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Short- Versus Long-Term Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation

An Individual Patient Data Pairwise and Network Meta-Analysis

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ABSTRACT

BACKGROUND Randomized controlled trials comparing short- (≤6 months) with long-term (≥1 year) dual antiplatelet therapy (DAPT) after drug-eluting stent(s) (DES) placement have been insufficiently powered to detect significant differences in the risk of major adverse cardiac events (MACE).

OBJECTIVES This study sought to compare clinical outcomes between short- (≤6 months) and long-term (1 year) DAPT and among 3 months, 6 months, and 1 year of DAPT post-DES placement by performing an individual patient data pairwise and network meta-analysis.

METHODS Randomized controlled trials comparing DAPT durations after DES placement were searched through the MEDLINE, EMBASE, and Cochrane databases and in international meeting proceedings. The primary study outcome was 1-year risk of MACE (cardiac death, myocardial infarction, or definite/probable stent thrombosis).

RESULTS Four trials including 8,180 randomized patients were identified. At 1-year follow-up, short-term DAPT was associated with similar rates of MACE (hazard ratio [HR]: 1.11; 95% confidence interval [CI]: 0.86 to 1.43; p = 0.44), but significantly lower rates of bleeding (HR: 0.66; 95% CI: 0.46 to 0.94; p = 0.03) versus prolonged DAPT. Comparable results were apparent in the landmark period between DAPT discontinuation and 1-year follow-up (for MACE: HR: 1.20; 95% CI: 0.77 to 1.89; p = 0.42) (for bleeding: HR: 0.44; 95% CI: 0.21 to 0.91; p = 0.03). There were no significant differences in 1-year rates of MACE among 3-month versus 1-year DAPT, 6-month versus 1-year DAPT, or 3-month versus 6-month DAPT.

CONCLUSIONS Compared with prolonged DAPT, short-term DAPT is associated with similar rates of MACE but lower rates of bleeding after DES placement. (J Am Coll Cardiol 2015;65:1092–102) © 2015 by the American College of Cardiology Foundation.

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The optimal duration of dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor after drug-eluting stent(s) (DES) implantation remains a matter of debate. Despite demonstration of improved efficacy, first-generation sirolimus-eluting stents and paclitaxel-eluting stent(s) (PES) result in greater rates of very late stent thrombosis (ST) and adverse cardiac events compared with bare-metal stents (1,2). Based on pathological findings showing delayed arterial endothelialization after sirolimus-eluting stents and PES implantation (3,4), as well as clinical retrospective studies suggesting higher rates of ST with first-generation DES versus bare-metal stents at time of DAPT discontinuation (5,6), the American College of Cardiology/American Heart Association guidelines extended the duration of DAPT from 3 months after sirolimus-eluting stents and 6 months after PES placement (per randomized clinical trials [RCT]) to at least 1 year (7). Thus, 1 year of DAPT has become the standard of care worldwide for patients receiving DES, irrespective of DES type and despite the absence of evidence-based RCT results.

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Because prolonged DAPT is associated with increased bleeding and health care costs (8), establishing optimal DAPT duration is of paramount importance. Yet observational studies have been inconsistent; some reports suggest increased rates of adverse events in patients with premature DAPT discontinuation (5,9), whereas others refute this association (10,11). Recently, several RCTs failed to show any benefit of prolonging DAPT (≥1 year) versus a shorter course, challenging the notion that 1 year of DAPT is necessary after DES implantation (12–16). However, given the low frequency of adverse events after DAPT discontinuation, all of these studies were insufficiently powered to detect modest but clinically meaningful differences in ischemic outcomes. For this reason, we performed an individual patient data meta-analysis of RCTs investigating the safety and efficacy of shortening DAPT to <1 year post-DES implantation.

METHODS

Eligible studies for this meta-analysis were RCTs comparing short-duration (3 or 6 months) with longer-duration DAPT (≥1 year). Randomized trials comparing 1 year with >1 year DAPT were excluded. Relevant RCTs were searched through MEDLINE, the Cochrane database, the EMBASE database, www.tctmd.com, www.clinicaltrials.gov, www.clinicaltrialresults.org, www.cardiosource.com, and abstracts and presentations from major cardiovascular meetings, using the keywords "randomized clinical trial," "drug-eluting stent," "dual antiplatelet therapy," "clopidogrel," "aspirin," and "thienopyridines." Two investigators (T.P. and A.M.) independently reviewed the titles, abstracts, and studies to determine whether they met the inclusion criteria. Reviewer conflicts were resolved by consensus. No language, publication date, or publication status restrictions were imposed. The most updated or inclusive data for a given study were abstracted. Internal validity of RCTs was assessed by evaluating concealment of allocation, blind adjudication of events, and inclusion of all randomized patients in the analysis.

The primary endpoint was the 1-year rate of major adverse cardiac events (MACE), including the composite of cardiac death, myocardial infarction (MI), or definite/probable ST. Secondary pre-specified

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)
CI = confidence interval
CrI = credible interval
DAPT = dual antiplatelet therapy
DES = drug-eluting stent(s)
HR = hazard ratio
MACE = major adverse cardiac event(s)
MI = myocardial infarction
OR = odds ratio
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stent(s)
RCT = randomized clinical trials
ST = stent thrombosis

