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Duration of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation

A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

BACKGROUND The optimal duration of dual antiplatelet therapy (DAPT) after drug-eluting stent (DES) implantation is unclear, and its risks and benefits may vary according to DES generation.

OBJECTIVES The goal of this study was to evaluate the efficacy and safety of DAPT after DES implantation.

METHODS We included randomized controlled trials that tested different durations of DAPT after DES implantation: shorter dual antiplatelet therapy (S-DAPT) was defined as the per-protocol minimum duration of DAPT after the procedure, and longer dual antiplatelet therapy (L-DAPT) was defined as the per-protocol period of more prolonged DAPT. The primary efficacy and safety outcomes were definite/probable stent thrombosis and clinically significant bleeding (CSB), respectively.

RESULTS Ten randomized controlled trials (N = 32,135) were included. Compared with L-DAPT, S-DAPT had an overall higher rate of stent thrombosis (odds ratio [OR]: 1.71 [95% confidence interval (CI): 1.26 to 2.32]; p = 0.001). The effect of S-DAPT on stent thrombosis was attenuated with the use of second-generation DES (OR: 1.54 [95% CI: 0.96 to 2.47]) compared with the use of first-generation DES (OR: 3.94 [95% CI: 2.20 to 7.05]; p for interaction = 0.008). S-DAPT had an overall significantly lower risk of CSB (OR: 0.63 [95% CI: 0.52 to 0.75]; p < 0.001). Finally, a numerically lower all-cause mortality rate was observed with S-DAPT (OR: 0.87 [95% CI: 0.74 to 1.01]; p = 0.073).

CONCLUSIONS S-DAPT had overall lower rates of bleeding yet higher rates of stent thrombosis compared with L-DAPT; the latter effect was significantly attenuated with the use of second-generation DES, although the analysis may have been limited by the varying DAPT durations among studies. All-cause mortality was numerically higher with L-DAPT without reaching statistical significance. Prolonging DAPT requires careful assessment of the trade-off between ischemic and bleeding complications. (J Am Coll Cardiol 2015;65:1298–310) © 2015 by the American College of Cardiology Foundation.

A period of dual antiplatelet therapy (DAPT) is required to prevent thrombotic complications after percutaneous coronary intervention (PCI) with drug-eluting stents (DES) (1,2). Interruption or disruption of DAPT during this period is associated with a high risk for ischemic events, including stent thrombosis, especially during the first weeks after DES implantation (3,4).

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The pathobiological rationale of DAPT after DES-PCI is based on the need to protect the stented vascular segment from the development of stent thrombosis while vascular healing and progressive strut endothelization are ongoing (5). In addition, more prolonged DAPT may confer protection from atherothrombotic events occurring outside the stented segment throughout the coronary vasculature (6).

Prolonged DAPT after the recommended period reduces stent-related and non-stent-related adverse ischemic events following PCI (7). Recently, the DAPT (Dual Antiplatelet Therapy) trial demonstrated reduced rates of stent thrombosis and myocardial infarction (MI) with DAPT extended beyond 1 year after DES implantation. However, this ischemic benefit was paired with an increased risk in bleeding and possibly subsequent all-cause mortality.

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Several randomized controlled trials (RCTs) have attempted to address the question of what would be the safest and shortest DAPT duration (ranging from 3 to 6 months) after implantation of first- and second-generation DES. Due to the rarity of stent thrombosis events, each trial had limited statistical power, and the safest and shortest DAPT duration has not yet been reliably determined. Previously published meta-analyses of RCTs comparing short- versus long-term DAPT had limited statistical power and showed no significant differences in antithrombotic efficacy between regimens, while longer dual antiplatelet therapy (L-DAPT) treatment was associated with an increased risk for bleeding (8,9). With inclusion of several recent large RCTs, the present meta-analysis has enhanced statistical power, and we therefore sought to assess the efficacy and safety of shorter dual antiplatelet therapy (S-DAPT) versus L-DAPT after DES implantation, with particular focus on the risk of stent thrombosis with the use of current (second-generation) DES.

METHODS

Study groups were pre-specified as follows: S-DAPT, defined as the per-protocol minimum duration of DAPT after DES implantation (after which, patients of this treatment arm were continued on aspirin alone); and L-DAPT, defined as the per-protocol period of prolonged DAPT in each trial. In addition, RCTs evaluating durations of DAPT were classified as abbreviated-term DAPT studies (i.e., RCTs evaluating S-DAPT duration of 3 or 6 months vs. longer duration) and extended-term DAPT studies (i.e., RCTs evaluating DAPT discontinuation at 12 months vs. longer duration).

The pre-specified primary efficacy outcome was the incidence of definite or probable stent thrombosis, as defined by using the criteria of the Academic Research Consortium (10). The main safety outcome was clinically significant bleeding (CSB), defined as a bleeding event fulfilling the definition of: 1) minor or major Thrombolysis In Myocardial Infarction (TIMI) bleeding; 2) type 3 or 5 bleeding according to the Bleeding Academic Research Consortium (BARC); 3) Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients major bleeding; or 4) Global Use of Strategies to Open Occluded Arteries moderate or severe bleeding (11). Bleeding definition details are described in Online Table 1. Additional outcomes of interest were MI, stroke, cardiovascular death, and all-cause mortality. Outcomes were reported at the maximum time of follow-up available (**Table 1**). The study was performed according to the Quality of Reporting of Meta-Analysis statement (12).

MEDLINE, Scopus, the Cochrane Library, and Internet sources were searched for abstracts, manuscripts, and conference reports; there were no language or date restrictions. All the RCTs comparing different durations of DAPT after implantation of a DES were included in the meta-analysis. The final search yielded 10 RCTs comparing various durations of S-DAPT and L-DAPT after implantation of different types of DES.

DATA EXTRACTION. Two investigators independently reviewed the studies and reported the results in a structured dataset. Disparities between investigators regarding the inclusion of each trial were resolved by consensus by a third independent investigator. Pre-specified data elements were extracted from each trial; these elements included S-DAPT and L-DAPT duration, maximum length of follow-up, sample size, baseline characteristics, outcome measures, and endpoints of interest. Events from each trial were recorded according to the intention-to-treat principle. Endpoint definitions used in each trial are outlined in Online Table 2.

