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Outcomes of ≤6-month versus 12-month dual antiplatelet therapy after drug-eluting stent implantation

A meta-analysis and meta-regression

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Abstract

Background: The benefit of ≤6-month compared with 12-month dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) with drug-eluting stent (DES) placement remains controversial. We performed a meta-analysis and meta-regression of ≤6-month versus 12-month DAPT in patients undergoing PCI with DES placement.

Methods: We conducted electronic database searches of randomized controlled trials (RCTs) comparing DAPT durations after DES placement. For studies with longer follow-up, outcomes at 12 months were identified. Odds ratios and 95% confidence intervals were computed with the Mantel–Haenszel method. Fixed-effect models were used; if heterogeneity (I^2) > 40 was identified, effects were obtained with random models.

Results: Nine RCTs were included with total n = 19,224 patients. No significant differences were observed between ≤6-month compared with 12-month DAPT in all-cause mortality (OR 0.87; 95% confidence interval (CI): 0.69–1.11), cardiovascular (CV) mortality (OR 0.89; 95% CI: 0.66–1.21), non-CV mortality (OR 0.85; 95% 0.58–1.24), myocardial infarction (OR 1.10; 95% CI: 0.89–1.37), stroke (OR 0.97; 95% CI: 0.67–1.42), stent thrombosis (ST) (OR 1.37; 95% CI: 0.89–2.10), and target vessel revascularization (OR 0.95; 95% CI: 0.77–1.18). No significant difference in major bleeding (OR 0.72; 95% CI: 0.49–1.05) was observed, though the all-bleeding event rate was significantly lower in the ≤6-month DAPT group (OR 0.76; 95% CI: 0.59–0.96). In the meta-regression analysis, a significant association between bleeding events and non-CV mortality with 12-month DAPT was found, as well as between ST and mortality in addition to MI with ≤6-month DAPT.

Conclusion: DAPT for ≤6 months is associated with similar mortality and ischemic outcomes but less bleeding events compared with 12-month DAPT after PCI with DES.

Abbreviations: ACC = American College of Cardiology, ACS = acute coronary syndrome, AHA = American Heart Association, BARC = Bleeding Academic Research Consortium, BMS = bare-metal stent, CAD = coronary artery disease, CI = confidence interval, CTO = chronic total occlusion, CV = cardiovascular, DAPT = dual antiplatelet therapy, DES = drug-eluting stent, ESC = European Society of Cardiology, LVEF = left ventricular ejection fraction, MI = myocardial infarction, NNH = number needed to harm, NNT = number needed to treat, NSTEMI = non-ST elevation myocardial infarction, OR = odds ratio, RCT = randomized controlled trial, ST = stent thrombosis, STEMI = ST-elevation myocardial infarction, TIMI = Thrombolysis In Myocardial Infarction, TVR = target vessel revascularization.

Keywords: drug-eluting stent, dual antiplatelet therapy, percutaneous coronary intervention

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1. Introduction

Percutaneous coronary intervention (PCI) with implantation of drug-eluting stents (DES) is associated with reduced restenosis and target lesion revascularization rates compared with bare-metal stents (BMS).[1] DES are however associated with increased risks of death and MI after premature discontinuation of dual antiplatelet therapy (DAPT) compared with BMS, mainly due to a higher incidence of late and very late stent thrombosis (ST).[2] On the other hand, prolonged treatment with DAPT is associated with increased risk of bleeding complications and morbidity.[3] More recently, second-generation DES have been reported to be associated with a lower risk of ST compared with first-generation DES,[4] calling the need for prolonged DAPT into question. In perioperative situations, clinical decision-making has to take into consideration the balance between bleeding risk and thrombotic risk in relation to surgical risk as well as the sequelae of rescheduling noncardiac surgery for high-risk stent patients.

Defining the optimal duration of DAPT after DES implantation is the objective of several randomized controlled trials (RCTs) and meta-analyses.[3,5] Recently, an updated version of the American College of Cardiology/American Heart Association (ACC/AHA) guideline on duration of DAPT in patients with coronary artery disease (CAD) was released with significant modifications from the past.[6] Both the updated ACC/AHA and European Society of Cardiology (ESC)[7] guidelines now recommend DAPT after DES placement for least 6 months in patients with stable CAD and at least 12 months in patients with acute coronary syndromes (ACS), with possible adjustment based on individual bleeding risk. In addition, elective noncardiac surgery for patients on DAPT following DES implantation is now a Class 1 recommendation in the current update, after a 6-month minimum DAPT duration, compared with the older recommendation of a minimum of 12 months. This marks a clearly significant change in the perioperative management of these patients.

Although a previously published meta-analysis investigated the risk profile of short-term versus long-term DAPT, it included the entire durations of short-term (including 12 months) and long-term DAPT (up to 36 months).[8] Other previously published meta-analyses included fewer RCTs.[9–11] An updated meta-analysis evaluating the risks and benefits of DAPT for $\leq$6 months compared with the exact time point of 12 months is lacking. Our aim was to undertake a systematic review and meta-analysis of RCTs evaluating efficacy and safety of $\leq$6-month compared with 12-month DAPT after PCI with DES implantation.

