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Bleeding-Related Deaths in Relation to the Duration of Dual-Antiplatelet Therapy After Coronary Stenting

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ABSTRACT

BACKGROUND Although some randomized controlled trials (RCTs) and meta-analyses have suggested that prolonged dual-antiplatelet therapy (DAPT) may be associated with increased mortality, the mechanistic underpinnings of this association remain unclear.

OBJECTIVES The aim of this study was to analyze the associations among bleeding, mortality, and DAPT duration after drug-eluting stent implantation in a meta-analysis of RCTs.

METHODS RCTs comparing different DAPT durations after drug-eluting stent placement were sought through the MEDLINE, Embase, and Cochrane databases and the proceedings of international meetings. Deaths were considered possibly bleeding related if occurring within 1 year of the episodes of bleeding. Primary analysis was by intention-to-treat. Secondary analysis was performed in a modified intention-to-treat population in which events occurring when all patients were on DAPT were excluded.

RESULTS Individual patient data were obtained for 6 RCTs, and aggregate data were available for 12 RCTs. Patients with bleeding had significantly higher rates of mortality compared with those without, and in a time-adjusted multivariate analysis, bleeding was an independent predictor of mortality occurring within 1 year of the bleeding episode (hazard ratio: 6.93; 95% confidence interval: 4.53 to 10.60; $p < 0.0001$). Shorter DAPT was associated with lower rates of all-cause death compared with longer DAPT (hazard ratio: 0.85; 95% confidence interval: 0.73 to 1.00; $p = 0.05$), which was driven by lower rates of bleeding-related deaths with shorter DAPT compared with prolonged DAPT (hazard ratio: 0.65; 95% confidence interval: 0.43 to 0.99; $p = 0.04$). Mortality unrelated to bleeding was comparable between the 2 groups. Similar results were apparent in the modified intention-to-treat population.

CONCLUSIONS Bleeding was strongly associated with the occurrence of mortality within 1 year after the bleeding event. Shorter compared with longer DAPT was associated with lower risk for bleeding-related death, a finding that may underlie the lower all-cause mortality with shorter DAPT in the RCTs of different DAPT durations after DES. (J Am Coll Cardiol 2017;69:2011–22) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

DAPT = dual-antiplatelet therapy

DES = drug-eluting stent(s)

HR = hazard ratio

IPD = individual patient data

ITT = intention-to-treat

MI = myocardial infarction

RCT = randomized controlled trial

Dual-antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ receptor inhibitor is the standard of care in patients with acute coronary syndromes and after drug-eluting stent (DES) implantation (1). Although DAPT reduces the risk for ischemic events, it also increases the risk for bleeding, presenting challenges in balancing efficacy and safety with respect to the optimal DAPT duration (2). Several randomized controlled trials (RCTs) have suggested that 1-year DAPT may not be necessary after DES implantation in selected patients and that 6 months or even 3 months of DAPT may be sufficient (3-6). In addition, some RCTs and meta-analyses have suggested that longer DAPT after DES implantation may be associated with increased rates of all-cause mortality compared with shorter DAPT, driven by increased noncardiac mortality not offset by reduced cardiac mortality with longer DAPT (7,8). Although some investigators have posited that this association may be due to chance (9), others believe that this finding is robust (2,10,11), and the absence of a signal toward a survival benefit with longer DAPT has influenced guidelines (1).

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In this regard, the mechanism(s) underlying the potentially greater mortality risk with longer DAPT is still a matter of debate. Although several studies have shown that bleeding is an independent predictor of mortality (12-14), no study has ever shown that the increased risk for mortality with longer DAPT compared with shorter DAPT is due to increased rates of bleeding-related deaths. Such an association would lend credence to the potential increase of mortality with longer DAPT. In this regard, the DAPT trial was the first to show reduced rates of mortality with shorter DAPT compared with longer DAPT (7), but a post hoc analysis investigating causes of late

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mortality with DAPT refuted a mechanistic association between bleeding and mortality (9). For this reason, we investigated the time-related association between bleeding and mortality and the impact of DAPT duration on bleeding-related and non-bleeding-related deaths after DES implantation using both individual patient data (IPD) and an aggregate databased meta-analysis.

METHODS

STUDY DESIGN AND SELECTION. For the present meta-analysis, RCTs comparing a shorter duration of DAPT with a longer duration of DAPT as defined in the component trials were considered. 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 "thienopyridine." Two investigators (T.P. and D.D.R.) independently reviewed the titles, abstracts, and studies to determine whether they met the inclusion criteria. Conflicts between reviewers were resolved by consensus. No language, publication date, or publication status restrictions were imposed. The most updated or most inclusive data for a given study were chosen for abstraction. Internal validity of RCTs was assessed by evaluating concealment of allocation, blind adjudication of events, and inclusion of all randomized patients in the analysis. Because patient-level data were not obtained for all the trials comparing shorter DAPT with longer DAPT after DES implantation, we used IPD to investigate the time-related association between bleeding and mortality and aggregate data to study the association between bleeding-related deaths and DAPT duration.

ENDPOINTS AND DEFINITIONS. The primary endpoint of the study was bleeding-related death. In keeping with prior research and considering that most patients included in the meta-analysis were followed for 1 year (15,16), deaths were considered possibly bleeding related if occurring within 1 year of the episode of bleeding. Bleeding events were used as defined and reported in the component trials of the meta-analysis. All bleeding events were considered, independent of the definitions used in the individual trials and the severity of the bleeding episodes. We used patient-level data from 6 RCTs (3–6,17,18), which were previously collected in an international collaborative project comparing 3- or 6-month DAPT with 1-year DAPT after DES implantation (19). Aggregate data from the remaining 6 trials were obtained directly from the principal investigators (20–24) or, in 1 case, from the published report (9). Bleeding-related death was adjudicated using IPD for 6 trials (3–6,17,18) by collecting raw data directly from the principal investigators for 5 trials (20–22,24,25), and from the published report for 1 trial (7). We performed analyses by intention-to-treat (ITT), as described in each original trial. In addition, to minimize the dilution of treatment effect by events occurring in the early period when both groups were treated with DAPT, landmark analyses were performed from the time of DAPT discontinuation in the shorter DAPT treatment group. Thus, in trials randomizing patients at the time of or 1 month after percutaneous coronary intervention, but before the time of DAPT allocation, patients with ischemic or bleeding events occurring before the landmark time point were excluded, resulting in a modified ITT population. The present review was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis statement (26).