STATISTICAL ANALYSIS. The odds ratios (ORs) associated with S-DAPT versus L-DAPT from the abstracted data were estimated. Analyses were stratified according to DAPT trial type (abbreviated-term and extended-term DAPT studies). The average effects for the outcomes and 95% confidence intervals (CIs) were calculated by means of random effects models according to the method of DerSimonian

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
CSB = clinically significant bleeding
DAPT = dual antiplatelet therapy
DES = drug-eluting stent(s)
L-DAPT = longer dual antiplatelet therapy
MI = myocardial infarction
OR = odds ratio
PCI = percutaneous coronary intervention
RCT = randomized controlled trial
S-DAPT = shorter dual antiplatelet therapy
TIMI = Thrombolysis In Myocardial Infarction

TABLE 1 Characteristics of the Randomized Clinical Trials

Study (Ref. #)	Year	Study Population (n)	S-DAPT (Months)	L-DAPT (Months)	Time of Follow-Up*	Placebo-Controlled	Primary Endpoint	Age (yrs)	DM (%)	ACS (%)	1G-DES (%)	2G-DES (%)
3- or 6-month DAPT discontinuation trials												
ISAR-SAFE (16)	2014	4,000	6	12	6	Yes	Composite of death, MI, stroke, stent thrombosis, or TIMI major bleeding at 15 months after PCI	67	25	40	10	89
ITALIC (17)	2014	1,822	6	12	6	No	Composite of death, MI, repeat TVR, stroke, or TIMI major bleeding at 12 months after PCI	62	37	24	–	100†
SECURITY (18)	2014	1,399	6	12	12‡	No	Composite of cardiac death, MI, stroke, stent thrombosis, or BARC 3 or 5 bleeding at 12 months after PCI	65	31	38§	–	100
OPTIMIZE (15)	2014	3,119	3	12	12	No	Composite of death, MI, stroke, or major bleeding at 12 months after PCI	62	35	32§	–	100
PRODIGY (20)	2012	1,970	6	24	23	No	Composite of death, MI, or cerebrovascular accidents at 24 months after PCI	68	24	75	25	50
EXCELLENT (19)	2011	1,443	6	12	12	No	Composite of cardiac death, MI, or TVR at 12 months after PCI	63	38	52	25	75
RESET (14)	2012	2,117	3	12	12	No	Composite of cardiac death, MI, stent thrombosis, ischemia-driven TVR, or bleeding at 12 months after PCI	62	29	54	21	85‖
12-month DAPT discontinuation trials												
DAPT (7)	2014	9,961	12	30	21	Yes	Stent thrombosis; composite of death, MI, or stroke; and moderate or severe GUSTO bleeding; at 18 months after randomization	62	31	43	38	60
DES-LATE (22)	2014	5,045	12	36	42	No	Composite of cardiac death, MI, or stroke at 24 months after randomization	62	28	61	64	30
ARCTIC-Interruption (21)	2014	1,259	12	18–30	17	No	Composite of death, MI, stroke or TIA, urgent revascularization, or stent thrombosis	64	34	–	40	63

*Refers to follow-up time from randomization (Online Figure 1 and Figure 2). †Only Xience V everolimus-eluting stent. ‡Maximum length of follow-up was 24 months; however, maximum duration of DAPT was 12 months. In the analyses, outcomes at 12 months have been included. §High-risk acute coronary syndromes excluded. ‖100% Endeavor zotarolimus-eluting stent in the 3-month group.

1G = first-generation; 2G = second-generation; ACS = acute coronary syndrome; ARCTIC-Interruption = Dual-Antiplatelet Treatment Beyond 1 Year After Drug-Eluting Stent Implantation; BARC = Bleeding Academic Research Consortium; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; DES-LATE = Duration of Clopidogrel Therapy After Drug-Eluting Stent; DM = diabetes mellitus; EXCELLENT = Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; GUSTO = Global Use of Strategies to Open Occluded Arteries; ISAR-SAFE = Safety and Efficacy of Six Months Dual Antiplatelet Therapy After Drug-Eluting Stenting; ITALIC = Is There A Life for DES After Discontinuation of Clopidogrel; L-DAPT = longer dual antiplatelet therapy; MI = myocardial infarction; OPTIMIZE = Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice; PCI = percutaneous coronary intervention; PRODIGY = Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study; RESET = REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation; S-DAPT = shorter dual antiplatelet therapy; SECURITY = Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Antiplatelet Therapy; TIA = transient ischemic attack; TIMI = Thrombolysis In Myocardial Infarction; TVR = target vessel revascularization.

and Laird (13). The test for small-study effects was conducted by using Harbord's modified test. Heterogeneity among trials for each outcome was calculated by means of I^2 test.

To assess the trade-off between stent thrombosis and CSB over time, the incidence rates of adverse events and corresponding incidence risk differences between groups were analyzed, taking into account the variable follow-up times within each study. To do so, we calculated stent thrombosis and CSB incidence rates per 100 person-years within each exposure group (S-DAPT and L-DAPT). The exposure time was calculated based on the mean follow-up time for each trial. The overall standardized incidence risk difference was calculated by assigning a weight to each RCT equal to the inverse of the variance of the effect estimate.

To evaluate the effects of DES generation on stent thrombosis, the results were stratified accordingly by using stent-level data when available (first- vs. second-generation DES). Studies in which the numbers of events with each specific DES type were not available were excluded from this analysis. First-generation DES included sirolimus-eluting and paclitaxel-eluting DES; second-generation DES included everolimus-eluting and zotarolimus-eluting DES.

We conducted sensitivity analyses (presented in the Online Appendix) to evaluate the impact of selected measures of study characteristics for stent thrombosis, MI, CSB, and all-cause mortality (Online Figure 3). Analyses were stratified according to prevalence of acute coronary syndrome (ACS) (>50%) and patients with a mean age ≥65 years. Considering the marked differences in trial size and reported outcomes of the recent DAPT trial (7), the study-specific influence on primary outcomes was estimated after removal of this trial from the

analysis and subsequent evaluation of the change in significance, magnitude, and direction of the effect. All sensitivity analyses were conducted with both a random effects model (primary analysis method) and a fixed effects model. Analyses were conducted by using Stata version 12.0 (Stata Corp., College Station, Texas).

RESULTS

Of the 7,885 citations found, 10 RCTs (n = 32,135) were identified (**Figure 1**); characteristics of these 10 studies are summarized in **Table 1**. Additional details are available in Online Table 2 and Online Figures 1 and 2.

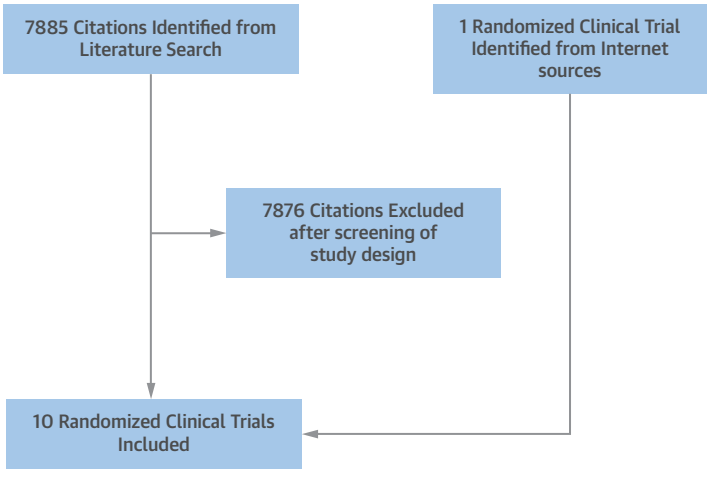
Two RCTs (RESET [REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation] and OPTIMIZE [Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice]) evaluated 3 months versus 12 months of DAPT (14,15). In the OPTIMIZE trial, second-generation DES were used in 100% of patients in both randomization arms. In the RESET trial, second-generation DES were used in 100% of patients in the 3-month arm and in 70% in the 12-month arm. In these 2 trials, the average age was 62 years, the prevalence of diabetes mellitus was 32%, and 43% had ACS.