2. Methods

2.1. Search strategy

We developed a protocol for this systematic review, which was posted online and registered in PROSPERO (International prospective register of systematic reviews, CRD42016036772). The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting recommendations statement for reporting systematic reviews and meta-analyses of RCTs[12] was applied (see Supplemental Digital Table 1, http://links.lww.com/MD/B492). We performed a comprehensive search of PubMed, CENTRAL, EMBASE, The Cochrane Central Register of Controlled Trials, the ClinicalTrials.gov Website, Google Scholar databases, the Scientific Session abstracts in Circulation, Journal of the American College of Cardiology, European Heart Journal, and American Journal of Cardiology from January 1990 to September 2016. Oral presentations and/or expert slide presentations were included (searched on the TCT (www.tctmd.com), EuroPCR (www.europcr.com), ACC (www.acc.org; content.onlinejacc.org), AHA (www.heart.org; circ.ahajournals.org/), and ESC (www.escardio.org) websites). We also performed manual searches of reference lists of studies, reviews, editorials, and letters, as well as related conference proceedings.

Search term keywords included: DES, percutaneous coronary intervention, antiplatelet therapy, ticagrelor, prasugrel, clopidogrel, and aspirin. The search was limited to human studies. Institutional Review Board approval was not obtained because this systematic review and meta-analysis do not involve human subjects.

2.2. Inclusion criteria

Studies meeting the following criteria were included: RCT design; evaluation of patients post-DES implantation including subjects randomized to $\leq$6-month versus $\geq$12-month DAPT with minimum follow-up period of 1 year. Two reviewers (PV and DB) independently extracted data. Disagreements were resolved by consensus or, if necessary, by a third party (PC).

2.3. Study endpoints

Ischemic endpoints were defined as incidence of ST (definite or probable), all-cause mortality, cardiovascular (CV) mortality, non-CV mortality, stroke, recurrent myocardial infarction (MI), and target vessel revascularization (TVR). The safety endpoint was defined as incidence of all-bleeding events and major bleeding events. Trial-specific definitions were used for secondary efficacy and safety endpoints. Short-term durations of 3 or 6 months were categorized as "$\leq$6 months duration." When publically available, outcomes at 12 months were extracted from the original literature and included in the "12-month duration" group. This applied to studies with longer follow-up, as well. If 12-month outcomes had not been published, original study authors were personally contacted and asked to provide the missing information.

2.4. Statistical analysis

Data were summarized across treatment arms using the Mantel–Haenszel odds ratio (OR) fixed-effects model. We evaluated heterogeneity of effects using the I-squared (I^2) statistic. In cases of heterogeneity (defined as $I^2 > 40\%$), random effects models were used. To address publication bias, we used 4 methods: funnel plots, Begg–Mazumdar test, Egger test, and Duval and Tweedie test. Sensitivity analyses were performed using the one-study-out method, addressing the influence of each study by testing whether deleting each one individually would significantly change the pooled results of the meta-analysis; a random effects model was also applied to all outcomes to assess if changes in the final effect would be observed. Finally, chronological cumulative analyses were used to test if the effect size and precision shifts were based on technical advancement of stents, antithrombotic therapy, and cardiac catheterization techniques.[13] The net clinical benefit (composite ischemic events minus major bleeding events) was defined as number needed to treat (NNT) minus number needed to harm (NNH). Furthermore, we performed a meta-regression of the effect sizes of ST and bleeding on mortality, TVR, and new MI. ORs for treatment effects in individual trials were log-transformed before being used

as independent variables in linear meta-regression analyses. Statistical analyses were performed by the Comprehensive Meta-Analysis version 2.0 software (Biostat, Inc., Englewood NJ). Two authors independently assessed the risk of bias using standard criteria defined in the Cochrane Handbook for Systematic Reviews of Interventions.

3. Results

The search strategy identified a total of 817 potential articles. After removal of duplicates and articles not meeting inclusion criteria, we screened 131 titles and abstracts. Of these, 12 were selected for further review (see flow diagram in Fig. 1). Finally, 9 RCTs[14–22] satisfied inclusion criteria, all of which were published in English language journals as full manuscripts. The primary characteristics of included trials are presented in Table 1. Overall, the 9 RCTs enrolled a total of 19,224 patients. Seven trials used a 6-month time frame for the shorter duration of DAPT with exception of RESET and OPTIMIZE, which evaluated a 3-month period. Duration of the longer DAPT time frame varied between 12 months (in 5 trials), 18 months (I-LOVE-IT 2), 24 months (PRODIGY and SECURITY), and 36 months (ITALIC). We obtained complete data for 12-month outcomes. SECURITY and ITALIC included patients treated with clopidogrel, ticagrelor, or prasugrel plus aspirin, while in the remaining 7 trials clopidogrel plus aspirin was used. Randomization occurred before or around the time of PCI, with exception of ISAR SAFE, which randomized patients after the first 6 months of DAPT. Different bleeding definitions varied across trials. TIMI definitions[23] were used in EXCELLENT, RESET, ISAR-SAFE, ITALIC, and IVUS-XPL. REPLACE-2,[24] and GUSTO[25] criteria were used in OPTIMIZE. Bleeding Academic Research Consortium (BARC)[26] definitions of bleeding were used in SECURITY, PRODIGY, and I-LOVE-IT 2.

