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Duration of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation in Patients With and Without Acute Coronary Syndrome: A Systematic Review of Randomized Controlled Trials

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Abstract

In this systemic review we evaluated the efficacy and safety of long duration dual anti-platelet therapy (DAPT) (L-DAPT) compared with short duration DAPT (S-DAPT) after drug-eluting stent (DES) implantation in patients who presented with or without acute coronary syndromes (ACS). We identified 8 randomized controlled trials in which 30,975 patients were randomized to S-DAPT versus L-DAPT (12,421 ACS and 18,554 non-ACS). Short duration dual anti-platelet therapy was associated with an increase in target vessel revascularization (TVR) in ACS patients, but the difference was not significant for non-ACS patients (odds ratio [OR] 5.04 [95% CI, 1.28-19.76], and OR, 0.89 [95% CI, 0.51-1.55], respectively). The risk of cardiac mortality was not significantly different with S-DAPT and L-DAPT for ACS (OR, 1.69 [95% CI, 0.82-3.50]) and non-ACS patients (OR, 0.89 [95% CI, 0.57-1.37]). For all cause mortality, myocardial infarction, and stent thrombosis, most of the events were derived from the DAPT study, thus a meta-analysis was not performed for these end points. Based on our review of the literature, we conclude that S-DAPT was associated with higher rates of stent thrombosis and myocardial infarction, and non-significant differences in all-cause mortality, with no significant interactions according to ACS vs non-ACS. However, in non-ACS patients, the benefit-risk profile favored S-DAPT, with lower all-cause mortality, whereas the trends were reversed in ACS. Additional studies are required to determine if the benefit-risk profile of S-DAPT vs L-DAPT varies according to clinical syndrome.

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Dual antiplatelet therapy (DAPT) using a combination of aspirin and a P2Y12 inhibitor (either a thienopyridine [clopidogrel or prasugrel] or the cyclopentyltriazolopyrimidine ticagrelor) is used for the prevention of ischemic complications after implantation of a drug-eluting stent (DES).[1-3] It is estimated that more than 10 million DESs have been implanted globally; however, the optimal duration of DAPT after DES implantation remains unclear.[1-3] The American College of Cardiology (ACC)/American Heart Association (AHA) recommends 12 months of DAPT after an acute coronary syndrome (ACS), irrespective of the revascularization strategy.[1,2] In a non-ACS setting, the ACC/AHA recommends continuation of DAPT for 12 months if patients are not at high risk for bleeding (eg, chronic kidney disease, anemia, age >75 years, or concomitant oral anticoagulant drug therapy).[1,2] On the other hand, the European guidelines recommend DAPT for a maximum of 12 months after ACS and for 6 months after DES for non-ACS indications.[3]

Pooled analyses of various randomized control trials (RCTs) evaluating the optimum duration of DAPT have reported conflicting results.[4-8] One of the reasons for the inconsistent results is use of the one-size-fits-all approach. However, different patient subgroups might behave differently, with some being more prothrombotic than others. After

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ACS, patients continue to have an increased coagulable state, platelet reactivity, and aggregability even months after clinical stabilization.[9] Dual antiplatelet therapy confers protection for both stent- and non–stent-related atherothrombotic events after DES implantation.[10] Thus, L-DAPT might be appropriate after DES implantation in the ACS setting.[11] Against this background, we performed a systematic review of RCTs to compare the efficacy and safety of S-DAPT (ie, ≤12 months) and L-DAPT (ie, >12 months) after DES implantation in patients who presented with or without ACS.

ARTICLE HIGHLIGHTS

- In patients with acute coronary syndrome (ACS), short-duration dual antiplatelet therapy (S-DAPT) is associated with higher rates of stent thrombosis, myocardial infarction, and target vessel revascularization, without a significant reduction in bleeding risk compared with long-duration DAPT (L-DAPT).
- In patients without ACS, S-DAPT is associated with an increased risk of myocardial infarction but overall lower all-cause mortality compared with L-DAPT.
- Thus, S-DAPT might be more appropriate in the non-ACS setting, and L-DAPT should be considered in an ACS setting, especially after drug-eluting stent implantation.