Five RCTs evaluated a 6-month versus either a 12-month DAPT regimen (ISAR-SAFE [Safety and Efficacy of Six Months Dual Antiplatelet Therapy After Drug-Eluting Stenting], ITALIC [Is There A Life for DES After Discontinuation of Clopidogrel], SECURITY [Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Antiplatelet Therapy], and EXCELLENT [Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting]) or a 24-month DAPT regimen (PRODIGY [Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study]) (16–20). In the recent ITALIC and SECURITY trials, second-generation DES were used in 100% of patients in both randomization arms. In the EXCELLENT and ISAR-SAFE trials, second-generation DES were used in >70% of patients. Finally, in the PRODIGY trial, second-generation DES were implanted in 50% of patients, while the remainder received bare-metal stents or first-generation DES. Across these 5 trials, the average patient age was 65 years, the prevalence of diabetes mellitus was 31%, and 46% had ACS.

Three RCTs (DAPT, DES-LATE [Duration of Clopidogrel Therapy After Drug-Eluting Stent], and ARCTIC-Interruption [Dual-Antiplatelet Treatment Beyond 1 Year After Drug-Eluting Stent Implantation]) explored the efficacy and safety of prolonged DAPT beyond 12 months after the original DES implantation (7,21,22). Second-generation DES were used in 30% of patients in the DES-LATE trial and in ≈60% of the population in the DAPT and ARCTIC-Interruption trials. Therefore, the mean second-generation DES use across the studies was 51%. The mean patient age among these 3 RCTs was 63 years, the prevalence of diabetes mellitus was 31%, and 52% had ACS. The mean weighted follow-up time among all 10 RCTs was 19.6 months; the mean weighted exposure time to antiplatelet therapy within the S-DAPT and L-DAPT groups was 8.5 and 23.2 months, respectively. All the endpoints of interest in each of the trials were independently adjudicated by a Clinical Event Committee (Online Table 3).

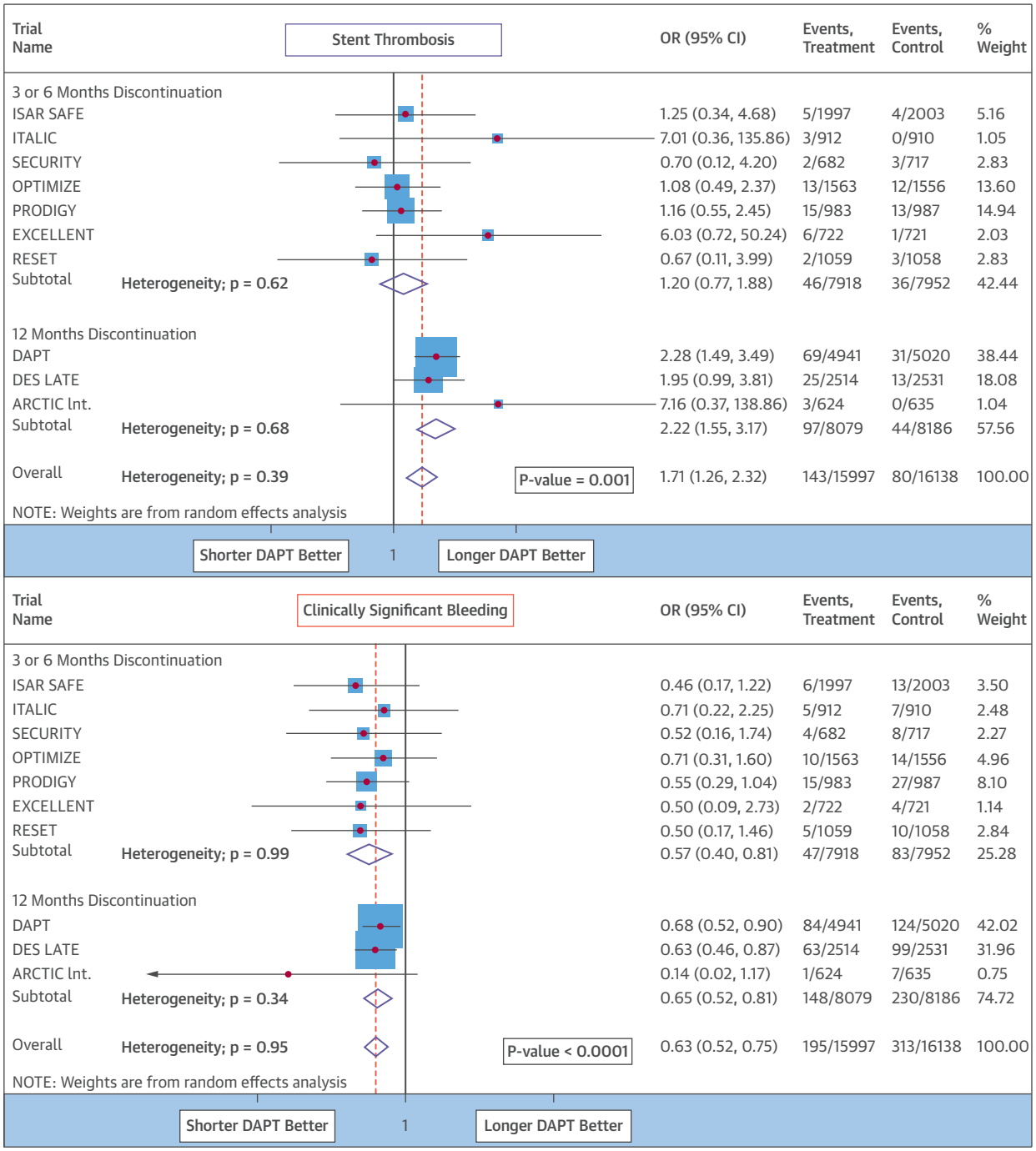
STENT THROMBOSIS. Rates of stent thrombosis were reported in all trials. The overall frequency of stent thrombosis in the S-DAPT group was 0.9% (143 of 15,997) compared with 0.5% (80 of 16,138) in the L-DAPT group. The combined OR for stent thrombosis with an S-DAPT regimen versus an L-DAPT regimen was 1.71 (95% CI: 1.26 to 2.32; p = 0.001) (**Figure 2**). The magnitude of the effect was attenuated in abbreviated-term DAPT studies (OR 1.20 [95% CI 0.77 to 1.88]) compared with extended-term DAPT studies (OR: 2.22 [95% CI: 1.55 to 3.17]; p for interaction = 0.044). There was no evidence of statistical heterogeneity among studies (p heterogeneity = 0.387). The test for small-studies effect was not significant (p = 0.905).