STATISTICAL ANALYSIS. For the IPD meta-analysis, data were combined in a single dataset. Continuous variables are presented as mean ± SD and were compared using a 2-way analysis of variance stratified by trial. Categorical variables are presented as counts and percentages and were compared using a conditional regression analysis stratified by trial. Mortality rates were estimated using the Kaplan-Meier method, and differences in mortality between patients with or without bleeding were compared using the log-rank test. To investigate the impact of bleeding and myocardial infarction (MI) on the subsequent risk for mortality, a Cox multivariate analysis was performed with bleeding and MI entered as time-adjusted binary covariates (27). Three time intervals were considered: from bleeding or MI to 30 days, from 31 days after bleeding or MI to 1 year, and >1 year. These time intervals were modeled as categorical variables and fitted in the multivariate model that also included age, sex, diabetes, hypertension, hypercholesterolemia, prior MI, and clinical presentation. Incidence rates were also computed using events divided by patients per time at risk. Notably, given the time-dependent nature of the analysis, time before bleeding was counted in the denominator of the incidence rate of patients with no bleeding.

Hazard ratios (HRs) and 95% confidence intervals (CIs) were used as the summary statistic for the aggregate data-based meta-analysis. Estimates of risk were extracted from the main publications of RCTs, obtained

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

Study	Short vs. Prolonged DAPT Duration (months)	Patients	Primary Endpoint	IPD	Design	Median Follow-Up (From PCI)	Results of the Primary Endpoint
ARCTIC-Interruption	12 vs. 18–30	12 months (n = 624) 18–30 months (n = 635)	Death/MI/ST/stroke/urgent revascularization	No	Superiority	29 months	Superiority of extended DAPT not demonstrated
DAPT	12 vs. 30	12 months (n = 4,941) 30 months (n = 5,020)	Death/MI/ST/stroke Definite/probable ST	No	Superiority	33 months	Superiority demonstrated for both coprimary endpoints
DES-LATE	12 vs. 36	12 months (n = 2,514) 36 months (n = 2,531)	Cardiac death/MI/stroke	No	Superiority	36 months	Superiority of shorter DAPT not demonstrated
EXCELLENT	6 vs. 12	6 months (n = 722) 12 months (n = 721)	Cardiac death/MI/ischemia-driven TVR	Yes	Noninferiority	1 yr	Noninferiority demonstrated
I LOVE IT 2	6 vs. 12	6 months (n = 909) 12 months (n = 920)	Cardiac death/target vessel MI/clinically indicated TVR	No	Noninferiority	18 months	Noninferiority demonstrated
ISAR-SAFE	6 vs. 12	6 months (n = 1,997) 12 months (n = 2,003)	Death/MI/ST/stroke/TIMI major bleeding	No	Noninferiority	15 months	No significant difference in net clinical outcome (early termination)
ITALIC	6 vs. 24	6 months (n = 953) 24 months (n = 941)	Death/MI/TVR/stroke/major bleeding	Yes	Noninferiority	36 months	Noninferiority demonstrated
OPTIDUAL	12 vs 48	12 months (n = 690) 48 months (n = 695)	Death/MI/stroke/major bleeding	No	Superiority	33 months	Superiority of extended DAPT not demonstrated
OPTIMIZE	3 vs. 12	3 months (n = 1,563) 12 months (n = 1,556)	Death/MI/CVA/major bleeding	Yes	Noninferiority	1 yr	Noninferiority demonstrated
PRODIGY	6 vs. 24	6 months (n = 751) 24 months (n = 750)	Death/MI/CVA	Yes	Superiority	2 yrs	Superiority of 24-month DAPT not demonstrated
RESET	3 vs. 12	3 months (n = 1,059) 12 months (n = 1,058)	Cardiac death/MI/ST/TVR/major bleeding	Yes	Noninferiority	1 yr	Noninferiority demonstrated
SECURITY	6 vs. 12	6 months (n = 682) 12 months (n = 717)	Cardiac death/MI/stroke/ST/major bleeding	Yes	Noninferiority	1 yr	Noninferiority demonstrated

CVA = cerebrovascular accident; DAPT = dual-antiplatelet therapy; DES-LATE = Optimal Duration of Clopidogrel Therapy With DES to Reduce Late Coronary Arterial Thrombotic Event; EXCELLENT = Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; I LOVE IT = Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary Revascularization; IPD = individual patient data; ISAR-SAFE = Intracoronary Stenting and Antithrombotic Regimen: Safety and Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting; ITALIC = Is There a Life for DES After Discontinuation of Clopidogrel; MI = myocardial infarction; OPTIDUAL = Optimal Dual Antiplatelet Therapy; OPTIMIZE = Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice; PCI = percutaneous coronary intervention; PRODIGY = The 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; SECURITY = Second Generation Drug-Eluting Stents Implantation Followed by Six Versus Twelve-Month - Dual Antiplatelet Therapy; ST = stent thrombosis; TIMI = Thrombolysis In Myocardial Infarction; TVR = target vessel revascularization.

from principal investigators, or calculated as previously described (28). The pooled HR was calculated by using both fixed-effect (inverse variance weighted) and random-effect (DerSimonian and Laird) models. The extent of small study effects and publication bias was assessed by visual inspection of funnel plots and the Egger test. Pairwise inconsistency was assessed using the I^2 statistic, with values <25%, ≥25% and ≤50%, and >50% representing mild, moderate, and severe heterogeneity, respectively. A p value <0.05 was considered to indicate statistical significance. Statistical analyses were performed using Stata version 12 SE (Stata Corp., College Station, Texas).