3.1. Quantitative data synthesis

3.1.1. Ischemic endpoints. No statistically significant benefit for ≤6-month compared with 12-month DAPT was found in terms of all-cause mortality (OR 0.87; 95% CI: 0.69–1.11), CV mortality (OR 0.89; 95% CI: 0.66–1.21), or non-CV mortality (OR 0.85; 95% 0.58–1.24). All-cause mortality occurred in 130 (1.35%) patients in the ≤6-month DAPT compared with 149 (1.54%) patients in the 12-month DAPT group. CV death occurred in 80 (0.83%) patients in the ≤6-month DAPT compared with 90 (0.93%) patients in the 12-month DAPT group, while non-CV death occurred in 50 (0.52%) patients in the ≤6-month DAPT compared with 59 (0.61%) patients in the 12-month DAPT group. Results are shown in Fig. 2.

The stroke rate did not statistically significantly differ between the 2 groups; 53 (0.55%) cerebrovascular events were observed in the ≤6-month DAPT versus 55 (0.57%) events in the 12-month DAPT group (OR 0.97; 95% CI: 0.67–1.42). Although no statistically significant differences were observed, there were more MI and ST events in the short-term compared with the long-term group. For MI, 175 (1.82%) events were observed in the ≤6-month DAPT compared with 161 (1.66%) events in the 12-month DAPT group (OR 1.10; 95% CI: 0.89–1.37). For ST, 49 (0.51%) events were observed in the ≤6-month DAPT group compared with 36 (0.37%) events in the 12-month DAPT group (OR 1.37; 95% CI: 0.89–2.10). However, in terms of TVR, 171 (2.59%) events were observed in the ≤6-month DAPT group compared with 180 (2.70%) events in the 12-month DAPT group (OR 0.95; 95% CI: 0.77–1.18). Results are shown in Fig. 3.

3.1.2. Bleeding endpoints. There was a statistically significant difference favoring ≤6-month DAPT for all-bleeding events (OR 0.76; 95% CI: 0.59–0.96), with 121 (1.36%) events in the ≤6-month DAPT group compared with 160 (1.78%) events in the 12-month DAPT group. No statistically significant difference was observed in terms of major bleeding events between the 2 groups (OR 0.72; 95% CI: 0.49–1.05), with 44 (0.45%) events in the ≤6-month DAPT group and 62 (0.64%) events in the 12-month DAPT group. Results are shown in Fig. 4.

3.1.3. Number needed to harm. The absolute difference in event rates yielded a NNH of 234 patients to cause one bleeding event with 12 months compared with ≤6-month DAPT.

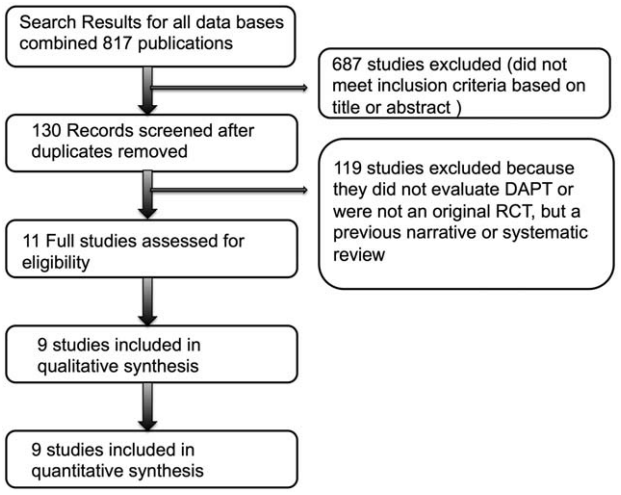

Figure 1. Summary of evidence search and selection. A total of 9 out of 817 studies initially identified were included after screening titles and reviewing full manuscripts. DAPT = dual antiplatelet therapy, RCT = randomized controlled trial.

3.2. Sensitivity analyses

Sensitivity analyses involving the removal of each of the RCTs one at a time, did not demonstrate any changes in the overall primary and secondary outcomes (see Supplemental Digital Fig. 1.A-I, http://links.lww.com/MD/B492). No changes in the final effect for all the outcomes were observed when random models were applied (see Supplemental Digital Fig. 2.A-I, http://links.lww.com/MD/B492). In the chronological cumulative analysis for each outcome no significant changes in the final effect outcomes were observed (see Supplemental Digital Fig. 3.A-I, http://links.lww.com/MD/B492).