FIGURE 1 Meta-Analysis Flow Diagram



After exclusion, 10 randomized controlled (n = 32,135) were included in the meta-analysis.

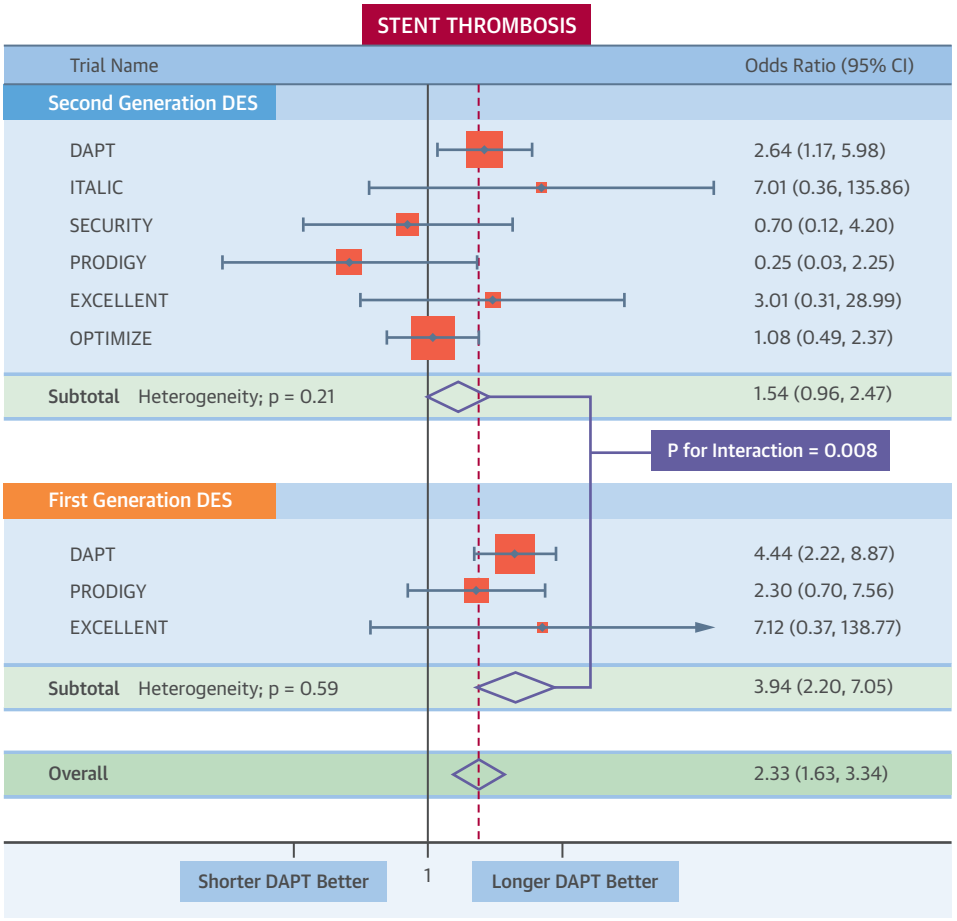
FIGURE 2 Stent Thrombosis and Clinically Significant Bleeding in Randomized Clinical Trials



Size of central markers reflects the weight of each study. CI = confidence interval; ARCTIC-Interruption = Dual-Antiplatelet Treatment Beyond 1 Year After Drug-Eluting Stent Implantation; DAPT = Dual Antiplatelet Therapy trial; DES-LATE = Duration of Clopidogrel Therapy After Drug-Eluting Stent; EXCELLENT = Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; ISAR-SAFE = Safety and Efficacy of Six Months Dual Antiplatelet Therapy After Drug-Eluting Stenting; ITALIC = Is There A Life for DES After Discontinuation of Clopidogrel; OPTIMIZE = Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice; OR = odds ratio; PRODIGY = Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study; RESET = REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation; SECURITY = Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Antiplatelet Therapy.

Rates of stent thrombosis with second-generation DES were reported in 6 RCTs (7,15,17–19,23); stent thrombosis rates with first-generation DES were reported in 3 RCTs (7,19,23). The mean weighted exposure DAPT time with S-DAPT was 7.8 and 10.9 months for second- and first-generation DES, respectively. Conversely, the mean weighted exposure DAPT time with L-DAPT was 20.3 months and 28 months for second- and first-generation DES, respectively. Frequencies and the combined ORs of stent thrombosis associated with DES generation are shown in the **Central Illustration**. The magnitude of the benefit of L-DAPT on stent thrombosis was significantly attenuated with second-generation DES. Stent thrombosis rates with second-generation DES were 0.6% (43 of 7,169) with S-DAPT and 0.4% (28 of

CENTRAL ILLUSTRATION **Stent Thrombosis With First- and Second-Generation Drug-Eluting Stents**



Giustino, G. et al. J Am Coll Cardiol. 2015; 65(13):1298–310.

A statistically significant interaction was observed between drug-eluting stent (DES) generation and dual antiplatelet therapy (DAPT) duration on risk of stent thrombosis. The mean weighted exposure time to shorter DAPT was 7.8 months for second-generation DES and 10.9 months for first-generation DES. The mean weighted exposure time to longer DAPT was 20.3 months for second-generation DES and 28 months for first-generation DES. Size of central markers reflects the weight of each study. CI = confidence interval; DAPT = Dual Antiplatelet Therapy trial; EXCELLENT = Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; ITALIC = Is There A LIfe for DES After Discontinuation of Clopidogrel; 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; SECURITY = Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Antiplatelet Therapy.

7,205) with L-DAPT, yielding a combined OR of 1.54 (95% CI: 0.96 to 2.47). The stent thrombosis rates with first-generation DES were 2.4% (54 of 2,284) with S-DAPT and 0.6% (14 of 2,354) with L-DAPT, yielding a combined OR of 3.94 (95% CI: 2.20 to 7.05). The test for interaction between DES generation and DAPT treatment duration was highly significant (p for interaction = 0.008).

CLINICALLY SIGNIFICANT BLEEDING. CSB rates used different definitions across trials. The Global Use of Strategies to Open Occluded Arteries definitions were used in the DAPT trial; a BARC 3 or 5 bleeding definition was used to extract CSB rates from the SECURITY trial; and a TIMI major or minor bleeding definition was used in the ISAR-SAFE, PRODIGY, RESET, and ITALIC trials. In the DES-LATE and EXCELLENT trials, the only available bleeding rate was major TIMI type. The incidence of CSB across all RCTs was 1.2% in the S-DAPT group (195 of 15,997) and 1.9% in the L-DAPT group (313 of 16,138), yielding a combined OR (Figure 2) with S-DAPT versus L-DAPT of 0.63 (95% CI: 0.52 to 0.75; p < 0.001). Results were consistent across abbreviated- and extended-term DAPT studies. There was no evidence of statistical heterogeneity among studies (p heterogeneity = 0.953).