received speaker fees from Abbott and Cardiovascular System Inc. Dr. Bhatt is on the advisory board of Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences; is on the Board of Directors of Boston VA Research Institute and the Society of Cardiovascular Patient Care; is Chair of the American Heart Association Get With The Guidelines Steering Committee; is on the Data Monitoring Committees at Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, and Population Health Research Institute; has received honoraria from the American College of Cardiology (Editor, *Clinical Trials*, *Cardiosource*), Belvoir Publications (Editor-in-Chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor-in-Chief, *Journal of Invasive Cardiology*), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, *Cardiology Today's Intervention*), and WebMD (CME steering committees); is the Deputy Editor of *Clinical Cardiology*; is the Section Editor for pharmacology for the *Journal of the American College of Cardiology*; has received research grants from Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Roche, Sanofi, and The Medicines Company; and has received unfunded research from FlowCo, PLx Pharma, and Takeda. Dr. Stone has served as a consultant for Boston Scientific, Eli Lilly, Daiichi-Sankyo, and AstraZeneca. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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endpoints included the 1-year rates of major and minor bleeding, cardiac death, all-cause death, MI, stroke, definite/probable ST, target vessel revascularization, and combinations of these endpoints. The endpoint definitions as applied in each trial were incorporated. In 3 trials, bleeding was defined according to the Thrombolysis In Myocardial Infarction criteria (13,14,16), whereas in 1 trial, the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events criteria were used (12). Patient-level data were obtained from the principal investigators of all qualifying trials and combined in a single pooled database. Frequentist pairwise meta-analysis based on individual patient data was performed to examine outcomes between patients treated with short-term (≤6 months) and prolonged (1 year) DAPT (data beyond 1 year were censored). A network meta-analysis was performed to compare outcomes of patients treated with 3-month versus 6-month versus 1-year DAPT (17). From the pooled patient-level database, we also examined the relative risk of MACE and bleeding with short-term versus prolonged DAPT in the following pre-specified subgroups: age, sex, diabetes, clinical presentation, multivessel coronary artery disease, and left anterior descending coronary artery disease. The intention-to-treat population was used for these analyses, including all patients according to randomized treatment arm regardless of actual treatment. Landmark analyses were performed at time of DAPT discontinuation using an "as treated" cohort. For this analysis, patients with clinical events (death, MI, definite/probable ST, stroke, target vessel revascularization, or major bleeding) occurring before the landmark time point, those with premature discontinuation of DAPT, and those in whom DAPT was prolonged ≥1 month beyond the period scheduled by randomization were excluded. Premature discontinuation of DAPT was defined as DAPT interruption occurring at least 1 month before the period scheduled by randomization, unless caused by an adverse event, such as bleeding. ST was defined according to the Academic Research Consortium criteria (18). The present review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses statements (19).

STATISTICAL ANALYSIS. Categorical variables are reported as count and percentages and compared with a conditional regression analysis stratified by trial. Continuous variables are reported as means and standard deviation and compared with a 2-way analysis of variance stratified by trial. Individual patient data meta-analysis was performed using a 1-stage approach. Patient data were combined in a single dataset and fitted in a Cox regression model stratified by trial, using trial identifiers as random effects. The proportional assumptions were verified using the Schoenfeld residuals. Results are reported as hazard ratio (HR) with 95% confidence interval (CI) and as event rates per 1,000 patient-years. To minimize bias, a multivariable Cox regression analysis was performed, stratified by trial, and adjusted for a propensity score determined using a logistic regression model for treatment with short-term versus prolonged DAPT. The following variables were considered for the propensity score determination: age, sex, hypertension, dyslipidemia, smoking, diabetes, prior MI, prior percutaneous coronary intervention (PCI), prior coronary artery bypass grafting, prior stroke, clinical presentation, diseased vessels per patient, type of DES implanted, and number of stents implanted. The number of patients needed to treat for an additional beneficial outcome and for an additional harmful outcome was computed as 1/risk difference, after imputing risk difference from HR obtained from Cox proportional hazards analysis stratified by trial with random effects and using the control event rate as reference, including point estimate and 95% CI. The instantaneous risk of MACE or bleeding for patients on DAPT versus those off DAPT was determined using kernel hazard functions in the landmark periods: 91 to 180 days, 181 to 270 days, and 271 to 365 days. Patients were stratified in these pre-specified intervals according to whether they were on or off DAPT in relation to their treatment assignment, with no crossover between randomization arms. Patients with clinical events occurring before the landmark time point were excluded from analysis, whereas those who prematurely discontinued DAPT or those who continued DAPT beyond the period of treatment assignment were censored according to their DAPT status. A simple Cox regression model was used to generate cumulative hazard function curves of events for each outcome for descriptive purposes. As a sensitivity analysis, we performed individual patient data network meta-analyses within a Bayesian framework with a 2-stage approach and fixed-effect methods, computing odds ratios (ORs) and 95% credible intervals (CrIs). Computations were performed with a 100,000-simulation burn-in phase with inference based on 150,000 simulations with 3 separate chains.

Extent of small study effects and publication bias was assessed by visual inspection of funnel plots and the Egger test. Pairwise inconsistency was assessed with the I^2 statistic, with values <25%, ≥25% to ≤50%, and >50% representing mild, moderate, and severe heterogeneity, respectively. Values of $p < 0.05$ were considered statistically significant.

Statistical analyses were performed using STATA version 12 SE (StataCorp, College Station, Texas) and WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge University, Cambridge, United Kingdom).

RESULTS

The study analysis flow diagram is shown in Online Figure 1. Of 911 potentially relevant articles screened, 4 trials met the inclusion criteria and were included in the final meta-analysis (12–14,16). Among 8,180 randomized patients, 2,622 were randomized to 3 months, 1,473 to 6 months, and 4,085 to at least 1 year of DAPT (including 3,335 to 1 year and 750 to 2 years of DAPT). The major characteristics of the included trials appear in **Table 1**. Two studies compared 3 months with 1 year of DAPT, another 6 months with 1 year of DAPT, and another 6 months with 2 years of DAPT. For this last trial, PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study), the data were censored at 1 year. PRODIGY also included a quarter of patients randomized to bare-metal stents at the index intervention; these patients were excluded to obtain a homogenous DES population. The major inclusion/exclusion criteria and internal validity assessment for each trial are reported in Online Table 1. Clinical, angiographic, and procedural characteristics of patients stratified by treatment are reported in **Table 2** for short-term (≤6 month) versus prolonged (1 year) DAPT, and in Online Table 2 for 3-month versus 6-month versus 1 year DAPT (see Online Table 3 for the definitions of each trial's clinical endpoints).

