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The optimal duration of dual antiplatelet therapy in patients receiving percutaneous coronary intervention with drug-eluting stents

Olusegun Sheyin[1], Xavier Perez[1], Bredy-Pierre-Louis[2], Damian Kurian[2]

[1]Department of Medicine, Harlem Hospital Center, Columbia University College of Physicians and Surgeons, New York, United States
[2]Division of Cardiology, Department of Medicine, Harlem Hospital Center, Columbia University College of Physicians and Surgeons, New York, United States

Abstract

Background: *The optimal duration of dual antiplatelet therapy (DAPT) following drug-eluting stent (DES) implantation remains a subject of an ongoing debate.*

Methods: *MEDLINE, EMBASE, Scopus and CENTRAL databases were searched for eligible randomized controlled trials (RCTs) that compared short-term (≤ 6 months) DAPT with long-term (≥ 12 months) DAPT following DES implantation. The primary endpoint was a composite of all-cause mortality, myocardial infarction (MI), target vessel revascularization (TVR), stroke, or major bleeding. The secondary outcome were the individual components of the primary outcome, cardiovascular death, stent thrombosis and any bleeding episode.*

Results: *A total of 15,378 patients from 7 RCTs were studied. There were no statistically significant differences between the short-term and long-term DAPT groups with respect to the occurrence of the primary outcome (risk ratio [RR] 1.017; 0.872–1.186; $I^2 = 0\%$), all cause death (RR 0.896; 0.708–1.134), cardiovascular death (RR 0.924; 0.668–1.279), MI (RR 1.139; 0.887–1.461), TVR (RR 1.174; 0.916–1.505), stent thrombosis (RR 1.264; 0.786–2.032), and stroke (RR 0.876; 0.685–1.611). However, there was a statistically significant lower risk of major bleeding in the short-term DAPT group (RR 0.57; 0.36–0.90; $p = 0.02$). There were no statistically significant differences in the sub-group analysis of patients with diabetes and patients presenting with acute coronary syndrome, RR 1.029; 0.745–1.421 and RR 1.062; 0.785–1.438, respectively.*

Conclusions: *There was no difference in efficacy outcomes between short-term and long-term DAPT following DES, even among high-risk patients. However, longer duration of DAPT was found to be associated with increased risk of major bleeding.* (Cardiol J 2016; 23, 3: 307–316)

Keywords: dual antiplatelet therapy, drug-eluting stent, bleeding, stent thrombosis

Introduction

Drug-eluting stents (DES) reduce the incidence of target lesion restenosis when compared with bare metal stents, yet they are prone to higher rates of stent thrombosis [1]. Dual antiplatelet therapy (DAPT), defined as the use of both aspirin and a P2Y12 receptor inhibitor, such as clopidogrel,

Address for correspondence: Olusegun Sheyin, MD, Department of Medicine, Harlem Hospital Center, 506 Lenox Avenue, New York, NY 10037, United States of America, tel: 212 939 2296, fax: 212 939 2263, e-mail: olusegun.sheyin@nychhc.org

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prasugrel or ticagrelor, reduces the risk of stent thrombosis [2]. However, the optimal duration of DAPT following DES implantation at percutaneous coronary intervention remains unknown. The American Heart Association/American College of Cardiology recommend DAPT to be extended to at least 12 months after DES implantation if patients are not at high risk of bleeding [3]. Conversely, the European Society of Cardiology recommends from 6 to 12 months of DAPT for patients following elective percutaneous coronary intervention (PCI) and DES implantation, or 12 months in acute coronary syndromes [4]. These guidelines are largely based on observational studies which showed that early discontinuation of P2Y12 receptor inhibitor therapy increased the risk of stent thrombosis [5–7]. Several randomized controlled trials (RCTs) comparing various durations of DAPT did not find any statistically significant differences in stent thrombosis rates [8–16]. However, these RCTs were not adequately powered to detect a statistically significant difference because of event rates being lower than expected and failure to recruit enough patients [11, 12, 16]. To address this limitation, a few meta-analyses have been conducted on the subject [17–22]. However, only the meta-analyses of RCTs by Pandit et al. [19], Liu et al. [18] and El-Hayek et al. [20] compared ≤ 6-month DAPT with ≥ 12-month DAPT. Finding no difference in efficacy outcomes between short- and long-term DAPT in these meta-analyses may have also been due to the low overall event rates. In addition, no sub-group analyses were performed in earlier meta-analyses. Hence, we conducted an updated meta-analysis of RCTs to determine the efficacy and safety of short-term (≤ 6 months) DAPT as compared with long-term (≥ 12 months) DAPT following DES implantation.