TRADE-OFF BETWEEN STENT THROMBOSIS AND BLEEDING. The overall standardized incidence risk difference for stent thrombosis and CSB between S-DAPT and L-DAPT (Table 2) yielded a rate difference of -0.45 per 100 persons/year (95% CI: -0.62 to -0.28) for CSB and 0.21 per 100 persons/year (95% CI: 0.11 to 0.31; p < 0.001) for stent thrombosis. Therefore, for every stent thrombosis event averted with L-DAPT, ~2.1 CSB events are estimated to occur. The Cochran-Mantel-Haenszel test for homogeneity between groups was not significant (p > 0.05 for both stent thrombosis and CSB outcomes).

MYOCARDIAL INFARCTION. MI was reported in all trials. The incidence of MI in the S-DAPT group and L-DAPT group was 2.6% (417 of 15,997) and 1.9% (306 of 16,138), respectively. The combined OR for MI associated with an S-DAPT regimen versus an L-DAPT regimen was 1.39 (95% CI: 1.20 to 1.62; p < 0.001) (Figure 3). The magnitude of the effect was attenuated in abbreviated-term DAPT studies (OR: 1.13 [95% CI: 0.88 to 1.44), compared with extended-term DAPT studies (OR: 1.57 [95% CI: 1.30 to 1.90; p for interaction = 0.035).

STROKE. Stroke was reported according to each trial's protocol definition. The incidence of stroke was 1.0% (148 of 15,997) in the S-DAPT group and 0.9% (153 of 16,138) in the L-DAPT group. The combined OR for stroke associated with S-DAPT versus L-DAPT was 0.99 (95% CI: 0.78 to 1.24; p = 0.907) (Figure 3). Results were consistent between abbreviated- and extended-term DAPT studies (p for interaction > 0.05).

MORTALITY. All-cause mortality was reported in all trials, and cardiovascular mortality was reported in 8 of 10 trials. The overall incidence of all-cause mortality in the S-DAPT group was 2.0% (312 of 15,997), whereas in the L-DAPT group, it was of 2.2% (361 of 16,138). S-DAPT was associated with a numerically lower all-cause mortality rate with a combined OR of 0.87 (95% CI: 0.74 to 1.01; p = 0.073) (Figure 4). Cardiovascular mortality rates were 1.3% (175 of 13,376) in the S-DAPT group and 1.4% in the L-DAPT group

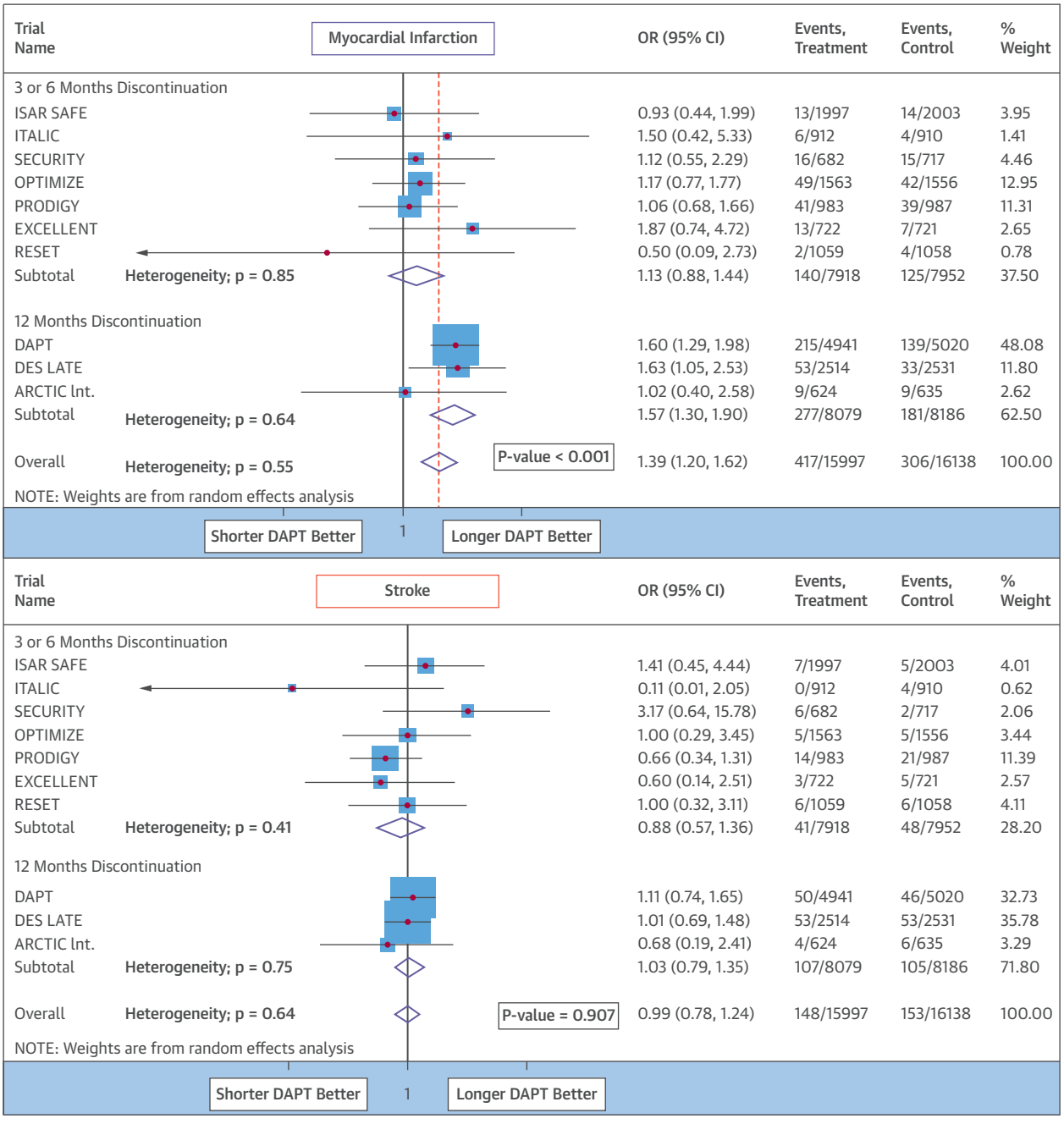
TABLE 2 IRs and Standardized IRDs for Stent Thrombosis and Clinically Significant Bleeding per 100 Persons/Year Between S-DAPT and L-DAPT