RESULTS

As shown in Online Figure 1, we screened 1,042 potentially relevant reports, among which 12 trials met the inclusion criteria (3-7,17,18,20-24). Patient-level data were collected for 6 trials (3-6,17,18) and aggregate data for the remaining 6 trials (9,20-24). The major characteristics of the included trials are shown in **Table 1**, the inclusion and exclusion criteria and internal validity assessment are reported in Online Table 1, the clinical characteristics of randomized patients stratified by DAPT duration are shown in Online Table 2, and the definitions of clinical endpoints appear in Online Table 3.

ASSOCIATION BETWEEN MORTALITY AND BLEEDING IN THE IPD META-ANALYSIS. The IPD meta-analysis included 6 RCTs with 11,473 randomized patients, 5,730 of whom were randomized to shorter DAPT and 5,743 to longer DAPT. Main characteristics of these patients stratified by DAPT duration are shown in **Table 2**. Shorter DAPT was associated with significantly lower rates of bleeding

(HR: 0.66; 95% CI: 0.49 to 0.88; p = 0.004) compared with longer DAPT. Among the 189 patients with bleeding, 36 died (19.0%). The association between bleeding and time to mortality is shown in **Figure 1**. Kaplan-Meier estimates of mortality in patients with bleeding were 13.4% at 30 days and 18.8% at 1 year. As shown in **Figure 2**, in a time-adjusted multivariate analysis, bleeding was an independent predictor of all-cause mortality occurring within 30 days (HR: 11.66; 95% CI: 6.91 to 19.71; p < 0.0001), between 1 month and 1 year (HR: 2.80; 95% CI: 1.37 to 5.71; p = 0.005), cumulative through 1 year (HR: 6.93; 95% CI: 4.53 to 10.60; p < 0.0001), but not beyond 1 year (HR: 0.71; 95% CI: 0.18 to 2.87; p = 0.63). MI was also associated with significantly higher rates of all-cause mortality occurring within 30 days (HR: 26.45; 95% CI: 16.15 to 43.32; p < 0.0001), between 1 month and 1 year (HR: 3.25; 95% CI: 1.55 to 6.81; p = 0.002), cumulative through 1 year (HR: 10.19; 95% CI: 6.78 to 15.30; p < 0.0001), but not beyond 1 year (HR: 1.53; 95% CI: 0.63 to 3.72; p = 0.35) (**Figure 2**). Incidence rates of mortality associated with bleeding or MI across all time intervals considered are also reported in **Figure 2**. Other variables independently associated with all-cause death were age (HR: 1.06; 95% CI: 1.05 to 1.08; p < 0.0001), diabetes (HR: 1.39; 95% CI: 1.08 to 1.79; p = 0.01), and clinical presentation with acute coronary syndromes (HR: 1.32; 95% CI: 1.01 to 1.73; p = 0.048). Of note, 8 of the 17 patients (47.1%) who had bleeding and MI died, 3 of whom had been treated with shorter DAPT and 5 with longer DAPT. Similar results were apparent in the landmark period between DAPT discontinuation and the end of follow-up (Online Table 4). Specifically, estimates of mortality in this population were 22.5 per 100 patient-years for those with bleeding versus 1.5 per 100 patient-years for those without bleeding (p < 0.0001).

CLINICAL OUTCOMES IN THE ITT POPULATION. Data on mortality, MI, and bleeding were obtained for all 12 RCTs including 34,880 randomized patients, 17,364 of whom were randomized to shorter DAPT and 17,516 to longer DAPT. After a median follow-up period of 16 months, shorter DAPT was associated with lower rates of all-cause death (HR: 0.85; 95% CI: 0.73 to 1.00; p = 0.05), noncardiac death (HR: 0.72; 95% CI: 0.55 to 0.94; p = 0.01), and any bleeding (HR: 0.66; 95% CI: 0.53 to 0.83; p < 0.0001) but higher rates of MI (HR: 1.33; 95% CI: 1.09 to 1.62; p < 0.0001) compared with longer DAPT (Online Figure 2). Among the 754 patients who had bleeding, 89 died (87 within 1 year and 2 beyond 1 year). As shown in the **Central Illustration** and Online Figure 3, shorter DAPT was associated with significantly lower rates of bleeding-related deaths compared with longer DAPT (HR: 0.65; 95% CI: 0.43 to 0.99; p = 0.04). Conversely, there was no significant difference between shorter versus longer DAPT in the rates of death not related to

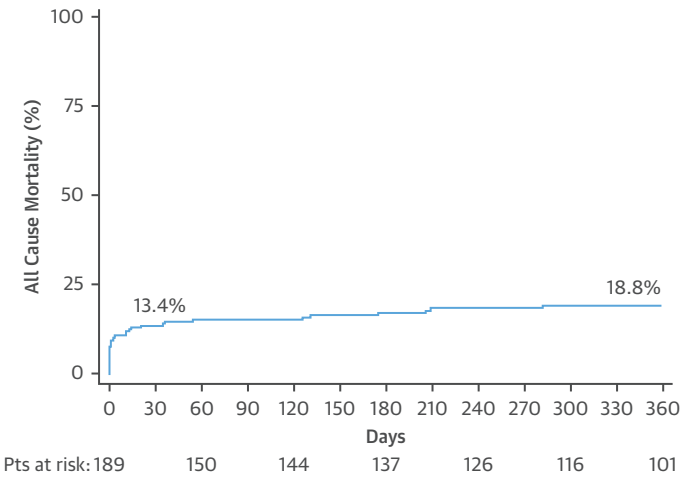
TABLE 2 Baseline Clinical, Angiographic, and Procedural Characteristics of Patients Included in the Individual Patient-Level Meta-Analysis (6 Randomized Trials) Stratified According to Dual-Antiplatelet Therapy Duration