Methods

We conducted a systematic review and meta-analysis, using methods that are in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement recommended by the Cochrane collaboration [23].

Study research

MEDLINE, EMBASE, Scopus and CENTRAL databases were systematically searched from inception to January 2015 for all published RCTs in humans that compared outcome in patients receiving short-term (≤ 6 months) DAPT with long-term (≥ 12 months) DAPT following DES implantation. Medical Subject Headings (MeSH) key terms 'duration', 'dual antiplatelet therapy', 'DAPT', 'drug-eluting stent' and 'DES' were used for the search. We subsequently searched and evaluated all reference lists of eligible articles obtained from the electronic search, and online resources such as Cardiosource and ClinicalTrials.gov to ensure identification of all published and unpublished studies on the subject.

Study selection, data extraction and endpoints

Two investigators (O.S. and X.P.) independently identified and scrutinized studies for potential inclusion based on title or title and abstract. Full articles were then retrieved for further assessment, and disagreements were resolved by consensus and discussion with a third investigator (B.P.-L.).

The primary endpoint of this analysis was a composite of all-cause moralty, myocardial infarction (MI), target vessel revascularization (TVR), stroke, or major bleeding. The secondary outcome were the individual components of the primary outcome, cardiovascular death, stent thrombosis and any bleeding episode. Major bleeding was also defined according to the Randomized Evaluation of PCI Linking Angiomax to reduced Clinical Events (REPLACE-2) as intracranial, intraocular, or retroperitoneal bleed, overt blood loss with a > 3 g/dL decrease in hemoglobin, any hemoglobin decrease > 4 g/dL, or transfusion of ≥ 2 units of blood products; or according to the severe or life-threatening Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (GUSTO) criteria as intracranial bleeding or bleeding which resulted in substantial hemodynamic compromise requiring intervention [24–27].

Selection criteria

We applied the following screening criteria to determine qualitative eligibility: original article; patients at least 18 years of age; duration of follow-up of at least 1 year; reported primary endpoint; and at least 100 patients included. Exclusion criteria applied included: on-going RCTs, RCTs comparing longer durations of DAPT, non-RCTs, editorial comments, reviews, and conference abstracts.

Quality assessment

The methodological quality of each trial was evaluated for risk of bias using standard criteria in the following areas: method of randomization; allocation concealment; patient, investigator, and

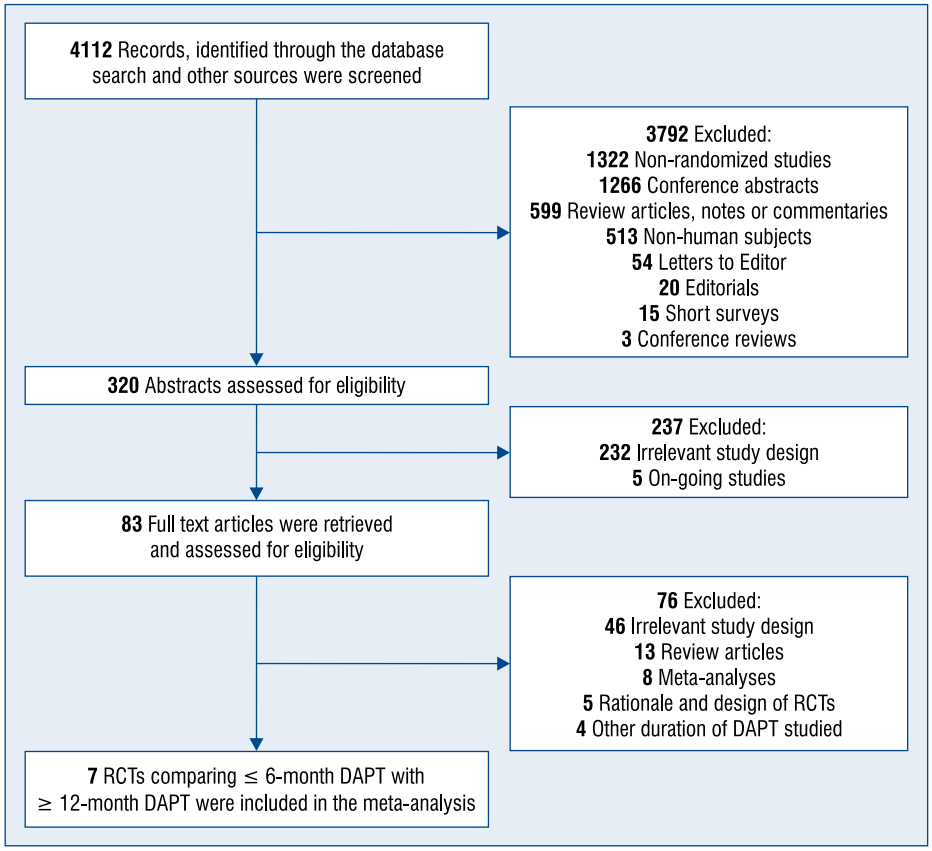

Figure 1. Study flow diagram; DAPT — dual antiplatelet therapy; RCTs — randomized controlled trials.

outcome assessor blinding; selective outcome reporting; incomplete outcome ascertainment; and other potential sources of bias as recommended by the Cochrane collaboration [28].