Estimates of risk and event rates of short- versus long-term DAPT are shown in **Table 3** and Online Table 4, respectively. At 1-year follow-up, there was no significant difference in the risk of MACE between treatment groups (HR: 1.11; 95% CI: 0.86 to 1.43; p = 0.44). Conversely, short-term DAPT was associated with significantly lower 1-year rates of any bleeding compared with prolonged DAPT (HR: 0.66; 95% CI: 0.46 to 0.94; p = 0.03), with a trend toward lower rates of major bleeding (HR: 0.58; 95% CI: 0.32 to 1.03; p = 0.06). The number needed to harm was 46 (95% CI: 65 to 32) for any bleeding and 148 for major bleeding, with an excess of 21 bleeds and 7 major bleeds for every 1,000 patients treated with long- rather than short-term DAPT. Results of short-term versus prolonged DAPT did not significantly change after adjusting for the propensity score (for MACE, adjusted HR: 1.28; 95% CI: 0.79 to 2.04; p = 0.67) (for major bleeding, adjusted HR: 0.42; 95% CI: 0.20 to 0.89; p = 0.03). **Figure 1** shows time-to-event curves for the principal clinical outcomes.

After excluding patients with major events (n = 258), those lost to follow-up before DAPT interruption (n = 78), those with premature DAPT discontinuation (n = 214), and those who continued DAPT beyond the period of assignment (n = 323), 7,307 patients remained for landmark analyses. Clinical, angiographic, and procedural characteristics of these patients are presented in Online Table 5 for short-term (≤6 month) versus prolonged (1 year) DAPT and in Online Table 6 for 3-month versus 6-month versus 1-year DAPT. There were no significant differences in MACE rates in the short- versus

TABLE 1 Main Characteristics of Randomized Trials Included in Meta-Analysis

Study (Ref. #)	n	Primary Endpoint	Design	Follow-Up	DAPT Duration (Months)	Primary Endpoint Results
EXCELLENT (13)	6 months (n = 722) 12 months (n = 721)	Cardiac death/MI/ischemia-driven TVR	Noninferiority	1 yr	6 vs. 12	Noninferiority demonstrated
OPTIMIZE (12)	3 months (n = 1,563) 12 months (n = 1,556)	Death/MI/CVA/major bleeding	Noninferiority	1 yr	3 vs. 12	Noninferiority demonstrated
PRODIGY (16)	6 months (n = 751) 12 months (n = 750)	Death/MI/CVA	Superiority	2 yrs	6 vs. 24	Superiority of 24-month DAPT not demonstrated
RESET (14)	3 months (n = 1,059) 12 months (n = 1,058)	Cardiac death/MI/ST/TVR/major bleeding	Noninferiority	1 yr	3 vs. 12	Noninferiority demonstrated

CVA = cerebrovascular accident; DAPT = dual antiplatelet therapy; EXCELLENT = Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; MI = myocardial infarction; OPTIMIZE = Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice; PRODIGY = Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study; RESET = REal Safety and Efficacy of a 3-month dual antiplatelet Therapy following E-ZES implantation; ST = stent thrombosis; TVR = target vessel revascularization.

TABLE 2 Baseline Clinical, Angiographic, and Procedural Patient Characteristics

	Short DAPT (≤6 Months)	Long DAPT (1 Year)	p Value
Age, yrs	63.1 ± 10.5	63.1 ± 10.7	0.90
Male	66.5% (2,725/4,095)	66.0% (2,696/4,085)	0.61
Hypertension	74.5% (3,052/4,094)	75.9% (3,098/4,084)	0.15
Diabetes mellitus	31.1% (1,274/4,095)	31.2% (1,274/4,085)	0.85
Hypercholesterolemia	62.2% (2,513/4,039)	63.9% (2,570/4,024)	0.12
Smoking	29.4% (944/3,210)	25.5% (858/3,362)	0.04
Prior myocardial infarction	20.5% (837/4,090)	20.5% (838/4,085)	0.94
Prior PCI	14.2% (579/4,090)	13.5% (552/4,085)	0.87
Prior CABG	5.1% (209/4,092)	5.9% (241/4,083)	0.11
Prior stroke	3.1% (127/4,083)	2.7% (110/4,074)	0.27
Renal dysfunction*	0.8% (19/2,532)	1.1% (27/2,529)	0.23
Left ventricular ejection <40%	8.6% (298/3,471)	8.1% (280/3,450)	0.47
Clinical presentation			0.90
Stable CAD	51.0% (1,955/3,837)	51.0% (1,943/3,810)	
Unstable CAD	29.5% (1,132/3,837)	29.6% (1,128/3,810)	
NSTEMI	11.2% (430/3,837)	11.3% (431/3,810)	
STEMI within 24 h	6.4% (246/3,837)	6.4% (242/3,810)	
STEMI >24 h–7 days	1.9% (74/3,837)	1.7% (66/3,810)	
Discharge medication			
Aspirin	99.9% (3,301/3,304)	99.7% (3,280/3,291)	0.05
Clopidogrel	99.8% (3,297/3,304)	99.8% (3,285/3,292)	0.99
Beta-blockers	62.9% (2,287/3,304)	70.5% (2,320/3,292)	0.25
ACE inhibitors/ARB	58.9% (1,946/3,304)	58.0% (1,910/3,292)	0.47
Statins	88.0% (2,906/3,304)	86.7% (2,854/3,292)	0.12
Diseased vessels/patient	1.53 ± 0.01	1.55 ± 0.01	0.34
Number of stented vessels/patient	1.22 ± 0.01	1.22 ± 0.01	0.85
Number of stents/patient	1.61 ± 0.02	1.53 ± 0.01	0.51
Number of lesions stented/patient	1.24 ± 0.01	1.28 ± 0.01	0.37
Total stent length/patient, mm	35.29 ± 0.48	35.83 ± 0.48	0.51
Smallest stent implanted, mm	3.10 ± 0.01	3.10 ± 0.01	0.71
DES type			<0.001
PES	6.3% (259/4,087)	6.3% (257/4,083)	
SES	4.0% (164/4,087)	12.4% (505/4,083)	
CoCr-EES	18.7% (765/4,087)	25.5% (1,042/4,083)	
ZES	70.4% (2,878/4,087)	55.1% (2,251/4,083)	
Mixed	0.5% (21/4,087)	0.7% (28/4,083)	
Stented coronary artery			
Left main	2.4% (80/3,374)	2.3% (77/3,367)	0.75
LAD	63.3% (2,419/3,824)	62.7% (2,383/3,800)	0.69
Left circumflex	31.4% (1,116/3,557)	32.3% (1,159/3,584)	0.80
Right	36.2% (1,302/3,599)	36.1% (1,290/3,575)	0.88
Bifurcation	15.6% (318/2,036)	16.7% (340/2,034)	0.29
Chronic total occlusion	2.9% (98/3,344)	2.5% (84/3,335)	0.11

Values are mean ± SD or % (n/N). *Defined as serum creatinine levels >2 mg/dl.