	Short DAPT (≤6 Months)	Long DAPT (≥1 yr)	p Value
Age, yrs	63.1 ± 10.7	63.2 ± 10.8	0.59
Male	70.3 (4,029/5,730)	69.5 (3,990/5,743)	0.30
Hypertension	78.0 (4,466/5,723)	78.6 (4,507/5,732)	0.37
Diabetes mellitus	31.4 (1,784/5,688)	31.7 (1,809/5,701)	0.63
Hypercholesterolemia	63.9 (3,599/5,632)	64.5 (3,634/5,637)	0.52
Smoking	22.6 (1,117/4,946)	21.7 (1,073/4,939)	0.29
Prior myocardial infarction	21.9 (1,129/5,166)	21.7 (1,121/5,157)	0.10
Prior PCI	18.3 (948/5,187)	17.0 (879/5,172)	0.16
Prior CABG	6.0 (312/5,188)	6.0 (325/5,167)	0.46
Prior stroke	4.2 (156/3,751)	3.7 (136/3,701)	0.31
Renal dysfunction*	0.6 (20/43,214)	0.8 (27/3,246)	0.30
Left ventricular ejection fraction <40%	8.1 (396/4,862)	7.7 (375/4,870)	0.45
Clinical presentation			0.76
Stable CAD	56.8 (3,132/5,515)	57.1 (3,167/5,543)	
Unstable CAD	29.0 (1,604/5,515)	28.6 (1,583/5,543)	
NSTEMI	8.3 (459/5,515)	8.8 (485/5,543)	
STEMI within 24 h	4.5 (246/5,515)	4.4 (242/5,543)	
STEMI >24 h to <7 days	1.3 (74/5,515)	1.2 (66/5,543)	
Discharge medications			
Aspirin	99.9 (3,976/3,982)	99.7 (3,993/4,007)	0.09
Clopidogrel	99.6 (3,966/3,982)	99.7 (3,997/4,008)	0.31
Beta-blockers	69.2 (2,286/3,304)	70.4 (2,320/3,292)	0.25
ACE inhibitors/ARBs	58.9 (1,946/3,304)	58.0 (1,910/3,392)	0.47
Statins	88.0 (2,906/3,304)	86.7 (2,854/3,292)	0.12
Diseased vessels/patient	1.50 ± 0.83	1.50 ± 0.82	0.66
Number of stented vessels/patient	1.21 ± 0.45	1.21 ± 0.45	0.78
Number of stents/patient	1.52 ± 0.84	1.53 ± 0.83	0.56
Number of lesions stented/patient	1.28 ± 0.54	1.29 ± 0.54	0.79
Total stent length/patient, mm	35.29 ± 24.32	35.83 ± 23.96	0.41
DES type			<0.01
PES	5.8 (259/4,500)	5.7 (257/4,537)	
SES	3.6 (164/4,500)	11.1 (505/4,537)	
CoCr-EES	20.0 (901/4,500)	25.9 (1,177/4,537)	
ZES fast release	70.1 (3,155/4,500)	56.7 (2,570/4,537)	
Mixed	0.5 (21/4,500)	0.6 (28/4,537)	
Stented coronary artery			
Left main	2.3 (80/3,374)	2.3 (77/3,367)	0.15
LAD	63.3 (2,419/3,824)	62.7 (2,383/3,800)	0.51
Left circumflex	31.4 (1,116/3,557)	32.3 (1,159/3,584)	0.26
Right	36.2 (1,302/3,599)	36.0 (1,290/3,575)	0.83
Bifurcation	9.5 (318/3,344)	10.2 (340/3,335)	0.28
Chronic total occlusion	2.9 (98/3,344)	2.2 (73/3,335)	0.30

