2014	MACCE: Death, MI, stroke
REAL/ZEST-LATE, 2010	MI or cardiac death

BARC: Bleeding Academic Research Consortium; MACCE: Major adverse cardiac and cerebrovascular event; MI: Myocardial infarction; NACE: Net adverse cardiac event; NACCE: Net adverse cardiac and cerebrovascular event; ST: Stent thrombosis; TVF: Target vessel failure; TVR: Target vessel revascularization; DAPT: Dual antiplatelet therapy; RCTs: Randomized controlled trials.