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blockade; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CoCr-EES = cobalt-chromium everolimus-eluting stent(s); DES = drug-eluting stent(s); LAD = left anterior descending artery; NSTEMI = non ST-segment elevation acute MI; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s); STEMI = ST-segment elevation acute MI; ZES = zotarolimus-eluting stent(s); other abbreviations as in Table 1.

prolonged-treatment groups in the period between DAPT interruption and 1-year follow-up (HR: 1.20; 95% CI: 0.77 to 1.89; p = 0.42) (**Table 3**, Online Table 4). In contrast, short-term DAPT was associated with significantly lower rates of major bleeding (HR: 0.30; 95% CI: 0.10 to 0.91; p = 0.03) and any bleeding (HR: 0.44; 95% CI: 0.21 to 0.91; p = 0.03) compared with prolonged DAPT. The number needed to harm was 78 (95% CI: 163 to 37) for any bleeding and 180 (95% CI: 544 to 59) for major bleeding, with an excess of 12 bleeds and 5 major bleeds for every 1,000 patients treated with long- rather than short-term DAPT. Results of short-term DAPT versus prolonged DAPT did not significantly change after propensity adjustment (for MACE, adjusted HR: 1.28; 95% CI: 0.80 to 2.04; p = 0.31) (for major bleeding, adjusted HR: 0.28; 95% CI: 0.07 to 1.10; p = 0.06).

The evidence network appears in Online Figure 2. No significant differences were apparent in the 1-year rates of MACE between 3- and 6-month DAPT (OR: 0.87; 95% CrI: 0.52 to 1.45), 3-month and 1-year DAPT (OR: 1.06; 95% CrI: 0.76 to 1.51), or 6-month and 1-year DAPT (OR: 1.23; 95% CrI: 0.84 to 1.82) (**Table 4**). In contrast, 6-month DAPT was associated with significantly lower rates of major bleeding compared with 1-year DAPT (OR: 0.38; 95% CrI: 0.14 to 0.95). No significant interactions were apparent between treatment assignments and pre-specified patient subgroups for risk of MACE at 1 year (**Figure 2**).

Kernel hazard functions showing the instantaneous risk of MACE or bleeding in patients on versus off DAPT in the landmark periods between 91 and 180 days, 181 and 270 days, or 271 and 365 days are shown in **Figure 3**. Although differences were not statistically significant between treatment groups for any endpoint, MACE rates were numerically lower and bleeding rates numerically higher for prolonged DAPT versus short-term DAPT at each landmark interval of time. No statistical heterogeneity was found for all pairwise analyses. Visual inspection of funnel plots did not suggest any small study effects or publication bias (Online Figure 3). The Egger test was not statistically significant (p = 0.10 for 1-year MACE; p = 0.74 for 1-year major bleeding).

DISCUSSION

This is the largest and most comprehensive report to date comparing clinical outcomes of short (≤6 months) with prolonged (1 year) DAPT after DES implantation. The principal findings are as follows: 1) at 1 year, short-term DAPT was associated with similar rates of MACE but lower rates of bleeding compared with prolonged DAPT (**Central Illustration**); 2) there were no significant differences in MACE rates between treatment groups in the period between DAPT discontinuation and 1-year follow-up, but there were lower rates of bleeding with short-term compared with prolonged DAPT; 3) these results were consistent across several pre-specified

subgroups of patients, with no interactions apparent between treatment assignment and age, sex, diabetes, clinical presentation, multivessel, or left anterior descending coronary artery disease; and 4) by Bayesian network meta-analysis, no significant differences in 1-year MACE rates were apparent between 3 and 6 months of DAPT, 3 months and 1 year of DAPT, or 6 months and 1 year of DAPT.

Establishing optimal DAPT duration is critical for balancing the risks of ischemic and bleeding complications after DES implantation. Acknowledging the limited statistical power of all current, relevant RCTs (12,14–16), we performed an individual patient data pairwise and network meta-analysis, including 8,180 patients receiving various types of first- and second-generation DES who were treated with DAPT for 3 months, 6 months, or 1 year. At 1-year follow-up, no significant differences in MACE rates were apparent between treatment groups. In contrast, short-term DAPT was associated with significantly lower rates of bleeding compared with prolonged DAPT. These findings are of clinical relevance given the strong association between major bleeding and adverse outcomes. In numerous studies, bleeding has emerged as an independent predictor for subsequent mortality in patients with acute coronary syndrome (ACS) and in those undergoing PCI, with a hazard equivalent to or even greater than that for MI (20–22).

One limitation of trials included in this meta-analysis is that patients were randomized at the time of PCI (or 1 month post-procedure), before 3- or 6-month planned DAPT discontinuation. Events thus occurring before DAPT discontinuation would serve only to dilute differences between treatment arms. For example, in the EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) trial, there was a numerically higher risk of 1-year ST with 6 compared with 12 months of DAPT (13). However, most of this difference accrued in the first 6 months from randomization, when all patients were on DAPT. Therefore, it is improper to attribute higher ST risk to the short-term DAPT strategy in this trial. Moreover, some patients in these trials would have already stopped DAPT before the planned randomization time of DAPT discontinuation (e.g., for an earlier bleeding episode) or would not be able to discontinue DAPT after that time period (e.g., because of an earlier ST). The ideal study design would have randomized patients free from MACE and bleeding at 3 or 6 months to either continue or discontinue DAPT, thereby mimicking the clinical decision that would be made in stable patients. Because of logistical considerations, none of the trials incorporated this optimal design.