3.3. Meta-regression analysis

A significant association was found between all-bleeding events and non-CV mortality ($P = 0.02$) with 12-month DAPT, with no significant associations were found between all-bleeding events and all-cause mortality or CV mortality with 12-month DAPT. No significant associations were found between major bleeding events and all-cause mortality, CV mortality, and non-CV mortality with 12-month DAPT; see Supplemental Digital Fig. 4, http://links.lww.com/MD/B492.

Table 1

Characteristics of included studies.

Trial	EXCELLENT		RESET		ITALIC		OPTIMIZE		SECURITY		ISAR-SAFE		PRODIGY		I-LOVE-IT 2		IVUS-XPL	
Study Population	N=1443		N=2117		N=1822		N=3119		N=1399		N=4005		N=2013		N=1829		N=1400	
Duration of DAPT	6 mo	12 mo	3 mo	12 mo	6 mo	24 mo	3 mo	12 mo	6 mo	12 mo	6 mo	12 mo	6 mo	24 mo	6 mo	12 mo	6 mo	24 mo
Follow Up	Up to 12 mo		Up to 12 mo		Up to 36 mo		Up to 12 mo		Up to 24 mo		Up to 6 mo		Up to 24 mo		Up to 18 mo		Up to 12 mo	
Primary endpoint	Composite of cardiac death, MI, or ID-TVR		Composite of cardiac death, MI, ST, ID-TVR, and TIMI major or minor bleeding		Composite of death, MI, urgent TVR, stroke, major bleeding		Composite of all-cause of death, MI, stroke, or major bleeding		Composite of cardiac death, MI, stroke, definite or probable stent thrombosis or bleeding (type 3 or 5 bleeding)		Composite of death, MI, stent thrombosis, stroke, TIMI major bleeding		Composite of death of any cause, myocardial infarction, or cerebrovascular accident		Composite of cardiac death, target vessel myocardial infarction, clinically indicated TVR		Composite of cardiac death, myocardial infarction, stroke, or TIMI major bleeding	
Exclusion criteria	MI within 72 h; cardiogenic shock; LVEF <25%; prior stent in target vessel; hgb <10 g/dL or PLT <100,000; creatinine >3.0 mg/dL or HD dependent; hepatic failure; major bleeding within 3 mo or major surgery within 2 mo; contraindication to antiplatelet therapy; true bifurcation lesions requiring 2 stents strategy; left main stenosis >50%; CTO; <1 y life expectancy		STEMI within 48 h; cardiogenic shock; LVEF <40%; cerebral/peripheral atherosclerotic disease; thromboembolic disease; prior ST; left main disease; CTO; restenotic lesion		Prior DES implantation within 1 y, PLT <100.000 or bleeding disorder, OAC or abciximab during hospital stay, contraindications to antiplatelet therapy, major surgery within preceding 6 wk, evidence of GI or GU bleeding, severe liver failure, any surgery scheduled during the year after enrollment, <2 y life expectancy		Primary or rescue PCI for STEMI; BMS in nontarget vessel in the last 6 mo; previous DES; saphenous vein graft lesion; in-stent restenosis of DES		STEMI within 48 h, NSTEMI in previous 6 mo, LVEF ≤30%; unprotected left main, in-stent restenosis, saphenous vein graft, contraindication to antiplatelet therapy; CKD; pregnancy or on lactation; active bleeding or significant risk of bleeding; uncontrolled hypertension; <2 y life expectancy		Age <18 years; active bleeding, bleeding diathesis, hx of intracranial bleeding, previous stent thrombosis; STEMI or NSTEMI during the