METHODS

Study Design

We followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement for reporting systematic reviews and meta-analyses of RCTs for the protocol of this systemic review.[12]

Data Sources and Search Strategy

We systematically searched the PubMed, Current Nursing and Allied Health Literature, Cochrane Central Register of Controlled Trials, Embase, Scopus, and Web of Science databases for randomized clinical trials comparing different durations of DAPT after DES implantation in patients with ACS (unstable angina, ST-segment elevation myocardial infarction [STEMI], or non-STEMI) and patients without ACS. Pertinent trials were also searched in ClinicalTrials.gov and in the proceedings of major international cardiology meetings (ACC, AHA, European Society of Cardiology, and The Society for Cardiac Angiography and Interventions). Dual antiplatelet therapy was defined as aspirin plus a P2Y12 receptor inhibitor after coronary DES implantation. Short- and long-duration DAPT were defined as durations of DAPT after DES implantation of 12 months or less and longer than 12 months, respectively. All relevant combinations of the following keywords were included in the database searches: *aspirin, P2Y12 receptor inhibitor, clopidogrel, Plavix, prasugrel, Effient, ticagrelor, Brilinta, thienopyridine, dual antiplatelet therapy, DAPT, drug-eluting stents, DES, acute coronary syndrome, ACS, unstable angina, non–ST-segment elevation myocardial infarction, NSTEMI, ST-segment elevation myocardial infarction, STEMI, non–acute coronary syndrome, non-ACS, death, all-cause mortality, survival, cardiac mortality, stent thrombosis, Thrombolysis In Myocardial Infarction (TIMI) bleeding, Global Utilization of Streptokinase and TPA for Occluded Arteries (GUSTO) bleeding, stroke, myocardial infarction, randomized controlled trial, random, random allocation, double-blind, and single-blind.* We manually searched references of identified studies. The search period was from January 1, 2002, through July 31, 2015. No language restrictions were applied. Studies that did not report the absolute numbers of events in patients with and without ACS after DES implantation were excluded from the analysis.

Data Extraction

Two reviewers (A.S., A.G.) independently screened the titles and abstracts for relevance. The manuscripts of selected titles/abstracts were reviewed for inclusion or exclusion using the previously mentioned selection criteria. Two reviewers (A.S., A.G.) independently determined the articles to be included and excluded, and data from the relevant articles were extracted using predefined extraction forms. Any disagreements in data extraction were discussed until consensus was reached. Baseline patient characteristics and outcomes (all-cause mortality, cardiac mortality, myocardial infarction [MI], stent thrombosis [ST], target vessel revascularization [TVR], major bleeding, stroke, and the net composite end point of various clinical outcomes [net adverse clinical events (NACE; all-cause mortality,

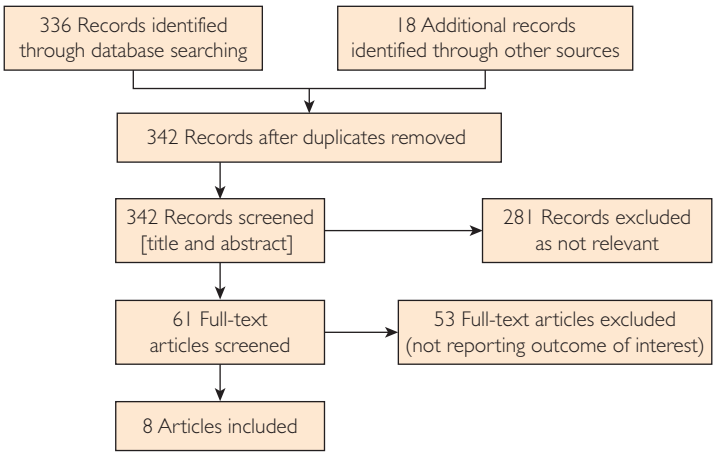

FIGURE 1. The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flowchart of the trial selection process.

cardiac mortality, MI, ST, TVR, stroke, and major bleeding)]) were abstracted for each study.