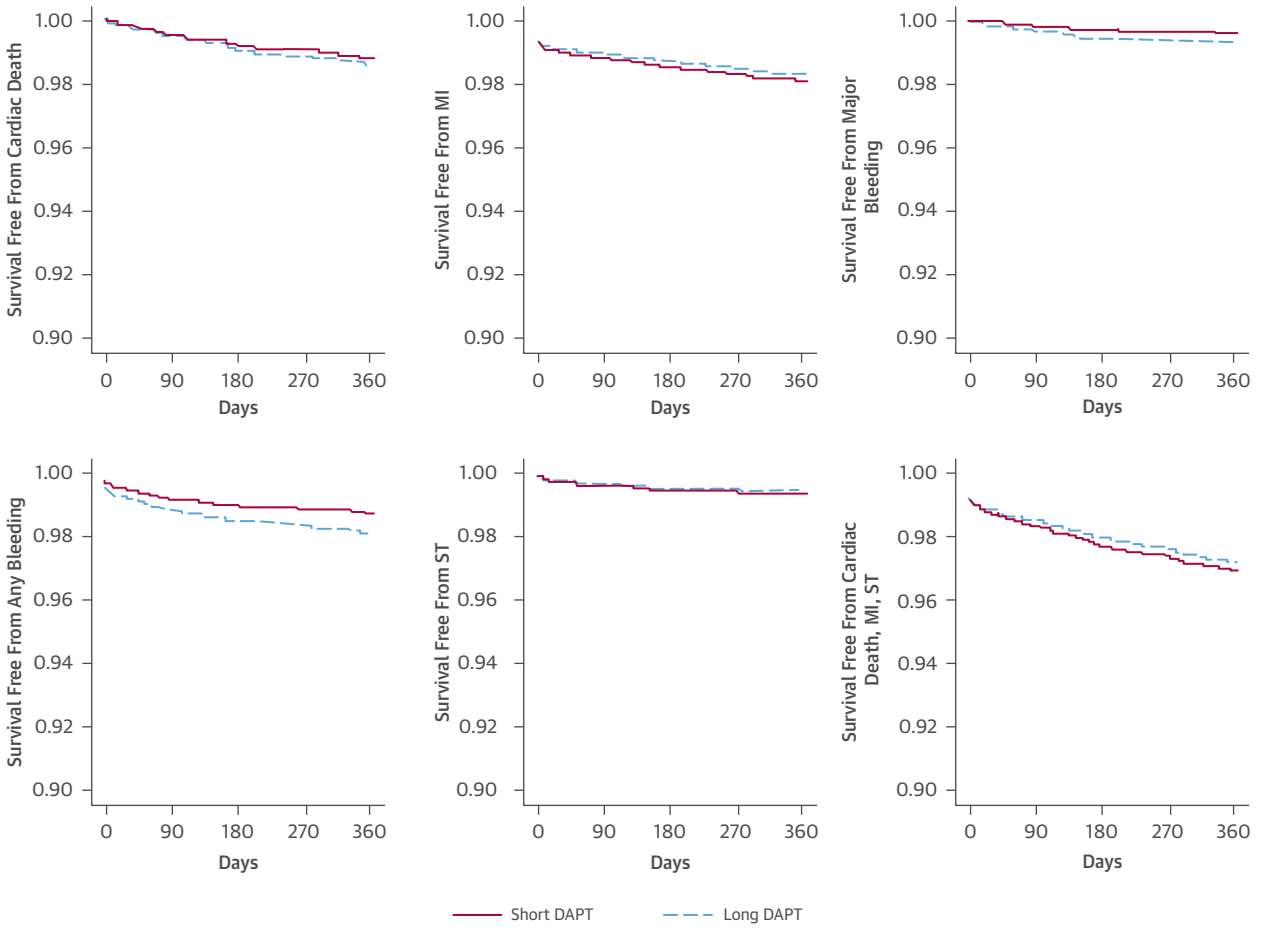
TABLE 3 Clinical Outcomes of Short- Versus Long-Term DAPT

	Hazard Ratio (95% CI)	p Value
Cumulative events at 1 yr*		
Cardiac death, MI, or definite/probable ST	1.11 (0.85–1.43)	0.44
Cardiac death	0.85 (0.59–1.25)	0.47
All-cause death	0.89 (0.66–1.20)	0.47
MI	1.11 (0.81–1.54)	0.52
Stroke	0.82 (0.55–1.52)	0.53
Definite/probable ST	1.19 (0.66–2.13)	0.57
Definite ST	1.14 (0.56–2.33)	0.73
Any bleeding	0.66 (0.46–0.94)	0.02
Major bleeding	0.58 (0.32–1.03)	0.06
Minor bleeding	0.76 (0.50–1.18)	0.22
TVR	1.14 (0.91–1.43)	0.26
Cardiac death, MI	1.08 (0.83–1.41)	0.56
Cardiac death, MI, stroke	1.01 (0.79–1.28)	0.96
Cardiac death, MI, stroke, or major bleeding	0.96 (0.77–1.21)	0.75
All-cause death, MI	1.00 (0.77–1.30)	0.98
All-cause death, MI, stroke	0.95 (0.74–1.22)	0.68
All-cause death, MI, stroke, or major bleeding	0.93 (0.73–1.19)	0.56
Events between DAPT discontinuation and 1 yr†		
Cardiac death, MI, or definite/probable ST	1.21 (0.77–1.89)	0.42
Cardiac death	1.25 (0.71–2.22)	0.43
All-cause death	1.14 (0.73–1.79)	0.58
MI	0.89 (0.47–1.67)	0.70
Stroke	0.74 (0.28–1.92)	0.54
Definite/probable ST	1.56 (0.44–5.56)	0.49
Definite ST	1.75 (0.42–7.14)	0.45
Any bleeding	0.44 (0.21–0.91)	0.03
Major bleeding	0.30 (0.10–0.91)	0.03
Minor bleeding	0.73 (0.28–1.92)	0.53
TVR	1.14 (0.86–1.52)	0.39
Cardiac death, MI	1.14 (0.73–1.79)	0.57
Cardiac death, MI, stroke	1.05 (0.69–1.59)	0.81
Cardiac death, MI, stroke, or major bleeding	0.94 (0.64–1.39)	0.76
All-cause death, MI	1.05 (0.69–1.59)	0.82
All-cause death, MI, stroke	1.01 (0.68–1.49)	0.95
All-cause death, MI, stroke, or major bleeding	0.91 (0.62–1.33)	0.63

*Intention-to-treat analysis. †As-treated analysis.
CI = confidence interval; other abbreviations as in Table 1.