last 6 mo after DES, previous ST, DES in left main at index intervention, OAC, planned major surgery within the next 6 mo with the need to d/c antiplatelet therapy, <1 y life expectancy		Age <18 y; known allergy to acetylsalicylic acid or clopidogrel; planned surgery within 24 mo of PCI unless DAPT could be maintained throughout perisurgical period; history of bleeding diathesis; major surgery within 15 d; active bleeding or previous stroke in the past 6 mo; concomitant or foreseeable need for oral anticoagulation therapy; pregnancy; life expectancy <24 mo		Known intolerance to study drug, metal alloys, or contrast media; life expectancy <1 y; restenotic lesion; stent implantation within 1 y; left ventricular ejection fraction <40%; severe renal or hepatic dysfunction; hemodynamic instability; planned surgery within 6 mo after index procedure; childbearing potential within 1 y; clinical indications of inability to tolerate DAPT for 12 mo		Age <20 and >80 y; STEMI within 48 h; contraindication to antiplatelet agents, bleeding history within 3 mo; known intolerance to study drugs; history of CVA, peripheral artery occlusive disease, thromboembolic disease or stent thrombosis; severe hepatic dysfunction; renal dysfunction (serum creatinine >2.0 mg/dL); significant leucopenia, neutropenia, thrombocytopenia, anemia, or known bleeding diathesis; cardiogenic shock; LVEF <40%; pregnancy or potential childbearing; life expectancy <1 y; left main disease requiring PCI; bifurcation lesion with 2-stent technique; CTO; DES implantation within 6 mo; in-stent restenosis lesion	
	Short	Long	Short	Long	Short	Long	Short	Long	Short	Long	Short	Long	Short	Long	Short	Long	Short	Long
No. of implanted stents, mean (SD)	1.6 (0.9)	1.6 (1.0)	1.27 (0.54)	1.27 (0.68)	1.7 (1.0)	1.7 (1.0)	1.6 (0.8)	1.6 (0.8)	1.64 (0.93)	1.60 (0.91)	1.67 (0.95)	1.69 (0.97)	1.57 (0.94)	1.52 (0.86)			1.6 (0.7)	1.6 (0.8)
Everolimus-ES, no. (%)	539 (74.8)	540 (74.8)	–	404 (30.0)	953 (100.0)	941 (100.0)	–	–	224 (20.1)	233 (20.3)	948 (47.5)	988 (49.3)	245 (24.9)	248 (25.1)	–	–	699 (100.0)	701 (100.0)
Bioresorbable everolimus-ES, no. (%)	–	–	–	–	–	–	–	–	–	–	10 (0.5)	5 (03)	–	–			–	–
Sirolimus-ES, no. (%)	182 (25.2)	182 (25.2)	–	383 (28.5)	–	–	–	–	–	–	499 (25)	482 (24.1)	–	–			–	–
Biodegradable sirolimus-ES, no. (%)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	909 (100.0)	920 (100.0)	–	–
Paclitaxel-ES, no. (%)	–	–	–	–	–	–	–	–	–	–	44 (2.2)	46 (2.3)	245 (24.9)	245 (24.8)	–	–	–	–
Zotarolimus-ES, no. (%)	–	–	–	559 (41.5)	–	–	1563 (100.0)	1556 (100.0)	470 (42.1)	464 (40.3)	312 (15.7)	294 (14.7)	–	–	–	–	–	–
Biomatrix-ES, no. (%)	–	–	–	–	–	–	–	–	80 (7.2)	86 (7.5)	–	–	–	–	–	–	–	–
Biolimus-ES, no. (%)	–	–	–	–	–	–	–	–	283 (25.3)	314 (27.3)	165 (8.3)	171 (8.5)	–	–	–	–	–	–
Bare-metal stent, no. (%)	–	–	–	–	–	–	–	–	16 (1.4)	11 (1)	8 (0.4)	6 (0.3)	246 (24.9)	246 (25.0)	–	–	–	–
Time to randomization	At index PCI		At index PCI		At index PCI		At index PCI		At index PCI		6 mo after index PCI		1 mo after index PCI		6 mo after index PCI		At index PCI	
Bleeding definition	TIMI		TIMI		TIMI		REPLACE-2 and GUSTO		BARC		TIMI		BARC		BARC		TIMI	