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

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

FIGURE 1 Mortality After the Occurrence of Bleeding

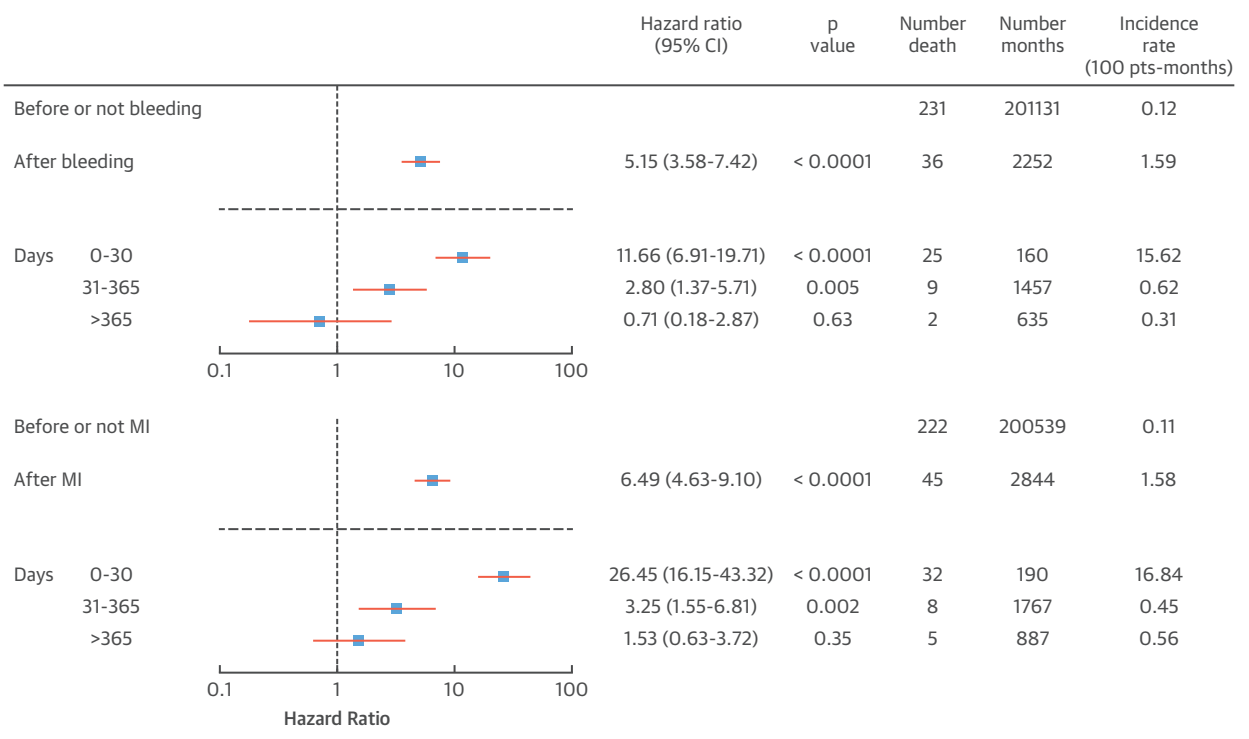


Patients (Pts) were censored at 1 year or earlier, depending on the duration of follow-up of the studies included in the meta-analysis. Most deaths occurred within 1 month of the episodes of bleeding.

bleeding (HR: 0.90; 95% CI: 0.75 to 1.07) (**Central Illustration**, Online Figure 3).

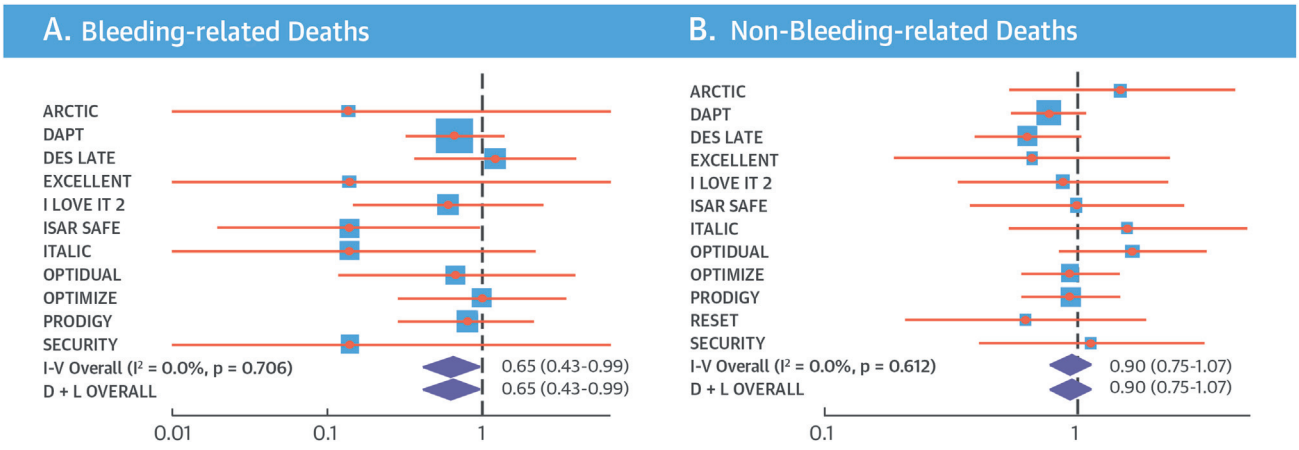
CLINICAL OUTCOMES IN THE MODIFIED ITT POPULATION. The modified ITT population consisted of 33,834 patients, 16,744 of whom were randomized to shorter DAPT and 17,100 to longer DAPT. As shown in Online Figure 4, results in the modified ITT population were similar to those in the ITT population. In particular, as shown in **Figure 3**, shorter DAPT was associated with lower rates of bleeding-related deaths compared with longer DAPT (HR: 0.59; 95% CI: 0.37 to 0.95; p = 0.02), whereas the rates of non-bleeding-related deaths were similar between the 2 groups (HR: 0.90; 95% CI: 0.74 to 1.10; p = 0.30). As shown in **Figure 4**, similar results were apparent in a sensitivity analysis in which bleeding-related death was defined as death occurring within 30 days from the episode of bleeding. Specifically, in this analysis including 9 RCTs and 20,567 patients, there were 10 episodes of bleeding-related death among the 10,191 patients randomized to shorter DAPT versus 21 episodes among the

FIGURE 2 Time-Adjusted Multivariate Analysis and Incidence Rates of All-Cause Mortality in the Intention-to-Treat Population



Bleeding and myocardial infarction (MI) were independent predictors of mortality occurring within 1 month and between 1 month and 1 year from each event, but not beyond 1 year after the event. CI = confidence interval; pts-months = patient-months.

CENTRAL ILLUSTRATION **Estimates of Risk in the Intention-to-Treat Population for Bleeding-Related Deaths and Deaths Not Related to Bleeding Between Shorter and Longer Dual-Antiplatelet Therapy**



Palmerini, T. et al. J Am Coll Cardiol. 2017;69(16):2011–22.