Statistical analysis

Data from each trial were entered on an intention-to-treat basis. Baseline characteristics were summarized and the differences between the two groups were compared using the Student's t tests for continuous variables and the χ^2 test categorical variables. The included studies were compared with risk ratios (RRs) as the measure of effect. Heterogeneity was assessed using Cohran's Q statistic and I^2 statistic ($[Q-df]/Q \times 100$) and was considered present at $p < 0.10$ and $I^2 > 50\%$ [29]. Pooling was performed according to the fixed effect model with summary effect estimates (95% confidence intervals). To assess for publication bias risk, funnel plots were evaluated.

Sensitivity analysis

Sensitivity analyses examining the robustness of the results were explored by comparing fixed-effect results with both random effects and Yusuf-Peto models. In addition, each study was sequentially removed to see if it impacts the pooled effect estimate. Sub-group analyses were performed according to trial duration, age ≥ 65 years, and patients with acute coronary syndrome (ACS), diabetes, reduced left ventricular ejection fraction (LVEF), complex lesions, and multi-vessel disease.

Two-sided p values were calculated, with a p value less than 0.05 considered significant for all tests. Statistical analyses were performed with Comprehensive Meta-Analysis version 3 software.

Results

Database search and other sources totally provided 4112 records. Of these records, 3,792 were excluded for various reasons (Fig. 1). Three hundred and twenty abstracts were assessed for eligibility from which 83 full articles were retrieved. However, only 7 RCTs fulfilled the inclusion and exclusion criteria mentioned above. The 7 RCTs recruited 15,378 patients across 229 sites worldwide (Table 1) [10–16].

Table 1. Characteristics of the included studies.

	EXCELLENT		ISAR-SAFE		ITALIC		OPTIMIZE		PRODIGY		RESET		SECURITY	
	Short (n = 722)	Prolonged (n = 721)	Short (n = 1997)	Prolonged (n = 2003)	Short (n = 912)	Prolonged (n = 910)	Short (n = 1563)	Prolonged (n = 1556)	Short (n = 737)	Prolonged (n = 741)	Short (n = 1059)	Prolonged (n = 1058)	Short (n = 682)	Prolonged (n = 717)
Presentation:														
SA/silent ischemia	353 (48.9%)	346 (48.0%)	1189 (59.5%)	1183 (59.1%)	560 (61.4%)	561 (61.6%)	1069 (68.4%)	1054 (67.7%)	194 (26.5%)	198 (26.7%)	471 (44.5%)	490 (46.3%)	341 (61.6%)	368 (61.6%)
ACS	369 (51.1%)	375 (52%)	794 (39.8%)	807 (40.3%)	211 (23.1%)	217 (23.8%)	494 (31.6%)	502 (32.3%)	542 (73.5%)	543 (73.3%)	588 (55.5%)	568 (53.7%)	213 (38.4%)	229 (38.4%)
DES type:														
Sirolimus	182 (25.2%)	182 (25.2%)	499 (25%)	483 (24.1%)	–	–	–	–	–	–	–	383 (28.5%)	–	–
Paclitaxel	–	–	44 (2.2%)	46 (2.3%)	–	–	–	–	245 (33.2%)	245 (33.1%)	–	–	–	–
Everolimus	540 (74.8%)	539 (74.8%)	948 (47.5%)	987 (49.3%)	912 (100%)	910 (100%)	–	–	247 (33.5%)	248 (33.5%)	–	404 (30.0%)	–	–
Zotarolimus	–	–	311 (15.6%)	294 (14.7%)	–	–	1563 (100%)	1556 (100%)	245 (33.2%)	248 (33.5%)	1341 (100%)	559 (41.5%)	470 (42.1%)	464 (40.3%)
Biolimus	–	–	166 (8.3%)	170 (8.5%)	–	–	–	–	–	–	–	–	363 (32.5%)	400 (34.8%)
Duration of DAPT	6 months	12 months	6 months	12 months	6 months	24 months	3 months	12 months	6 months	24 months	3 months	12 months	6 months	12 months
Duration of follow-up	12 months		15 months		36 months		12 months		24 months		12 months		12 months	
Major exclusion criteria	MI within 72 h Cardiogenic shock LVEF < 25% Prior stent in target vessel True bifurcation lesion requiring 2 stents strategy Left main stenosis > 50% Chronic total occlusion Serum creatinine ≥ 3.0 mg/dL Elective surgery planned within 12 months Life expectancy < 1 year		Clinical symptoms or signs of ischemia and/or angiographic lesions requiring revascularization Active bleeding, bleeding diathesis or history of intracranial bleeding STEMI and NSTEMI in the past 6 months after DES Previous stent thrombosis Prior stent in left main artery Oral anticoagulation therapy Planned major surgery within 6 months with need to discontinue APT		Prior DES implantation within 1 year Platelet count < 100,000/μL or bleeding diathesis Oral anticoagulation therapy or abciximab Contraindication to APT Major surgery within preceding 6 weeks GI/GU bleeding Severe liver failure Planned surgery within 1 year after enrolment		Primary rescue PCI for STEMI BMS in non-target vessel in the last 6 months Previous DES Saphenous vein graft lesion Scheduled elective surgery within 12 months after PCI Known hypersensitivity to APT In-stent restenosis of a DES		Concomitant or foreseeable need for oral anticoagulation Known allergy to APT Planned surgery within 24 months of PCI Major surgery within 15 days Active bleeding or previous stroke within6 months Life expectancy < 24 months		STEMI within 48 h Cardiogenic shock LVEF < 40% Cerebral/peripheral atherosclerotic disease Thrombo-embolic disease Prior stent thrombosis Left main disease Chronic total occlusion Re-stenotic lesion		Saphenous vein graft In-stent restenosis Unprotected left main artery STEMI within 48 h NSTEMI in prior 6 months LVEF ≤ 30% Known hypersensitivity to APT, heparin, or contrast media History of thrombo-cytopenia with APT CKD (creatinine > 2 mg/dL) Active bleeding Life expectancy < 24 months	