	Stent Thrombosis						Clinically Significant Bleeding					
	S-DAPT		L-DAPT				S-DAPT		L-DAPT			
Study (Ref. #)	No. of Events	IR*	No. of Events	IR*	IRD*	95% CI*	No. of Events	IR*	No. of Events	IR*	IRD*	95% CI*
ARCTIC-Interruption (21)	3	0.33	0	0	0.33	-0.04 to 0.72	1	0.11	7	0.78	-0.67	-1.29 to -0.04
DAPT (7)	69	0.80	31	0.35	0.44	0.22 to 0.67	84	0.98	124	1.42	-0.44	-0.77 to -0.12
DES-LATE (22)	25	0.29	13	0.15	0.13	0.00 to 0.27	63	0.73	99	1.14	-0.41	-0.70 to -0.13
EXCELLENT (19)	6	0.83	1	0.14	0.69	-0.02 to 1.41	2	0.28	4	0.56	-0.27	-0.94 to 0.38
ISAR-SAFE (16)	5	0.50	4	0.40	0.10	-0.48 to 0.69	6	0.60	13	1.30	-0.70	-1.56 to 0.16
ITALIC (17)	3	0.66	0	0	0.66	-0.08 to 1.40	5	1.10	7	1.54	-0.44	-1.94 to 1.05
OPTIMIZE (15)	13	0.84	12	0.77	0.06	-0.56 to 0.69	10	0.64	14	0.90	-0.26	-0.88 to 0.35
PRODIGY (23)	15	0.80	13	0.69	0.11	-0.44 to 0.66	15	0.80	27	1.44	-0.64	-1.32 to 0.03
RESET (14)	2	0.19	3	0.28	-0.09	-0.50 to 0.31	5	0.47	10	0.95	-0.48	-1.20 to 0.24
SECURITY (18)	2	0.29	3	0.42	-0.12	-0.75 to 0.49	4	0.59	8	1.12	-0.53	-1.50 to 0.43
Combined	–	–	–	–	0.21	0.11 to 0.31	–	–	–	–	-0.45	-0.62 to -0.28

*Results expressed as 100 persons/year.

CI = confidence interval; IR = incidence rate; IRD = incidence risk difference; other abbreviations as in Table 1.

FIGURE 3 Myocardial Infarction and Stroke in Randomized Clinical Trials



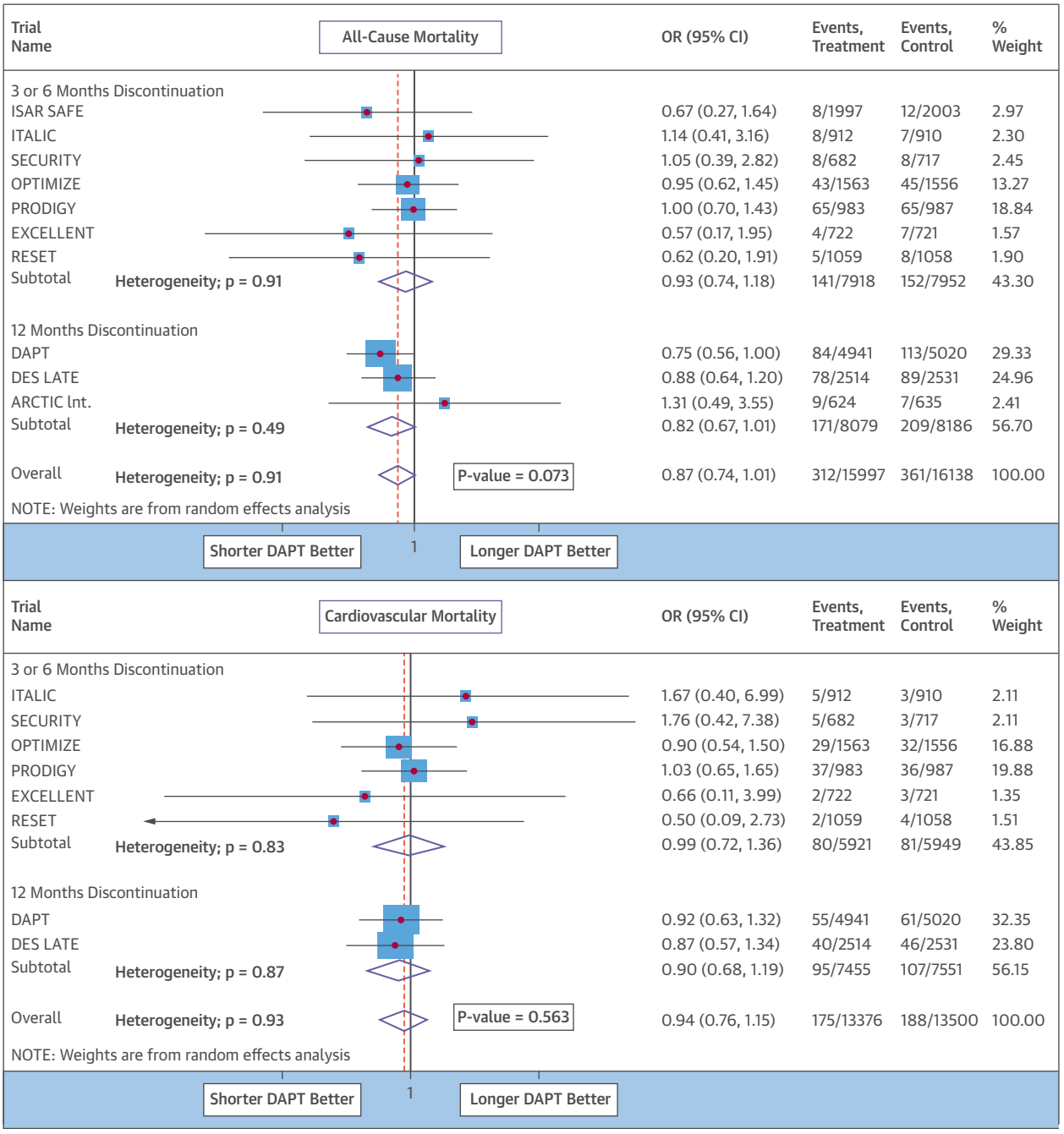
Size of central markers reflects the weight of each study. Abbreviations as in Figure 2.

(188 of 13,500), yielding an OR for S-DAPT versus L-DAPT of 0.94 (95% CI: 0.76 to 1.15; p = 0.563). Results were consistent between abbreviated- and extended-term DAPT studies for both mortality endpoints (p for interaction >0.05).

DISCUSSION

The main results of this meta-analysis including >30,000 patients from RCTs are as follows: 1) L-DAPT was associated with a lower risk of definite/probable

FIGURE 4 All-Cause and Cardiovascular Mortality in Randomized Clinical Trials



Size of central markers reflects the weight of each study. Abbreviations as in Figure 2.

stent thrombosis and MI compared with S-DAPT, and the magnitude of the effect was attenuated in abbreviated-term DAPT studies compared with extended-term studies; 2) L-DAPT was associated with a significantly higher risk of CSB, yielding an excess of ~2.1 CSB events for each episode of stent thrombosis averted; 3) the benefit of L-DAPT on stent thrombosis was significantly attenuated with use

of second-generation DES compared with first-generation DES; and 4) a numerically lower, albeit not statistically significant, all-cause mortality was observed with S-DAPT.