Statistical Analyses

All statistical analyses were performed according to the recommendations of the Cochrane Collaboration using Review Manager version 5.1 (The Nordic Cochrane Center, The Cochrane Collaboration). A random effects model with inverse variance weighting was used to calculate odds ratios (ORs) and 95% CIs associated with S-DAPT vs L-DAPT for the previously mentioned end points. Forest plots were used to observe the overall effect of studies. Heterogeneity between studies was assessed using the Cochran Q test and the I^2 statistic, which denotes the percentage of total variation across studies that is a result of heterogeneity rather than of chance. Heterogeneity was considered significant at $P<.05$. Publication bias was estimated by funnel plots (plotting of standard error of the logarithm of the OR against the logarithm of the OR) and the Egger regression test (2-sided $P<.05$ was considered statistically significant). Objective evaluation of study quality and risk of bias in reporting data for each RCT was performed according to Cochrane metrics.

RESULTS

Study Outlines and Characteristics

A total of 336 publications were found on the initial search; after abstract and manuscript evaluation, 8 studies were selected for final analysis (Figure 1). In the 8 selected RCTs, 30,975 patients were randomized to receive S-DAPT (n=15,435) or L-DAPT (n=15,540) (Tables 1 and 2).[13-20] Of 30,975 patients 12,421 had DES implantation after ACS and 18,554 had DES implantation in a non-ACS setting. Of these 8 studies, only 3 reported the previously specified end points separately for patients with and without ACS with S-DAPT and L-DAPT[15,17,20]; the other 5 reported outcomes in terms of NACE only.[13,14,16,18,19] Mean follow-up in the included studies varies from 9 to 24 months after the completion of L-DAPT. Use of second-generation DESs varies from 36% to 100%. Baseline characteristics of the patients and studies included in the final analysis are summarized in Tables 1 and 2. Risk-of-bias assessments for randomized clinical trials included in the study are summarized in Table 3.

Clinical Outcomes

All-cause Mortality. All-cause mortality was reported in 13,470 patients (4368 with and 9102 without ACS). After DES implantation, a significant reduction in all-cause mortality with S-DAPT compared with L-DAPT was demonstrated in the Dual Antiplatelet Therapy Study.[20] However, in patients with ACS, there were no differences between the S-DAPT and L-DAPT arms for all-cause mortality.[20]

Cardiovascular Mortality. Cardiovascular mortality was reported in 15,587 patients (4969 with and 10,618 without ACS). There was no significant difference in cardiovascular mortality with S-DAPT and L-DAPT in ACS (OR, 1.69; 95% CI, 0.82-3.50) and non-ACS (OR, 0.89; 95% CI, 0.57-1.37) settings (Figure 2).

Myocardial Infarction. A total of 360 MI events were reported in 15,587 patients (131 in 4969 patients with ACS and 229 in 10,618 patients without ACS) in 3 studies. Most of the events were derived from the Dual Antiplatelet Therapy Study (344 of 360), in which, compared with L-DAPT, S-DAPT was associated with an increase in MI in both patient groups (ACS: OR, 2.29 [95% CI, 1.58-3.34]; and non-ACS: OR, 1.64 [95% CI, 1.25-2.15]). In the ITALIC (Is There A LIfe for DES After Discontinuation of Clopidogrel) study, there

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TABLE 1. Baseline Characteristics of the 8 Studies Included in the Analysis[a]