Short dual-antiplatelet therapy (DAPT) was associated with significantly lower rates of bleeding-related deaths compared with prolonged DAPT **(A)**, whereas no significant difference was apparent in deaths not related to bleeding between the 2 groups **(B)**. D+L = DerSimonian and Laird; DES-LATE = Optimal Duration of Clopidogrel Therapy With DES to Reduce Late Coronary Arterial Thrombotic Event; EXCELLENT = Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; I LOVE IT = Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary Revascularization; I-V = inverse variance; ISAR-SAFE = Intracoronary Stenting and Antithrombotic Regimen: Safety and Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting; ITALIC = Is There a Life for DES After Discontinuation of Clopidogrel; OPTIDUAL = Optimal Dual Antiplatelet Therapy; OPTIMIZE = Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice; PRODIGY = The 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; SECURITY = Second Generation Drug-Eluting Stents Implantation Followed by Six Versus Twelve-Month - Dual Antiplatelet Therapy.

10,376 assigned to longer DAPT (HR: 0.49; 95% CI: 0.24 to 0.99; p = 0.04).

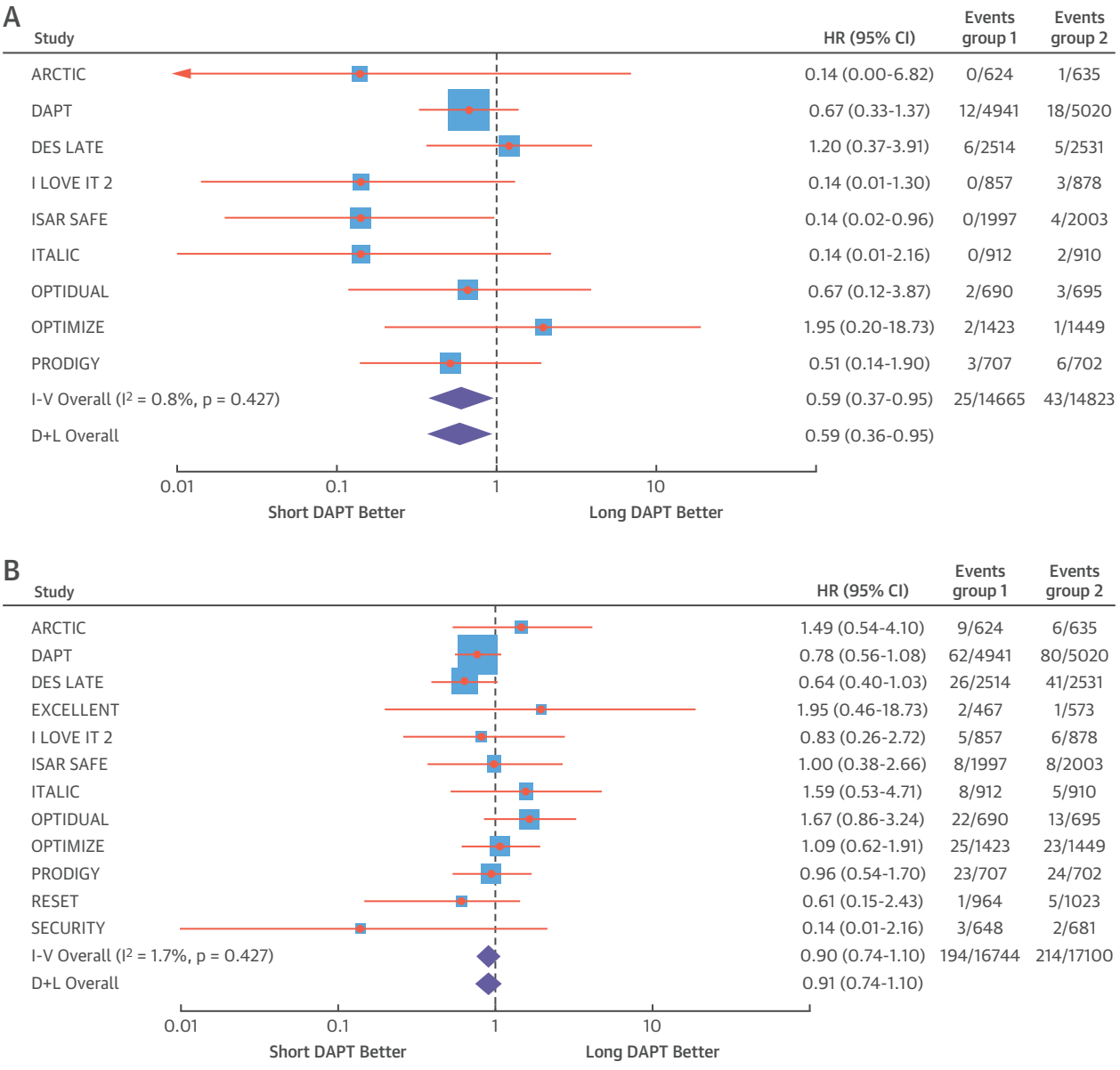
ADDITIONAL ANALYSES. No significant heterogeneity was present in any pairwise analyses. As shown in Online Figure 5, visual inspection of funnel plots did not suggest publication bias for all-cause mortality. By Egger's test, there was no publication bias or small study effects (p = 0.74).

DISCUSSION

In the present study, we investigated the time-related association between bleeding and mortality as well as the association between bleeding-related deaths and DAPT duration after DES implantation in an aggregate-based meta-analysis of 12 RCTs, with IPD analyses from 6 RCTs. The principal findings are as follows: 1) patients with bleeding had significantly higher rates of all-cause mortality compared with patients without bleeding, and in a time-adjusted multivariate analysis, bleeding was an independent predictor of mortality occurring within 1 year of its occurrence; 2) in the ITT population, shorter DAPT was associated with significantly lower rates of bleeding-related deaths compared with longer DAPT, whereas no significant difference was apparent between the 2 DAPT strategies in the rates of death not related to bleeding; and 3) similar results were apparent in the modified ITT population in which events occurring when patients in both randomization arms were on DAPT were excluded.