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Table 1. cont. Characteristics of the included studies.

	EXCELLENT		ISAR-SAFE		ITALIC		OPTIMIZE		PRODIGY		RESET		SECURITY	
	Short (n = 722)	Prolonged (n = 721)	Short (n = 1997)	Prolonged (n = 2003)	Short (n = 912)	Prolonged (n = 910)	Short (n = 1563)	Prolonged (n = 1556)	Short (n = 737)	Prolonged (n = 741)	Short (n = 1059)	Prolonged (n = 1058)	Short (n = 682)	Prolonged (n = 717)
Primary end point	Target vessel failure (composite cardiac death, MI or TVR during the 12-month period after randomization)		Composite of death, MI, stent thrombosis, stroke or TIMI major bleeding 15 months after DES		Composite of death, MI, repeat emergency TVR, stroke or TIMI major bleeding within 12 months of stenting		Net adverse clinical and cerebral events (NACCE): composite of death from any cause, MI, stroke or major bleeding		Death from any cause, non-fatal MI or cerebrovascular accident		Composite of death from all causes, MI or stent thrombosis		Composite of cardiac death, MI, stroke, definite or probable stent thrombosis and BARC criteria type 3 or 5	
Secondary end point	Individual components of the primary end point Death from any cause Death or MI Stent thrombosis Major bleeding (TIMI criteria) MACCE: death, MI, stroke or any revascularization Safety end point: death, MI, stroke, stent thrombosis or TIMI major bleeding		Individual components of the primary end point		Primary outcome at 24 and 36 months Individual components of the primary end point Minor and minimal bleeding at 12, 24 and 36 months		Stent thrombosis Target lesion and target vessel revascularization MACE: death from any cause, MI, emergent CABG or TVR Any bleeding — Major bleeding and other bleeding (GUSTO or REPLACE-2)		Individual components of the primary end point Cardiovascular death Stent thrombosis		Individual components of the primary end point		Composite of cardiac death, MI, stroke, stent thrombosis, or BARC 2, 3 or 5 bleeding at 12 and 24 months Cumulative incidence of the individual components of the primary end point at 12 and 24 months MI TVR (CABG or PCI) Bleeding events All-cause mortality at 6, 12 and 24 months	
P2Y12 inhibitor	Clopidogrel		Clopidogrel		Clopidogrel, prasugrel, ticagrelor		Clopidogrel		Clopidogrel		Clopidogrel		Clopidogrel	
Trial setting	19 sites in Korea		40 sites in Europe, China, Japan and USA		70 sites in Europe and the Middle East		33 sites in Brazil		3 sites in Italy		26 sites in Korea		38 sites in Italy, Spain and the Netherlands	