CURRENT KNOWLEDGE REGARDING OPTIMAL DAPT DURATION. Optimal duration of DAPT after DES implantation is an important subject of debate. Current European Society of Cardiology and American Heart Association/American College of Cardiology guidelines recommend a minimum duration of DAPT of 6 to 12 months and 12 months, respectively (1,2). Concurrently, certain second-generation DES types have a 3-month DAPT indication, per the European device regulatory agency.

Concerns regarding late and very late stent thrombosis with first-generation DES motivated the scientific community to investigate the potentially beneficial role of long-term DAPT. Several observational studies and registries found a strong and independent association between DAPT cessation and stent thrombosis (24,25), particularly when cessation occurs early after DES implantation (3). Importantly, the concerns regarding stent thrombosis after stopping DAPT led to the development of newer generation DES, with improved vascular healing and re-endothelialization properties (26–28). Permanent polymer DES and bioresorbable polymer DES have shown improved safety compared with initial first-generation DES (29,30).

The improved safety of current-generation DES constituted the basis to evaluate abbreviated regimens of DAPT duration after PCI. Before the present meta-analysis, 7 trials evaluated the safety and efficacy of interrupted DAPT at 3 or 6 months compared with prolonged DAPT at 12 or 24 months (14–20). Interestingly, a significant increased hazard for ischemic events with reduced DAPT duration did not occur in any of these trials. Conversely, an increased risk for bleeding events was observed in the PRODIGY trial that compared 6 versus 24 months of DAPT after the implantation of various stent types (20). Therefore, in all of these RCTs, S-DAPT seemed to be noninferior to a regimen of L-DAPT. However, several issues must be considered when interpreting these results. First, most of these trials were underpowered to detect differences in hard endpoints because of study design issues, slow enrollment, and lower-than-expected event rates. Second, except for the ISAR-SAFE trial, all of these studies were open-label (not placebo controlled). Third, primary endpoint definitions were heterogeneous, making comparisons between trials limited and somewhat inappropriate when ischemic and bleeding events were included in the composite primary endpoint definition. Fourth, in some of these studies, noninferiority was demonstrated for margins fixed as absolute risk difference but not relative risk difference (EXCELLENT and OPTIMIZE); because the observed active control rate was lower than expected, fixing the margin in terms of absolute risk difference may have biased the results favoring noninferiority.

The recently published DAPT trial randomized 9,961 event-free patients after the first year following DES-PCI to either continue with DAPT for another 18 months or to stop the thienopyridine (7). This trial changed the perspective on L-DAPT by demonstrating a significant long-term benefit in stent-related and non-stent-related thrombotic events with the prolonged DAPT regimen. Nevertheless, the ischemic benefit with L-DAPT was paired with an increased risk in major bleeding and a significantly higher noncardiovascular mortality. However, a recent meta-analysis of RCTs evaluating extended DAPT in different clinical scenarios (including PCI, atrial fibrillation, stroke, and vascular surgery) did not support an association between all-cause, noncardiovascular, or cardiovascular mortality and a longer DAPT regimen (31).

CLINICAL IMPLICATIONS. The results of the present meta-analysis, which included all of the most recent trials evaluating optimal DAPT duration after PCI with DES, offer useful insights regarding the impact of extended DAPT on clinical outcomes and on the unfavorable role of first-generation DES as an important ischemic risk modifier. According to our results, L-DAPT is associated with a significant reduction in late stent thrombosis and MI risk in patients undergoing PCI with DES implantation. Importantly, after exclusion of the DAPT trial from the analysis (the sensitivity analysis is presented in the Online Appendix), the association between S-DAPT and stent thrombosis was of only borderline significance (numerically higher, without reaching statistical significance) according to the more rigorous random effects model approach. This finding suggests that a thrombotic benefit with DAPT might become evident with longer exposure to treatment. However, L-DAPT is a therapeutic strategy not exempt from risk, particularly in relation to bleeding. In fact, the thrombotic benefit of L-DAPT was counterbalanced by an increase in bleeding risk that was consistent across the examined trials. Interestingly, the risk reduction in stent thrombosis and MI with L-DAPT did not translate into an all-cause or cardiovascular mortality benefit. Conversely, L-DAPT was associated

with a numerically higher all-cause mortality (without statistical significance) compared with S-DAPT. The validity and consistency of this finding remain controversial.

The clinical message of the present meta-analysis is that the trade-off between ischemic and bleeding events with L-DAPT is a matter of concern and should be carefully evaluated when the decision to continue DAPT after a recommended period is considered. We found that for each stent thrombosis event averted by prolonging DAPT, an excess of 2.1 CSB events would be expected. Moreover, the risk of late and very late stent thrombosis with S-DAPT is notably increased in patients receiving a first-generation DES, which are used rarely (if at all) at the present time. Assuming a comparable bleeding risk across stent generations with provision of prolonged DAPT, our findings suggest that the risk/benefit ratio for extending DAPT has an important variation according to type of DES used. In the current cardiology practice, only the results of second-generation DES are clinically applicable. Accordingly, the prevention of a single episode of late stent thrombosis will require exposing a larger number of patients with a second-generation DES to potentially serious bleeding harm (**Central Illustration**). This difference is clinically relevant when the decision to prolong DAPT after the initial recommended period is being considered. The interaction between DAPT duration and DES generation was previously described by Camenzind et al. (32); in the absence of DAPT prolonged beyond 1 year, stent thrombosis at 3 years was significantly lower with a second-generation DES, whereas no differences between first- and second-generation DES were observed with extended-term DAPT treatment.

The counterbalancing influences of preventing thrombosis while simultaneously increasing bleeding risk may account for the lack of mortality benefit (and possibly the suggestion of increased all-cause mortality) observed with extended DAPT duration. Beyond risk of stent thrombosis, it would still be acceptable to use an extended DAPT regimen; the goal would be to offer a broader coronary atherothrombotic benefit in terms of MI protection (often unrelated to a stent thrombosis event) in patients who are tolerating the initially recommended DAPT duration well and have been judged to be at moderate or high ischemic risk along with having a low bleeding hazard. Therefore, the optimal duration of DAPT with current-generation DES outside ACS remains undefined, and the timing of interruption of the thienopyridine can be as short as 3 or 6 months after stent implantation. Finally, considering the continuous device and pharmacology evolution, further trials are needed to evaluate optimal duration with use of the current- and forthcoming-generation DES and the high-potency antiplatelet drugs.

STUDY LIMITATIONS. The main limitation of the present study is the lack of patient-level data, which does not allow us to evaluate ischemic and net composite endpoints or perform time-to-event analyses and covariate-adjusted analyses among different types of DAPT discontinuation and durations. Patient-level data would allow identifying independent predictors of ischemic and bleeding events using different durations of DAPT as a risk modifier. In addition, the different studies did not explicitly report results of all the clinical endpoints according to stent type.