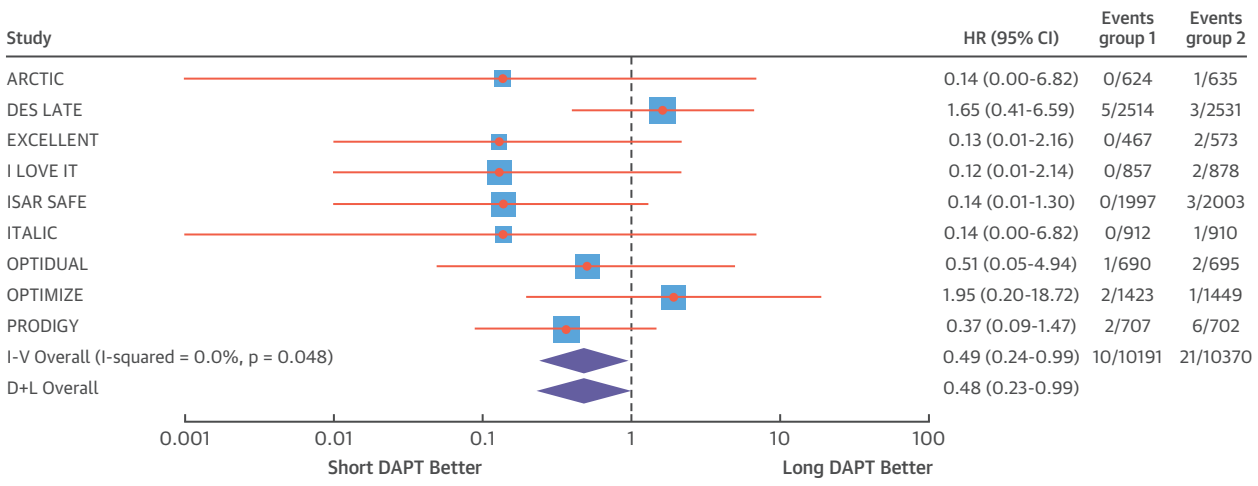
RISK VERSUS BENEFIT WITH PROLONGED DAPT. Although prolonging DAPT beyond 1 year after DES implantation significantly reduces the risk for stent thrombosis and major adverse cardiovascular events (7), studies have demonstrated that this practice substantially increases the risk for bleeding and may result in greater mortality (8). Specifically, in the DAPT trial, continued treatment with aspirin and a thienopyridine compared with aspirin monotherapy between 12 and 30 months after DES implantation reduced the risk for stent thrombosis by 71% and major adverse cardiovascular events by 29% but increased the risk for bleeding by 93% (7). All-cause mortality was also nominally (p = 0.05) increased with longer DAPT compared with shorter DAPT in that trial, which was due to an increased risk for non-cardiovascular mortality not offset by a concomitant

FIGURE 3 Estimates of Risk in the Modified Intention-to-Treat Population for Bleeding-Related Deaths and Deaths Not Related to Bleeding Between Shorter and Longer Dual-Antiplatelet Therapy



Short dual-antiplatelet therapy (DAPT) was associated with significantly lower rates of bleeding-related deaths compared with prolonged DAPT **(A)**, whereas no significant difference was apparent in deaths not related to bleeding between the 2 groups **(B)**. CI = confidence interval; DAPT = dual-antiplatelet therapy; DES-LATE = Optimal Duration of Clopidogrel Therapy With DES to Reduce Late Coronary Arterial Thrombotic Event; EXCELLENT = Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; I LOVE IT = Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary Revascularization; ISAR-SAFE = Intracoronary Stenting and Antithrombotic Regimen: Safety and Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting; ITALIC = Is There a Life for DES After Discontinuation of Clopidogrel; OPTIDUAL = Optimal Dual Antiplatelet Therapy; OPTIMIZE = Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice; PRODIGY = The 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; SECURITY = Second Generation Drug-Eluting Stents Implantation Followed by Six Versus Twelve-Month - Dual Antiplatelet Therapy.

FIGURE 4 **Sensitivity Analysis Showing Estimates of Risk for Bleeding-Related Death, Defined as Death Occurring Within 30 days of Bleeding, in the Modified Intention-to-Treat Population Between Shorter and Longer Dual-Antiplatelet Therapy**



Short DAPT was associated with significantly lower rates of bleeding-related deaths compared with prolonged DAPT. Abbreviations as in Figure 3.

decrease in cardiovascular mortality (7). However, because mortality was not the primary endpoint of the DAPT trial, it remained undetermined whether those findings were real or the play of chance. A pairwise and Bayesian network meta-analysis comparing shorter DAPT with longer DAPT in patients undergoing DES implantation from 10 randomized trials with 31,666 patients was subsequently performed to address this issue (8). In that study, shorter DAPT was strongly associated with decreased bleeding and mortality compared with longer DAPT, confirming the findings from the DAPT trial. However, the correlates of mortality were not specifically investigated, and the potential mechanism(s) underlying the reduced risk for mortality with shorter DAPT compared with longer DAPT remained speculative, adding uncertainty to the validity of the association.

ASSOCIATION BETWEEN BLEEDING AND MORTALITY. As numerous studies have reported a strong association between bleeding and mortality (12–14), the most intuitive explanation for the greater mortality in patients treated with longer rather than shorter DAPT would be an excess in bleeding-related deaths. However, a post hoc analysis from the DAPT trial suggested that the increased risk for mortality with continued thienopyridine compared with aspirin monotherapy was not due to an excess in bleeding-related deaths but was rather related to an excess of cancer-related deaths with longer DAPT, likely due to chance (9). No prior studies have specifically looked for a relationship between the excess hazard of bleeding and death with longer DAPT.