ACS — acute coronary syndrome; APT — antiplatelet therapy; BARC — Bleeding Academic Research Consortium; BMS — bare metal stent; CABG — coronary artery bypass grafting; CKD — chronic kidney disease; DAPT — dual antiplatelet therapy; DES — drug eluting stent; GI — gastro-intestinal; GU — genitourinary; GUSTO — Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries; LVEF — left ventricular ejection fraction; MACCE — major adverse cardiac and cerebrovascular events; MACE — major adverse cardiac events; MI — myocardial infarction; NACCE — net adverse clinical and cerebral events; NSTEMI — non-ST elevation myocardial infarction; PCI — percutaneous coronary intervention; REPLACE-2 — Randomized Evaluation of PCI Linking Angiomax to reduced Clinical Events; SA — stable angina; STEMI — ST elevation myocardial infarction; TIMI — Thrombolysis in Myocardial Infarction; TVR — target vessel revascularization

Table 2. Baseline patient clinical and angiographic characteristics.

Variables	≤ 6-month DAPT (n = 7672)	≥ 6-month DAPT (n = 7706)	P
Age [years]	64.1 ± 10.2	64.3 ± 10.4	0.23
Male gender	5595 (72.9%)	5591 (72.6%)	0.98
Hypertension	5942 (77.5%)	6026 (78.2%)	0.94
Diabetes mellitus	2359 (30.7%)	2366 (30.7%)	1.00
Dyslipidemia	5313 (69.3%)	5363 (69.6%)	0.97
Current smoker	1834 (23.9%)	1815 (23.6%)	0.96
Previous MI	1613 (21.0%)	1564 (20.3%)	0.89
Previous PCI[a]	783 (15.9%)	712 (14.3%)	0.77
Previous CABG	570 (7.4%)	566 (7.3%)	0.97
Congestive heart failure[b]	895 (14.3%)	904 (14.5%)	0.97
Clinical presentation:			
Stable angina/silent ischemia	4177 (54.4%)	4200 (54.5%)	0.99
Unstable angina/NSTEMI	2880 (37.5%)	2891 (37.5%)	1.00
STEMI	416 (5.4%)	434 (5.6%)	0.94
LVEF[c]	59.0 ± 14.8	58.9 ± 14.2	0.67
Discharge medications[d]:			
ACE-inhibitor	555 (31.2%)	592 (33.3%)	0.88
ARB	567 (31.8%)	532 (29.9%)	0.89
Beta-blocker	1139 (64.0%)	1175 (66.0%)	0.92
Statin	1527 (85.7%)	1496 (84.1%)	0.94
Angiographic findings:			
Single vessel disease	3948 (51.5%)	3991 (51.8%)	0.97
Multi-vessel disease	3724 (48.5%)	3715 (48.2%)	0.97
LAD lesion	4434 (57.8%)	4446 (57.7%)	0.99
Left circumflex artery lesion[e]	2115 (30.4%)	2069 (29.6%)	0.90
RCA lesion[e]	2515 (36.2%)	2557 (36.6%)	0.96
Left main lesion[e]	48 (0.69%)	42 (0.60%)	0.93
CABG[e]	94 (1.4%)	83 (1.2%)	0.88
Complex lesions (ACC/AHA B2, C)	5289 (61.1%)	5187 (59.5%)	0.85

[a]No data available from ISAR-SAFE and PRODIGY; [b]No data available from PRODIGY and SECURITY; [c]No data available from ISAR-SAFE, ITALIC and OPTIMIZE; [d]Data available from EXCELLENT and RESET; [e]No data available from EXCELLENT; DAPT — dual antiplatelet therapy; MI — myocardial infarction; PCI — percutaneous coronary intervention; CABG — coronary artery bypass grafting; STEMI — ST elevation MI; NSTEMI — non-ST elevation MI; LVEF — left ventricular ejection fraction; ACE — angiotensin converting enzyme; ARB — angiotensin receptor blocker; LAD — left anterior descending coronary artery; RCA — right coronary artery; ACC — American College of Cardiology; AHA — American Heart Association

In order to receive short-term DAPT and long-term DAPT, 7672 and 7706 patients were randomized, respectively. The two groups studied were similar with respect to baseline clinical and angiographic characteristics (Table 2). Women were under-represented when compared with men. All the trials except PRODIGY exclusively utilized DES for PCI. In order to maintain consistency in our analysis, we included data from the DES subgroup in the PRODIGY trial that was subsequently published [14]. Follow-up duration was 12 months in 4 trials [10, 13, 15, 16], and 15 months, 24 months and 36 months in the remaining 3 trials [11, 12, 14]. The composite primary end-point was similar in all 7 studies, except for the non-inclusion of stroke in 2 studies [10, 15] and bleeding in 1 study [14].