To address this limitation, we performed a landmark analysis of events in the period between DAPT discontinuation and 1-year follow-up, based on actual patient DAPT status (“as treated” cohort). We excluded patients with major events, those lost to follow-up before the landmark time point of DAPT discontinuation, those with premature DAPT discontinuation, and those who continued DAPT beyond the assigned period (unless caused by an earlier adverse event). In this landmark analysis, DAPT discontinuation at 3 or 6 months did not produce higher rates of MACE compared with DAPT continuation to 1 year but was associated with

FIGURE 1 Efficacy and Safety Endpoints



Cumulative hazard curves derived from Cox regression analysis show key efficacy and safety endpoints for short (≤6 months) dual antiplatelet therapy (DAPT) versus prolonged (1 year) DAPT. MI = myocardial infarction; ST = stent thrombosis.

significantly lower rates of bleeding, including major bleeding, confirming the main results of the (intention-to-treat) meta-analysis.

By Bayesian network meta-analysis, no significant differences were apparent in MACE rates between 3 and 6 months of DAPT or either of those time periods versus 1-year DAPT, suggesting that even 3 months of DAPT may suffice after DES implantation. Importantly, no significant differences in clinical, angiographic, and procedural characteristics were apparent among patients treated for the periods of DAPT treatment studied, with DES use the only exception. The even distribution of most effect modifiers across the 3 treatment groups represents, therefore, an unbiased basis for indirect comparisons. However, because of the limited number of studies included, this analysis was insufficiently powered to draw definitive conclusions.

Moreover, kernel hazard functions implemented in the landmark periods of 91 to 180 days, 181 to 270 days, and 271 to 365 days suggest slightly increased rates of ischemic events in each interval of time in patients off compared with on DAPT. These differences were far from being statistically significant; thus, whether these findings are real or chance remains undetermined. Based on this meta-analysis, we estimated that 53,656 patients would be necessary to determine whether the small difference observed between treatment groups is real, with $\alpha = 0.05$ and $\beta = 0.90$. Nonetheless, this potential small benefit associated with prolonged DAPT is clinically more than offset by this strategy's increased risk of major bleeding.

Our findings should be considered in light of the recently reported DAPT trial in which 9,961 patients who were event-free 1 year after DES implantation were randomized to continued thienopyridine

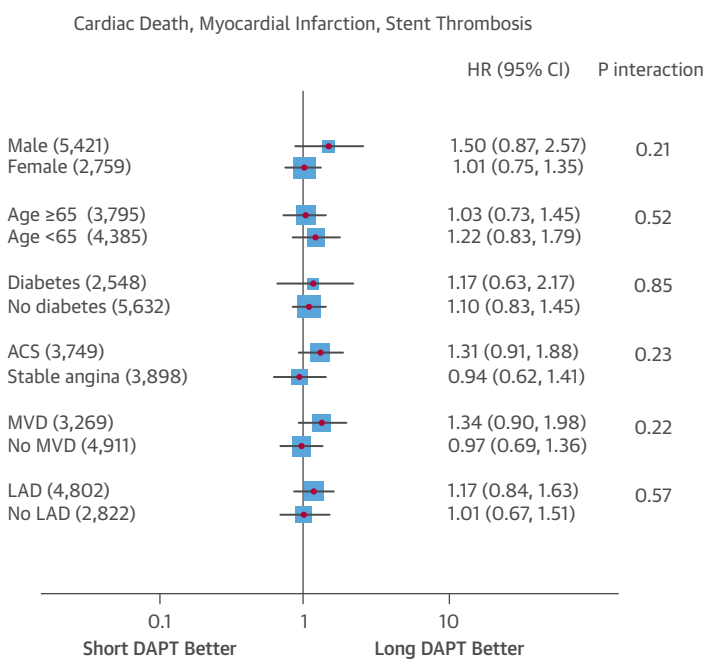
TABLE 4 Effect Estimates for Cumulative 1-Year Events

	3- vs. 6-Month DAPT	3-Month vs. 1-Year DAPT	6-Month vs. 1-Year DAPT	3- or 6-Month vs. 1-Year DAPT	3- vs. 6-Month or 1-Year DAPT
Cardiac death, MI, or definite/probable ST	0.87 (0.52–1.45)	1.06 (0.76–1.51)	1.24 (0.84–1.82)	1.14 (0.88–1.40)	1.06 (0.75–1.52)
Cardiac death	0.94 (0.45–1.96)	0.84 (0.52–1.41)	0.89 (0.51–1.54)	0.88 (0.61–1.25)	0.85 (0.52–1.41)
All-cause death	1.05 (0.58–1.85)	0.89 (0.59–1.35)	0.85 (0.57–1.28)	0.88 (0.66–1.18)	0.83 (0.59–1.35)
MI	0.88 (0.47–1.67)	1.11 (0.73–1.70)	1.25 (0.77–2.04)	1.16 (0.85–1.59)	1.10 (0.72–1.70)
Stroke	1.92 (0.59–6.25)	1.00 (0.42–2.56)	0.52 (0.23–1.12)	0.70 (0.39–1.21)	0.99 (0.41–2.38)
Definite or probable ST	0.55 (0.18–1.59)	1.00 (0.49–2.00)	1.82 (0.81–4.17)	1.30 (0.77–2.27)	1.02 (0.49–2.13)
Definite ST	0.33 (0.07–1.43)	0.64 (0.18–1.89)	1.89 (0.80–4.76)	1.25 (0.64–2.50)	0.65 (0.21–1.79)
Any bleeding	1.37 (0.66–2.78)	0.75 (0.47–1.08)	**0.53 (0.28–0.94)**	**0.65 (0.45–0.92)**	0.71 (0.46–1.08)
Major bleeding	1.70 (0.54–5.88)	0.66 (0.31–1.39)	**0.38 (0.14–0.95)**	**0.52 (0.30–0.93)**	0.66 (0.31–1.39)
Minor bleeding	1.11 (0.42–3.03)	0.78 (0.48–1.28)	0.69 (0.30–1.64)	0.76 (0.50–1.16)	0.78 (0.47–1.27)
TVR	1.05 (0.67–1.67)	1.22 (0.89–1.67)	1.15 (0.83–1.61)	1.19 (0.95–1.49)	1.22 (0.89–1.67)
Cardiac death, MI	0.93 (0.54–1.59)	1.08 (0.75–1.54)	1.16 (0.79–1.72)	1.11 (0.86–1.45)	1.06 (0.75–1.52)
Cardiac death, MI, or stroke	1.06 (0.66–1.72)	1.06 (0.76–1.47)	1.00 (0.70–1.41)	1.03 (0.81–1.32)	1.06 (0.76–1.47)
Cardiac death, MI, stroke, or major bleeding	1.00 (0.63–1.59)	0.96 (0.71–1.30)	0.95 (0.68–1.35)	0.95 (0.76–1.20)	0.95 (0.70–1.30)
All-cause death, MI	0.98 (0.61–1.56)	1.03 (0.75–1.43)	1.05 (0.75–1.47)	1.05 (0.83–1.33)	1.04 (0.76–1.43)
All-cause death, MI, or stroke	1.12 (0.71–1.72)	1.05 (0.77–1.41)	0.94 (0.68–1.30)	0.99 (0.79–1.23)	1.05 (0.78–1.43)
All-cause death, MI, stroke, or major bleeding	1.02 (0.66–1.59)	0.94 (0.69–1.25)	0.91 (0.66–1.25)	0.93 (0.75–1.14)	1.06 (0.75–1.52)