Second, the lower rate of stent thrombosis observed with second-generation DES could be related to the fact that the duration of the RCTs with more frequent second-generation DES use were those with shorter term follow-up; therefore, the lower exposure and follow-up time might have accounted for the lower event rates. However, lower incidence of late and very late stent thrombosis with second-generation DES compared with older generation DES is strongly supported by earlier clinical evidence (28,29).

Third, we did not perform a risk/benefit trade-off analysis between MI and bleeding because clinical event severity was not available in the studies, and thus the external validity of such results would be poor. Fourth, another limitation of the meta-analysis is the substantial diversity in protocol designs of the included abbreviated- and extended-term DAPT RCTs; caution is therefore required in interpreting any overall effect estimate for S-DAPT versus L-DAPT. Finally, we found heterogeneity at the sensitivity analysis regarding the effect of S-DAPT on stent thrombosis following exclusion of the DAPT trial. This finding suggests that the thrombotic benefits associated with DAPT become evident over time and that the overall effect of S-DAPT on stent thrombosis might have been attenuated by the abbreviated-term DAPT trials. Therefore, to clarify the effect of extended DAPT on ischemic and bleeding outcomes, and eventually survival, additional randomized data evaluating longer DAPT duration in contemporary clinical practice are needed.

CONCLUSIONS

S-DAPT was associated with significantly higher definite or probable stent thrombosis rates compared with L-DAPT. The magnitude of the effect of S-DAPT on stent thrombosis was significantly attenuated with the use of second-generation DES. However, the thrombotic benefit of L-DAPT was paired with a higher risk of bleeding and numerically higher all-cause mortality. The results of the present meta-analysis indicate that the risk/benefit ratio between stopping or continuing DAPT after an initially recommended period should be carefully individualized considering the trade-off between ischemic and bleeding future risk.

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PERSPECTIVES

COMPETENCIES IN MEDICAL KNOWLEDGE: DAPT is associated with protection against ischemic events but increases the risk of bleeding in patients with DES. The benefit of extended DAPT is strongly significant in patients treated with first-generation DES and attenuated with the use of current second-generation DES.

COMPETENCY IN PATIENT CARE: Physicians should carefully evaluate patients' ischemic and bleeding risks and consider the type of stent implanted, in addition to how well therapy has been tolerated, in determining how long to extend DAPT (beyond an initial period) after DES implantation.

TRANSLATIONAL OUTLOOK: Additional randomized trials are needed to evaluate the optimum duration of DAPT in patients with the latest generation DES devices and high-potency antiplatelet drugs.

REFERENCES

1. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol 2011;58:e44–122.

2. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014;35:2541–619.

3. Mehran R, Baber U, Steg PG, et al. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. Lancet 2013;382:1714–22.

4. van Werkum JW, Heestermans AA, Zomer AC, et al. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. J Am Coll Cardiol 2009;53:1399–409.

5. Holmes DR Jr., Kereiakes DJ, Garg S, et al. Stent thrombosis. J Am Coll Cardiol 2010;56:1357–65.

6. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226–35.

7. Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014;371:2155–66.

8. Stefanini GG, Siontis GC, Cao D, Heg D, Juni P, Windecker S. Short versus long duration of DAPT after DES implantation: a meta-analysis. J Am Coll Cardiol 2014;64:953–4.

9. Cassese S, Byrne RA, Tada T, King LA, Kastrati A. Clinical impact of extended dual antiplatelet therapy after percutaneous coronary interventions in the drug-eluting stent era: a meta-analysis of randomized trials. Eur Heart J 2012;33:3078–87.

10. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.

11. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736–47.

12. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet 1999;354:1896–900.

13. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.

14. Kim BK, Hong MK, Shin DH, et al. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). J Am Coll Cardiol 2012;60:1340–8.

15. Feres F, Costa RA, Abizaid A, et al. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. JAMA 2013;310:2510–22.

16. Schulz-Schupke S, Byrne RA, Ten Berg JM, et al. ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 versus 12 months of clopidogrel therapy after drug-eluting stenting. Eur Heart J 2015 Jan 23 [E-pub ahead of print].

17. Gilard M, Barragan P, Noryani AA, et al. Six-month versus 24-month dual antiplatelet therapy after implantation of drug eluting stents in patients non-resistant to aspirin: ITALIC, a randomized multicenter trial. J Am Coll Cardiol 2015;65:777–86.

18. Colombo A, Chieffo A, Frasheri A, et al. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. J Am Coll Cardiol 2014;64:2086–97.

19. Gwon HC, Hahn JY, Park KW, et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. Circulation 2012;125:505–13.

20. Valgimigli M, Campo G, Monti M, et al. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. Circulation 2012;125:2015–26.

21. Collet JP, Silvain J, Barthelemy O, et al. Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomised trial. Lancet 2014;384:1577–85.

22. Lee CW, Ahn JM, Park DW, et al. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: a randomized, controlled trial. Circulation 2014;129:304–12.

23. Valgimigli M, Borghesi M, Tebaldi M, Vranckx P, Parrinello G, Ferrari R. Should duration of dual antiplatelet therapy depend on the type and/or potency of implanted stent? A prespecified analysis from the PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY (PRODIGY). Eur Heart J 2013;34:909–19.

24. Airoldi F, Colombo A, Morici N, et al. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. Circulation 2007;116:745–54.

25. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293:2126–30.

26. Dangas GD, Serruys PW, Kereiakes DJ, et al. Meta-analysis of everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease: final 3-year results of the SPIRIT clinical trials program (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions). J Am Coll Cardiol Intv 2013;6:914–22.

27. Camenzind E. Final five-year results from the randomized drug-eluting stent trial PROTECT: the Patient-Related Outcomes With Endeavor vs Cypher Stenting Trial. European Society of Cardiology Congress; September 2, 2014; Barcelona, Spain 2014.

28. Finn AV, Joner M, Nakazawa G, et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation 2007;115:2435–41.

29. Baber U, Mehran R, Sharma SK, et al. Impact of the everolimus-eluting stent on stent thrombosis: a meta-analysis of 13 randomized trials. J Am Coll Cardiol 2011;58:1569–77.

30. Stefanini GG, Byrne RA, Serruys PW, et al. Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. Eur Heart J 2012;33:1214–22.

31. Elmariah S, Mauri L, Doros G, et al. Extended duration dual antiplatelet therapy and mortality: a systematic review and meta-analysis. Lancet 2015;385:792–8.

32. Camenzind E, Boersma E, Wijns W, et al. Modifying effect of dual antiplatelet therapy on incidence of stent thrombosis according to implanted drug-eluting stent type. Eur Heart J 2014;35:1932–48.

KEY WORDS bleeding, myocardial infarction, percutaneous coronary intervention, stent thrombosis

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