Endpoints

The endpoints are shown in Figures 2 and 3.

Primary endpoint. The primary outcome occurred in 309 (4.0%) patients who received short-term DAPT and in 305 (4.0%) patients who received long-term DAPT. There were no statis-

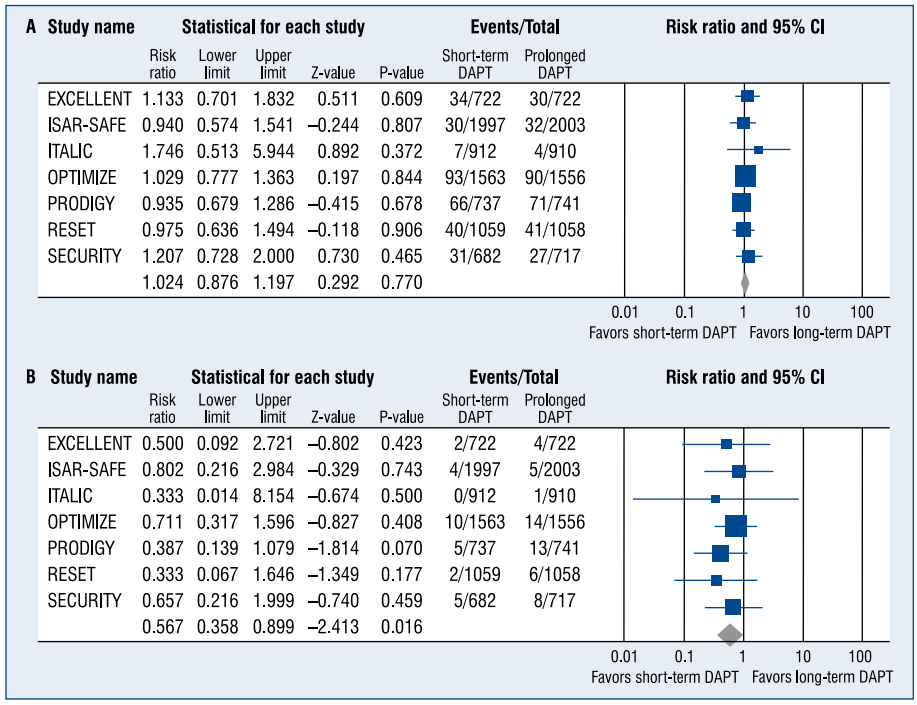

Figure 2. Forest plot reporting the risk ratios with 95% confidence intervals (CI) (designated lower limit and upper limit) of the primary outcome (**A**) and major bleeding (**B**) in patients from 7 randomized controlled trials treated with short--term (≤ 6 months) dual antiplatelet therapy (DAPT) compared with patients treated with long-term (≥ 12 months) DAPT.

tically significant differences between the short-term and long-term DAPT groups with respect to the occurrence of the primary outcome (pooled risk ratio [pRR] 1.02; 0.87–1.19; $I^2 = 0\%$) (Fig. 2).

Secondary endpoints. There was no statistically significant difference in risk of all-cause mortality (pRR 0.90; 0.71–1.13; $I^2 = 0\%$), cardiovascular death (pRR 0.92; 0.67–1.28; $I^2 = 0\%$), MI (pRR 1.14; 0.89–1.46; $I^2 = 0\%$), stent thrombosis (pRR 1.264; 0.79–2.03; $I^2 = 0\%$), TVR (pRR 1.17; 0.91–1.51; $I^2 = 0\%$), and cerebrovascular accidents (pRR 0.88; 0.69–1.61; $I^2 = 0\%$), between short and long duration of DAPT. However, major bleeding occurred in 28 (0.4%) patients in the short-term DAPT group and in 51 (0.7%) patients who received long-term DAPT. As shown in Figures 2 and 3, there was a significantly lower risk of major bleeding with short-term DAPT when compared with the long-term DAPT group (pRR 0.57; 0.36–0.90; $I^2 = 0\%$; $p = 0.02$).