Estimates of risk are reported as odds ratio and 95% credible interval. Statistically significant differences are highlighted in **bold**.
Abbreviations as in Table 1.

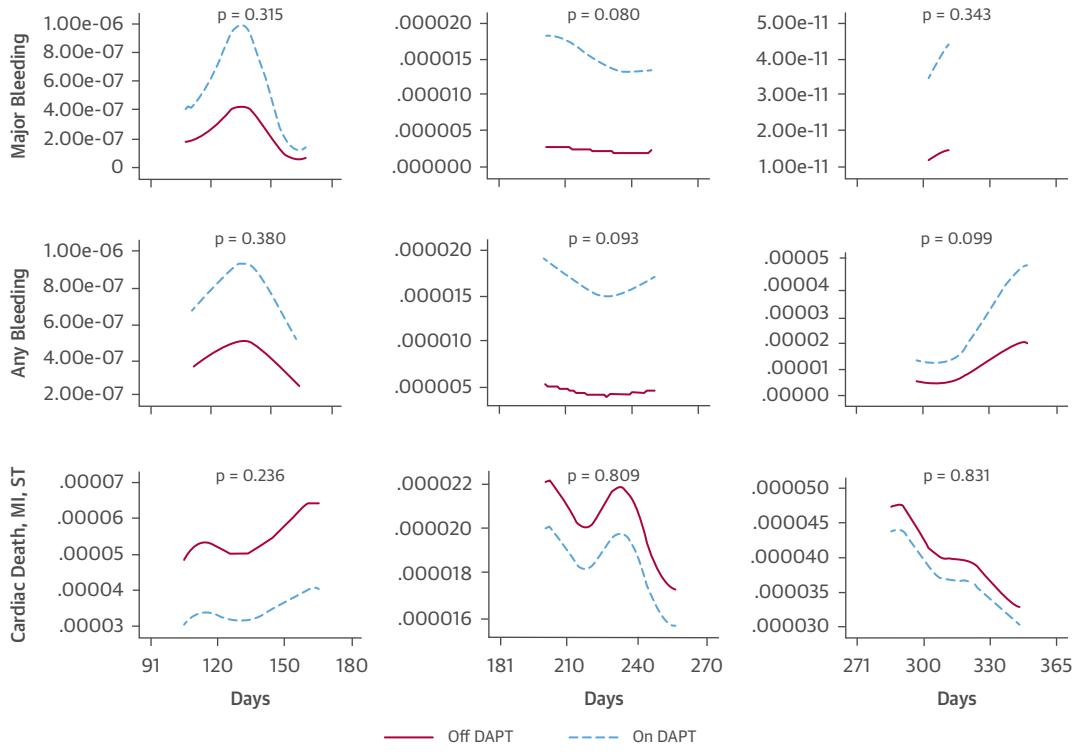
treatment or placebo for another 18 months (23). In that trial, prolonged DAPT significantly reduced the risk of ST and MACE compared with aspirin only, albeit with increased bleeding. All-cause mortality was increased in the prolonged DAPT arm, which may or may not have been caused by chance. Importantly, the subgroup analysis of patients with versus without ACS has not been reported. ST risk in the DAPT trial between 1 and 2.5 years after DES implantation was 1.4% in control subjects (higher than expected from prior large-scale studies) (24), driven by especially high rates in patients receiving PES. Among patients treated with everolimus-eluting stents in DAPT, the absolute reduction in ST with prolonged DAPT was only 0.4% with no significant difference in MACE (although bleeding still increased). In contrast, our results are consistent with the recently reported ISAR-SAFE (Intracoronary Stenting and Antithrombotic Regimen: Safety and Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting) and ITALIC (Is There A Life for DES after Discontinuation of Clopidogrel) results, which showed no additional benefits of prolonging DAPT from 6 to either 12 or 24 months, respectively, with contemporary DES (25,26). Thus, the optimal duration of DAPT after DES implantation may vary in relation to patient characteristics and stent type, suggesting that ongoing risk of ischemia versus bleeding should be considered for each patient when determining DAPT duration.

FIGURE 2 Patient Subgroups and DAPT Duration



Interaction is analyzed between various pre-specified subgroups of patients and DAPT duration; the hazard ratio (HR) and 95% confidence interval (CI) are for the composite of cardiac death, MI, or ST. ACS = acute coronary syndrome(s); LAD = left anterior descending; MVD = multivessel disease; other abbreviations as in Figure 1.