BARC = Bleeding Academic Research Consortium, BMS = bare-metal stent, CTO = chronic total occlusion, DAPT = dual antiplatelet therapy, DES = drug eluting stent, GUSTO = global use of strategies to open occluded arteries, ID-TVR = ischemia driven target vessel revascularization, ISR = in-stent restenosis, LVEF = left ventricular ejection fraction, MI = myocardial infarction, NSTEMI = non-ST segment-elevation myocardial infarction, OAC = oral anticoagulant, PCI = percutaneous coronary intervention, REPLACE-2 = randomized evaluation in PCI linking angiomax to reduced clinical events-II, ST = stent thrombosis, STEMI = ST segment elevation myocardial infarction, TIMI = Thrombolysis In Myocardial Infarction.

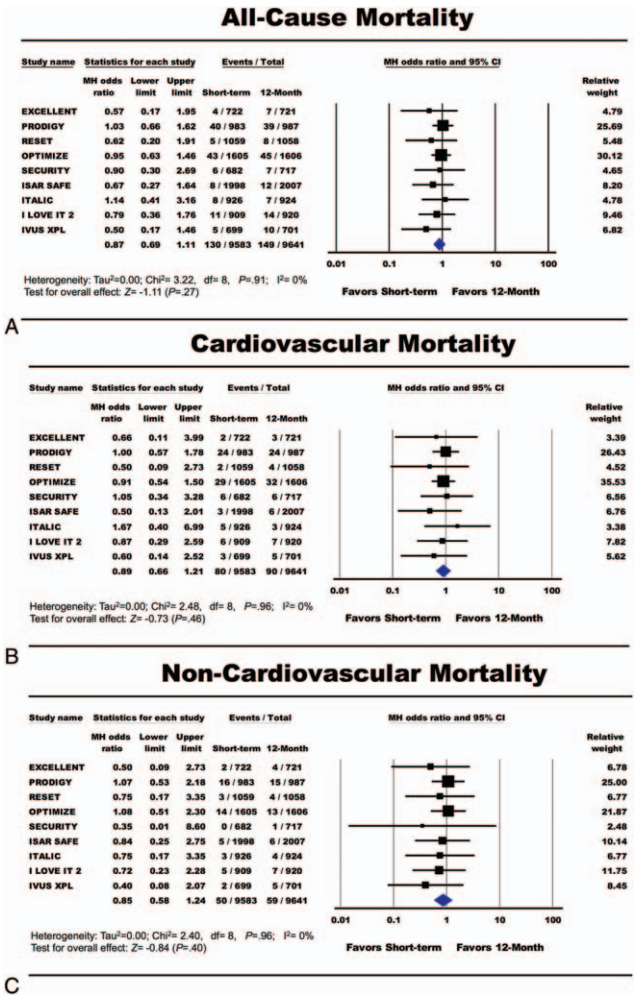

Figure 2. Forest plot of the odds ratios of (A) all-cause mortality, (B) cardiovascular mortality, and (C) noncardiovascular mortality in patients treated with ≤6-month DAPT compared with 12-month DAPT. Diamonds indicate the overall summary estimates (the width of the diamond represents 95% CI, the width of the shaded square indicates population size). CI = confidence interval, DAPT = dual antiplatelet therapy.

A significant association was found between ST events and all-cause mortality ($P=0.01$), CV mortality ($P=0.01$), and MI ($P=0.02$) with ≤6-month DAPT. No significant association was found between ST and TVR with ≤6-month DAPT; see Supplemental Digital Fig. 5, http://links.lww.com/MD/B492.

3.4. Bias

Funnel plot distribution for efficacy and safety endpoints is shown in see Supplemental Digital Fig. 6, http://links.lww.com/MD/B492. The funnel plot did not reveal asymmetry, suggesting lack of bias for all outcomes except for definite and probable ST. However, after quantifying the observed bias with other methods (Begg–Mazumdar, Egger, and Duval and Tweedie trim and fill test), there was no evidence of publication bias (see Supplemental Digital Fig. 7.A-I for each individual outcome, http://links.lww.com/MD/B492). Individual study quality appraisal and risk of bias for the included RCTs are summarized in Supplemental Digital Table 2, http://links.lww.com/MD/B492.

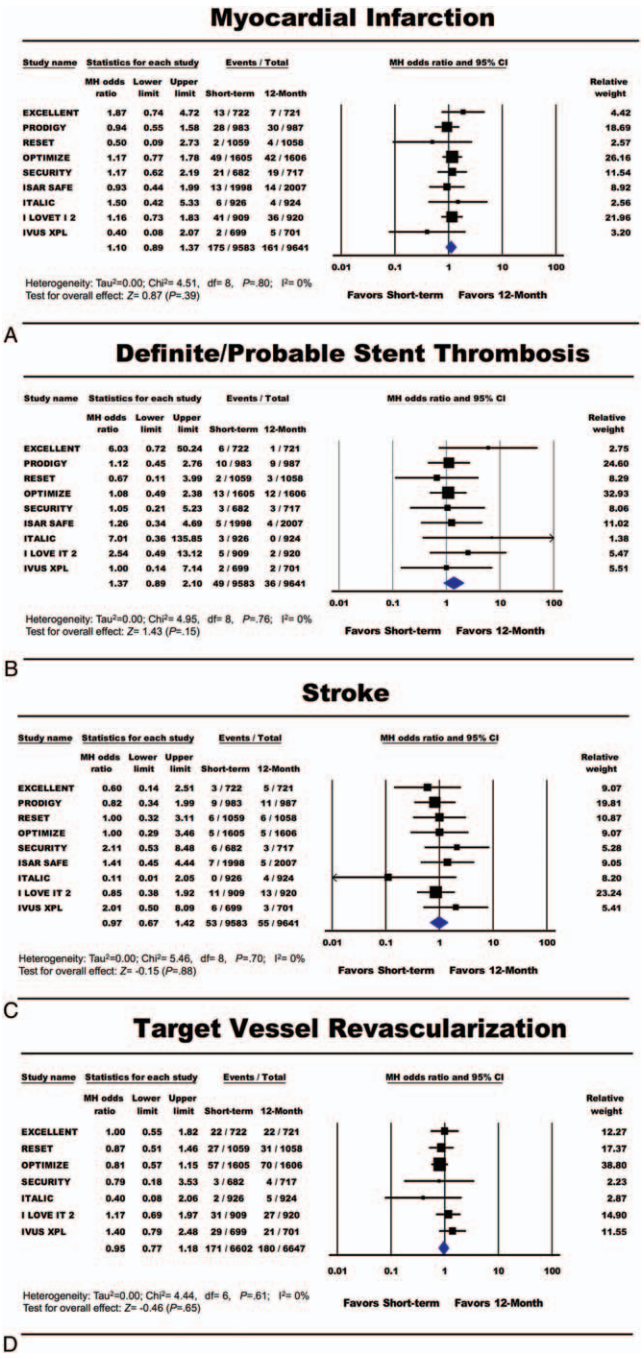

Figure 3. Forest plot of the odds ratios of (A) myocardial infarction, (B) stroke, (C) definite/probable stent thrombosis, and (D) target vessel revascularization in patients treated with ≤6-month DAPT compared with 12-month DAPT. Diamonds indicate overall summary estimates (the width of the diamond represents 95% CI, the width of the shaded square indicates population size). CI = confidence interval, DAPT = dual antiplatelet therapy.