Sensitivity and sub-group analyses

Similar results were obtained when analysis was performed using the fixed-effects, random effects and Yusuf-Peto models. Sequential removal of each study from the analysis did not impact the pooled effect estimate. As shown in Figure 3, there was no statistically significant difference in risk of the primary endpoint among patients presenting with ACS (pRR 1.06; 0.79–1.44; $I^2 = 0\%$), patients with diabetes (pRR 1.03; 0.75–1.42; $I^2 = 0\%$), reduced LVEF (pRR 0.81; 0.44–1.49; $I^2 = 0\%$), complex lesions (pRR 1.00; 0.75–1.33; $I^2 = 0\%$), multi-vessel disease (pRR 1.24; 0.88–1.73; $I^2 = 0\%$), and patients at least 65 years of age (pRR 0.83; 0.75–1.33; $I^2 = 0\%$) who received short--term DAPT as compared with long-term DAPT.

There was no statistically significant difference in risk of the primary endpoint between patients treated with 3–6 months of DAPT vs. 12-month DAPT (pRR 1.04; 0.87–1.25; $I^2 = 0\%$), 6 months vs. 12 months of DAPT (pRR 1.09; 0.81–1.46; $I^2 = 0\%$), 3 months vs. 12 months of DAPT (pRR 1.01; 0.79–1.30; $I^2 = 0\%$), or 6 months vs. 24 months of DAPT (pRR 0.95; 0.69–1.31; $I^2 = 0\%$).

Discussion

Findings

In our meta-analysis of 15,378 patients who received DES following PCI, we did not find any difference in risk of the primary outcome, all-

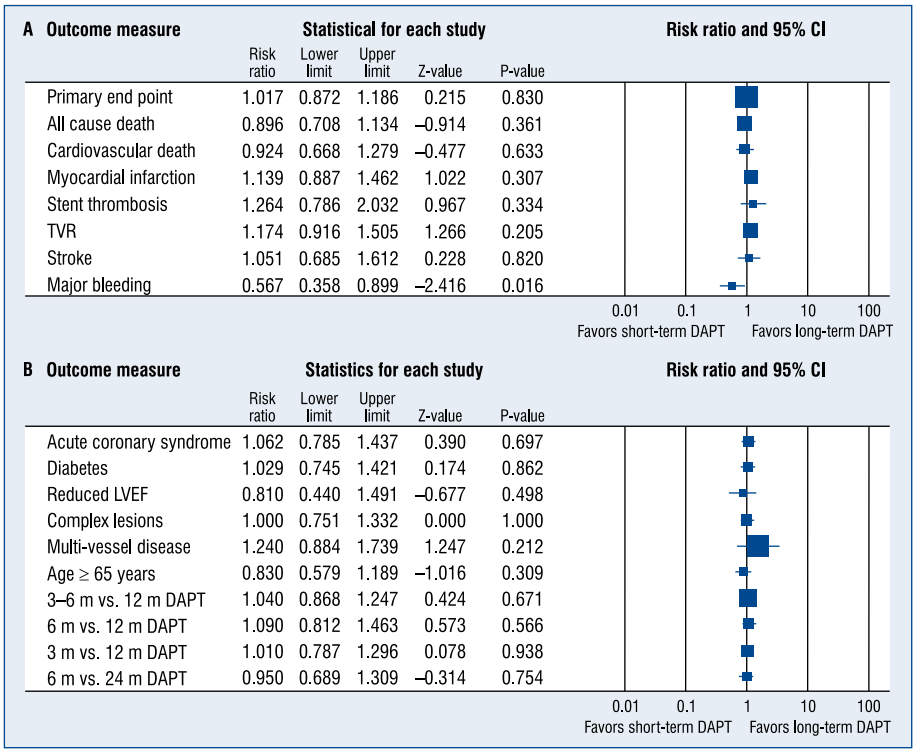

Figure 3. Pooled analysis of studies comparing short-term (≤ 6 months) dual antiplatelet therapy (DAPT) with long--term (≥ 12 months); **A.** Forest plot reporting summary risk ratios with 95% confidence intervals (CI) (designated lower limit and upper limit) for the comparison of ≤ 6 months DAPT vs. ≥ 12 months DAPT with respect to the primary outcome, all cause death, cardiovascular death, myocardial infarction, definite or probable stent thrombosis, target vessel revascularization (TVR), stroke and major bleeding; **B.** Forest plot reporting summary risk ratios with 95% CI of the comparison in various sub-groups; m — months; LVEF — left ventricular ejection fraction.

-cause mortality, cardiovascular death, MI, TVR, stent thrombosis, and cerebrovascular accidents between the short-term and long-term DAPT groups. However, patients treated with short-term DAPT were at a significantly lower risk of major bleeding. We did not find any difference in the risk of the primary endpoint based on DAPT duration and on sub-group analyses, according to age and the presence of diabetes, ACS, reduced LVEF, complex lesions, or multi-vessel disease.