We therefore undertook the present meta-analysis using IPD from 6 RCTs and aggregate data from 12 RCTs. Our study confirms the strong association between bleeding and mortality and has newly demonstrated a significant reduction of bleeding-related deaths with shorter DAPT compared with longer DAPT, underlying the mortality reduction with shorter DAPT. In contrast, non-bleeding-related deaths were not significantly different with the 2 strategies. Of note, bleeding-related deaths were numerically higher with longer DAPT compared with shorter DAPT also in the DAPT trial, although the difference was not statistically significant (9). Moreover, those patients at increased risk for bleeding with prolonged DAPT in the DAPT trial (DAPT score ≤2) had also substantially greater mortality with longer compared with shorter DAPT, supporting the link between bleeding and mortality (29).

MECHANISTIC UNDERPINNINGS OF INCREASED MORTALITY WITH BLEEDING. Bleeding might influence mortality through several mechanisms, including direct bleeding-related deaths, bleeding lowering the threshold for ischemia, heart failure or arrhythmias, the deleterious effect of red blood cell transfusions, and discontinuation of DAPT and other beneficial medications (2). Indeed, most of the bleeding-related deaths in our dataset (69%) occurred within 30 days of the episodes of bleeding, an interval

of time that is compatible with a causal relationship between bleeding and mortality. This finding is consistent with prior studies that have reported a strong association between bleeding and short-term mortality in patients with acute coronary syndrome (15). However, in our analysis, bleeding was associated with increased mortality occurring not only within 30 days but also between 1 month and 1 year. In this regard, in the PREMIER (Prospective Registry Evaluating Myocardial Infarction: Events and Recovery) registry of 2,498 patients with acute MI, patients with bleeding during hospital admissions were less likely to be on aspirin, thienopyridines, statins, angiotensin-converting enzyme inhibitors, and beta-blockers even 1 year after the episodes of bleeding (30). Thus, the late mortality associated with an episode of bleeding may be related not only to the interruption of antiplatelet therapy but also to discontinuation of other medications known to improve the prognosis of patients with coronary artery disease. Further studies are required to determine whether bleeding affects early versus late mortality through different mechanisms.

PRIOR META-ANALYSES. Several meta-analysis examining the effect of DAPT duration after DES placement have been reported (8,19,31). Distinctive aspects of the present meta-analysis are the inclusion of 2 more RCTs, the investigation of the time-related association between bleeding and mortality, and the evaluation of bleeding-related and non-bleeding-related deaths in relation to DAPT duration. With 3,214 more randomized patients than in previous studies, we were able not only to confirm the increased risk for mortality with longer DAPT compared with shorter DAPT but, more important, to establish the reduction in bleeding-related deaths with shorter DAPT as the likely explanation of the lower rate of all-cause mortality with the shorter regimen.

STUDY LIMITATIONS. A limitation of several of the RCTs included in this meta-analysis is the fact that patients were randomized at the time of percutaneous coronary intervention (or 1 month after the procedure) (3–6,17,18), not at the time of DAPT allocation. Thus, events occurring prior to DAPT discontinuation in the aspirin monotherapy arm would serve only to confound any differences between the treatment arms. To address this limitation, we performed a landmark analysis of events in the period between DAPT discontinuation and the end of follow-up, excluding events occurring before the landmark time point of DAPT discontinuation. In this modified ITT cohort, similar results were apparent as in the ITT population. Indeed, the difference in bleeding-related deaths between shorter DAPT versus longer DAPT was even more evident in the modified ITT population than in the ITT population.

Several other limitations of this study should be acknowledged. As with any meta-analysis, our report shares the limitations of the original studies. Specifically, adjudication of bleeding and bleeding-related death may be challenging even in randomized trials, and therefore these findings should be interpreted with caution. Definitions of bleeding differed across trials, and events in the meta-analysis were considered as adjudicated in the individual trials, potentially introducing effect modifiers. A significant proportion of implanted DES consisted of first-generation devices, which are no longer used in clinical practice. Several trials included in the meta-analysis were open label, potentially introducing bias. Because the timing of mortality after bleeding was not available for the DAPT trial, we considered all reported bleeding-related deaths as occurring within 1 year of the episodes of bleeding (9). Most patients included in the meta-analysis were treated with clopidogrel as adjunctive therapy to aspirin. It remains undetermined whether our results would have been different with the new and more potent antiplatelet drugs prasugrel and ticagrelor. Additionally, the majority of patients in the included trials did not have high-risk acute coronary syndromes, so the present analysis of stented patients does not contradict the finding that prolonged DAPT appears beneficial in patients with prior acute coronary syndrome who are at low risk for bleeding (32,33). As data on protocol violations such as crossover rates between treatment arms or premature DAPT discontinuation were not systematically reported in all RCTs included in the meta-analysis, we could not perform a “per protocol” analysis, which could have contributed valuable information to the study. The pattern of DAPT cessation was not analyzed in any of the trials included in the meta-analysis, a recent study revealing a strong association between modality of DAPT cessation and mortality (10). Finally, even though the present study is the strongest analysis to date linking differences in mortality with shorter versus longer DAPT to a reduction in bleeding-related deaths, our analysis cannot establish causality as the role of unmeasured confounders cannot be excluded.

CONCLUSIONS

Although longer DAPT reduces the risk for ischemic events compared with shorter DAPT, longer DAPT is also associated with greater mortality due to an increase in bleeding-related deaths.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

In patients with DES, mortality is often related to bleeding within the previous year, and the risk for bleeding-related death is lower with shorter DAPT therapy.

TRANSLATIONAL OUTLOOK: Further studies are warranted to identify patients most likely to benefit from extending DAPT therapy for more than 1 year after DES.

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KEY WORDS drug-eluting stent, dual antiplatelet therapy, mortality

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