4. Discussion

The optimal duration of DAPT after PCI with DES implantation has not been clearly defined. Therefore, we undertook a systematic review and updated meta-analysis comparing 2 DAPT strategies with specific durations of 6 months or less compared with 12 months. This meta-analysis is one of the largest meta-analyses thus far, enrolling 19,224 patients from 9 RCTs and analyzing only individual endpoints in an effort to minimize the

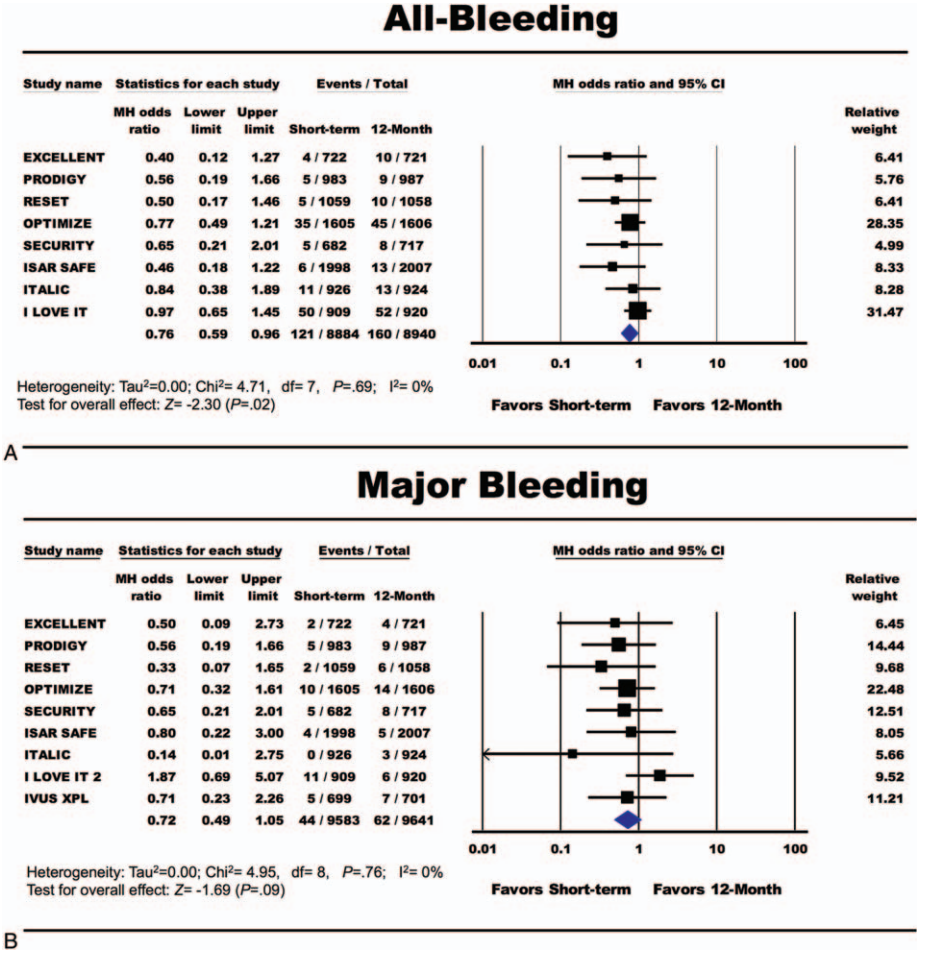

Figure 4. Forest plot of the odds ratio of (A) all-bleeding and (B) major bleeding events in patients treated with ≤6-month DAPT compared with 12-month DAPT. Diamonds indicate overall summary estimates (the width of the diamond represents 95% CI, the width of the shaded square indicates population size). CI = confidence interval, DAPT = dual antiplatelet therapy.

ambiguity among different definitions used for composite endpoints in the individual trials. In this meta-analysis, we constructed endpoints based on individual endpoints from each trial, contrary to a previously published meta-analysis, which utilized the composite endpoints reported in each trial.[3] We also specifically defined a 12-month DAPT duration compared to a prior meta-analysis, which defined "long-term" based on each individual trial, ranging from 12 to 36 months.[8] Of note-this is also one of the first meta-regressions performed addressing the association between of ST and bleeding events with mortality, TVR, and new MI.

Our meta-analysis has 4 main findings. First, ≤6-month compared with 12-month DAPT is associated with a reduced risk of bleeding events. Second, no statistically significant difference in ischemic and thrombotic events was observed between ≤6-month versus 12-month DAPT. Third, a statistically significant association was found between all-bleeding events and non-CV mortality with 12-month DAPT, as well as between ST events and all-cause mortality, CV, and MI with ≤6-month DAPT. Based on our results, ≤6-month DAPT is noninferior to 12-month DAPT in terms of efficacy endpoints. Finally, ≤6-month DAPT is associated with less bleeding episodes.