Comparison with other studies

The findings of this study are similar to the 3 previously published meta-analyses comparing ≤ 6-month DAPT with ≥ 12-month DAPT [18–20]. In addition to the 4 studies included in the El-Hayek et al. [20] and Pandit et al. [19] meta-analyses, our study included 3 recently published studies: ISAR--SAFE, ITALIC and SECURITY [11, 12, 16]. The findings from our study are more robust due to the sample size, nearly twice as large as those in the earlier meta-analysis and due to the performance of analyses in high-risk patient sub-groups. Since our study is investigating the efficacy and safety of even shorter duration of DAPT when compared to the standard recommended therapy of at least 12 months, RCTs with short-term DAPT duration more than 6 months were excluded.

Concerns regarding the safety of short-term DAPT were raised in the meta-analysis of 8157 patients by Hayek et al. [20] because of the finding of an almost 2-fold (1.75), though non-significant risk of stent thrombosis among patients who discontinued P2Y12 therapy after 6 months. In comparison, the risk of stent thrombosis in our study, with almost twice as many patients was 1.26. Nevertheless, the recently published DAPT study with 9961 patients comparing 12-month DAPT with 30-month DAPT found a statistically significant decrease in the rate of stent thrombosis [30], suggesting that the trend of increased risk of stent thrombosis found in our study and the earlier meta-analyses may become significant if patients are followed longer. Even though the DAPT study also demonstrated a significant decrease in MI and major cardiovascular and cerebrovascular events

(MACCE) with 30 months of DAPT, there was a paradoxical increased risk of all-cause mortality with prolonged DAPT when the analysis was conducted at 33 months (hazard ratio [HR] 1.36; p = 0.04). Furthermore, the increase in stent thrombosis, MI and MACCE with 12-month DAPT did not translate to an increased risk of death, as there was no difference in death from cardiac or vascular causes (HR 1.00; 0.66–1.52 and 0.98; 0.28–3.39, respectively). Hence prolonging DAPT duration to 30 months had no effect on cardiovascular mortality, but led to an almost 2-fold increase in non-cardiovascular mortality (HR 1.86; p = 0.01).

Clinical implications

Our study confirms the finding that ≤ 6 months of DAPT is equally effective as ≥ 12 months of DAPT reported by previously published RCTs with much smaller sample sizes and potential for type II error. In addition, we found that long-term DAPT is associated with increased risk of major bleeding events. Hence, long-term DAPT has the potential of leading to increased morbidity, in addition to higher cost of treatment and pill burden when compared with short-term DAPT.

Strengths and limitations of the study

This is the largest meta-analysis to date on RCTs comparing outcome in patients receiving ≤ 6-month DAPT with ≥ 12-month DAPT following DES implantation. All the studies included were of high quality and visual inspection of the funnel plot did not reveal any evidence of publication bias. In addition, our meta-analysis is the first to demonstrate no difference in outcome between short-term and long-term DAPT even among the high-risk patient sub-groups, including patients presenting with ACS and patients with diabetes, severely depressed LVEF, complex lesions, and multi-vessel disease.

As expected in any meta-analysis, our study utilized data that were reported in each of the included RCTs. With the exception of the ISAR-SAFE trial, all the included RCTs were not double blind but open-label by design, which introduces the possibility of ascertainment bias in the results. There is also a possibility that selection bias may have been present, since none of the studies reported whether allocation concealment was performed. However, there were no differences between the two groups in the baseline characteristics of the included subjects. Despite pooling data from 15,378 patients, the total number of stent thrombosis events remained low (< 0.5%). Hence, our analysis has the potential for a type II error. Analysis according to the type of implanted DES was not possible due to the fact that this information was available only in 2 of the included studies. Finally, with the exception of 1 trial, our study included only RCTs of patients who were treated with the P2Y12 inhibitor clopidogrel. The trial in which patients were treated with ticagrelor, prasugrel or clopidogrel did not report outcome based on the P2Y12 treatment received. Thus, it is uncertain whether the use of newer more potent P2Y12 inhibitors, including ticagrelor and prasugrel, would alter the safety and efficacy of prolonged DAPT.

Conclusions

This meta-analysis did not find any difference in efficacy outcomes between short-term and long--term DAPT following DES. Short-term DAPT was equally effective as long-term DAPT in preventing the primary outcome even in high-risk patients. However, longer duration of DAPT was found to be associated with increased risk of major bleeding in our study, in addition to increased non-cardiovascular and all-cause mortality demonstrated in the DAPT study. Larger, adequately powered RCTs for low event rates are needed to confirm these findings.

Conflict of interest: None declared

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