FIGURE 3 Event and Bleeding Risk by Kernel Hazard Function



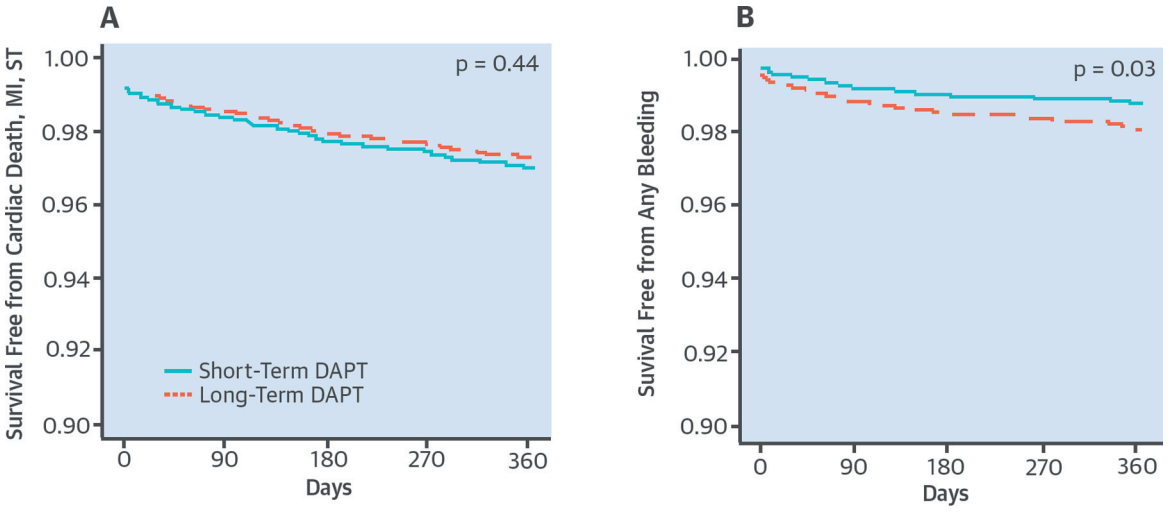
Instantaneous risk of major adverse cardiac events and bleeding were determined by kernel hazard function in patients on DAPT versus those off DAPT between 91 to 180 days, 181 to 270 days, and 271 to 365 days. No significant difference in ischemic events was apparent at any time interval. Abbreviations as in Figure 1.

Our meta-analysis confirms and extends the results from previous reports (27-29). However, a major limitation of previous meta-analyses was the inclusion of trials comparing 1 year with 2 years of DAPT along with shorter-term DAPT trials; consequently, 1-year DAPT was considered "prolonged" therapy in some studies but "short term" in others (27-29). Additionally, trials with heterogeneous study designs were included, such that in some trials patients were randomized at time of PCI (14-16), whereas in others, event-free patients at 1 year were considered for randomization (15). Beyond addressing these drawbacks, our study's most unique aspect is the analysis of patient-level data, allowing adjustments for measured confounders and the analysis of interaction between DAPT duration and pre-specified subgroups of patients, as well as the crossed comparison among 3 months versus 6 months versus 1 year of DAPT.

STUDY LIMITATIONS. As with any meta-analysis, our report shares the original studies' limitations. Patients included were, in general, at low risk, with the exception of the PRODIGY trial patients (16). Moreover, most patients were treated with everolimus-eluting stents or zotarolimus-eluting stents, which have been associated with low event rates. Nonetheless, with an observed MACE rate of 3% in the short-term DAPT group, our study had 90% power to detect a 40% relative risk reduction in MACE rates in the long-term DAPT group with $\alpha = 0.05$. However, the present study was underpowered for lower-frequency event rates, such as ST, for which ~50,000 patients would have been required to demonstrate differences between groups given the observed event rates. Furthermore, subgroup analysis is inherently underpowered and should be considered exploratory and hypothesis-generating only. The same is true for landmark analyses. We therefore do not currently recommend that DAPT be discontinued before 1 year in high-risk patients, particularly those with troponin-positive ACS.

Because zotarolimus- and everolimus-eluting stents were implanted in most patients in the component studies, the results of the present meta-analysis cannot be extrapolated to other types of DES.

CENTRAL ILLUSTRATION **Dual Antiplatelet Therapy Duration After Drug-Eluting Stent Implantation**



Palmerini, T. et al. J Am Coll Cardiol. 2015; 65(11):1092–102.

In a meta-analysis of trials considering time on dual antiplatelet therapy (DAPT) after implantation of drug-eluting stents, short-term (≤6 months) pharmacotherapy produced similar rates of major adverse cardiac events **(A)** but significantly less bleeding **(B)** than longer-term (≥1 year) DAPT. MI = myocardial infarction; ST = stent thrombosis.

Additionally, any possible interaction between DES type and DAPT duration, as suggested by some studies (30), cannot be excluded and deserves further investigation.

All trials included in the meta-analysis were open label, potentially introducing performance bias. Definitions of some clinical endpoints differed slightly across trials, potentially introducing effect modifiers. All patients included in the meta-analysis were treated with clopidogrel as adjunctive therapy to aspirin. It remains undetermined whether results would have differed with the newer, more potent antiplatelet drugs prasugrel and ticagrelor, which is most relevant in patients with ACS. There were few bleeds in patients treated with 3 or 6 months of DAPT, making our analyses insufficiently powered to determine potential differences between these 2 strategies. Finally, few patients with renal dysfunction were enrolled in the included clinical trials; therefore, we could not assess this variable's impact as a possible effect modifier.

CONCLUSIONS

In a meta-analysis of 8,180 patients treated with DES, short-term DAPT was associated with similar rates of MACE but lower rates of bleeding compared with prolonged DAPT. These data suggest that a short-term DAPT strategy is appropriate for selected patients post-DES in the contemporary era, especially those without high-risk clinical or lesion characteristics. The decision to use short-term DAPT should also be conditioned on the individual risk (and likely impact) of ischemic versus bleeding complications for each patient. Additional study is required to determine whether 3 or 6 months of DAPT is preferred in patients for whom an abbreviated regimen is chosen.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In selected patients, a shorter period (3 to 6 months) of DAPT is associated with similar rates of adverse ischemic events and less major bleeding than treatment for 1 year, improving net clinical patient outcomes after DES deployment.

TRANSLATIONAL OUTLOOK: Further studies are needed to define the characteristics of patients who benefit from shorter or longer periods of DAPT after DES implantation.

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KEY WORDS bleeding, major adverse cardiac event(s), stent thrombosis

APPENDIX For supplemental tables and figures, please see the online version of this article.