Prolonged DAPT has been thought to be protective for ST and its resulting complications including death. The evidence for prolonged therapy after stent implantation is based on trials evaluating either BMS or first generation DES.[27] The widespread use of second- and third-generation DES, which have a similar safety profile as BMS, call the utility of long-term DAPT into question. Furthermore, whether prolonged DAPT duration can prevent late ST is debatable. Our findings are discordant with the DAPT trial,[28] which showed that overall ischemic event rates and ST were lower with 30 rather than 12 months of DAPT after stenting, the rate of MI not related to stenting was also lower (1.8% vs 2.9%; hazard ratio 0.59; $P < 0.001$). However, the risk of bleeding was increased. Moreover, a recently published meta-analysis which analyzed 12-month versus prolonged DAPT duration.[11] The authors reported that continuation of DAPT beyond 1 year was not associated with lower risk of ST, lower rates of major adverse CV, and cerebrovascular events, but did confer a higher bleeding risk. Our meta-regression analysis reflects the aforementioned findings, with a significant association between bleeding and non-CV mortality with 12-month DAPT, results also consistent with the findings of the DAPT trial[28] where bleeding events were related to trauma and cancer causes, in addition to the significant association between ST and MI, as well as mortality with short-term DAPT.

Even if DAPT prolongation could decrease ST, the benefit of preventing that event may not outweigh the risk of bleeding with prolonged DAPT.[29] For instance, the CURE PCI trial reported a 31% relative risk reduction in ischemic events following the

extension of clopidogrel therapy for a mean of 8 months beyond the standard 4-week treatment after BMS.[30] On the other hand, the reduction in ischemic events in the main CURE trial[31] occurred at an expense of a 38% increased risk of major bleeding events. Advocates of prolonged DAPT also argue for the benefit of prolonged DAPT in reducing ischemic events. However, based on recent evidence, the benefit of DAPT with regard to preventing ischemic events may occur mainly during the first 6 months of treatment.[27]

In the contemporary era of DES, ST, and bleeding have a different impact on adverse events. Extra attention should be paid to identify the group of patients that would benefit from >6-month DAPT. For example, some patient groups may derive greater benefit, such as those with complex PCI, less than optimal stenting result, prior ST or a CV ischemic event within the first 12 months of DAPT, long lesions, thrombus-containing lesions, and implantation of an older-generation DES.[32] Based on the EXCELLENT trial,[14] diabetic patients may benefit from prolonged DAPT because of their increased proinflammatory and prothrombotic state. Additionally, a high prevalence of aspirin resistance has been demonstrated in this population. On the other hand, patients with advanced age or chronic kidney disease that have a high bleeding risk may benefit from ≤6-month DAPT. Clearly the latter 2 are an example of higher-risk subsets of patients need careful assessment of risk/benefit relating to DAPT cessation prior to noncardiac surgery. Patients with acute coronary syndrome (ACS) and high-risk features were not enrolled in the majority of the included RCTs. Therefore, our results do not apply to this patient population. Further studies evaluating 12-month or shorter duration of DAPT are warranted in the aforementioned high-risk group patients.

The superiority of the newer and more potent P2Y12 inhibitors prasugrel and ticagrelor over clopidogrel in reducing ischemic endpoints has been established in recent trials of patients with ACS, though at the expense of bleeding events.[33,34] Nearly all trials included in this meta-analysis utilized clopidogrel, and thus, conclusions on safety outcomes for the newer medications cannot be drawn from our study. The efficacy of the newer agents compared with clopidogrel-based DAPT needs to be assessed in specifically designed studies.

We propose that the decision of DAPT duration should be tailored to each patient according to individual bleeding and ischemic risks.

4.1. Limitations

This meta-analysis has several limitations. First of all, this meta-analysis was performed on study-level data. Second, the studies included in the meta-analysis enrolled a heterogeneous population, utilized a variety of different study protocols, endpoint definitions, and short DAPT durations. Third, despite pooling data from RCTs with 19,224 patients, the total number of events was relatively low and thus limits the strength of the conclusion on differences in rare events such death and ST. Moreover, most of these studies excluded high-risk patients and enrolled low-risk patients, many of whom remained event-free after index PCI; thus, our findings are not generalizable to high-risk patients such as those with left main artery disease or high-risk lesions. Lastly, different stent types and generations were utilized, leaving the question of variable DAPT duration for each individual DES platform open.

Despite these limitations, the consistency of magnitude, the directionality of the overall effect, and the stability of the results after sensitivity analyses support the validity of the conclusions. These data represent a relevant contribution to define the optimal duration of DAPT after DES implantation.

5. Conclusion

Based on this meta-analysis and meta-regression, ≤6-month DAPT may be a reasonable strategy in certain patients to help decrease the bleeding risk with comparable efficacy against ST and ischemic complications. Clinicians should utilize the results of this analysis and translate them to the individual patient keeping in mind that 12-month DAPT bleeding risk seems to be significantly associated with non-CV mortality, whereas ≤6-month DAPT seems to be significantly associated with CV mortality and new MI. Therefore, DAPT duration-shortening should be individualized to each patient weighing the bleeding versus thrombotic risk.

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