Study[b]	Design	Time to randomization	Inclusion criteria	Exclusion criteria	Primary end point
RESET (2012)	Randomized, open label, multicenter	At index PCI	Age, 20-85 y; ≥50% stenosis; elective PCI; stable angina, unstable angina, or acute MI	CI to antiplatelets; STEMI ≤48 h; cerebrovascular accident; peripheral artery disease; thromboembolism; ST; ISR; CTO; LMA stenosis >50%; history of DES implantation; cardiogenic shock	Composite of cardiac death, MI, ST, ischemia-driven TVR, or bleeding 12 mo after PCI
OPTIMIZE (2014)	Randomized, open label, multicenter	At index PCI	Stable angina or silent ischemia or low risk of ACS as defined by unstable angina or recent (but not acute) MI (<30 d)	STEMI for primary or rescue PCI; BMS <6 mo before the index procedure; previous treatment with DES; scheduled surgery ≤12 mo; CI to antiplatelets; ISRs	Composite of death, MI, stroke, or major bleeding 12 mo after PCI
ISAR-SAFE (2014)	Randomized, double blind, multicenter	6 mo after index PCI	Patients taking clopidogrel at 6 (−1/+2) mo after PCI with DES	Previous ST; DES in LMA; MI in the previous 6 mo; planned major surgery within next 6 mo; CI to antiplatelets; OAC; previous ICH	Composite of death, MI, stroke or ST, or TIMI major bleeding 15 mo after PCI
PRODIGY (2012)	Randomized, open label, multicenter	1 mo after index PCI	Age, ≥18 y; ≥1 50% coronary artery lesion; PCI suitability; chronic stable coronary artery disease or ACS (non-STEMI or STEMI)	History of bleeding diathesis; major surgery ≤15 d; planned surgery ≤24 mo requiring DAPT interruption; active bleeding or stroke in the past 6 mo; concomitant anticoagulation therapy	Composite of death, MI, or cerebrovascular accidents 24 mo after PCI
ITALIC (2014)	Randomized, open label, multicenter	At index PCI	Age, ≥18 y; eligible for PCI with ≥1 Xience V DES; all clinical situations excluding primary PCI for acute MI and treatment of LMA	Previous DES ≤1 y; bleeding diathesis; CI to antiplatelet agents; major surgery within the preceding 6 wk; scheduled surgery ≤1 y after enrollment	Composite of death, MI, repeated TVR, stroke, or TIMI major bleeding 12 mo after PCI
ARCTIC-interruption (2014)	Randomized, open label, multicenter	12 mo after index PCI	Age, ≥18 y and eligible for PCI with planned use of ≥1 DES	Primary PCI for STEMI; chronic anticoagulation or bleeding diathesis; CI to antiplatelet agents; active bleeding or major surgery within 3 mo; scheduled surgery ≤1 y	Composite of death, MI, stroke, or TIA; urgent revascularization or ST
DES-LATE (2014)	Randomized, open label, multicenter	12 mo after index PCI	DES ≤12 mo; on DAPT; no MACE (MI, stroke, repeated PCI) or major bleeding since PCI	CI to antiplatelet drugs, concomitant vascular disease or recent ACS requiring clopidogrel use	Composite of cardiac death, MI, or stroke 24 mo after PCI
DAPT (2014)	Randomized, double blind, multicenter	12 mo after index PCI	Age, >18 y undergoing FDA-approved PCI with DES or BMS; no MACE or bleeding ≤12 mo after procedure	Planned major surgery ≤30 mo after enrollment; OAC; both BMS and DES during index procedure; PCI or surgery between 6 wk post-PCI and randomization	ST; composite of death, MI, and stroke; and moderate or severe GUSTO bleeding

[a]ACS = acute coronary syndrome; BMS = bare metal stent; CI = contraindication; CKD = chronic kidney disease; CTO = chronic total occlusion; DAPT = dual antiplatelet therapy; DES, drug-eluting stent; ECG = electrocardiogram; FDA = Food and Drug Administration; GUSTO = Global Utilization of Streptokinase and TPA for Occluded Arteries; ICH = intracranial hemorrhage; ISR = instent restenosis; LMA = left main artery; MACE = major adverse cardiac event; MI = myocardial infarction; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; ST = stent thrombosis; STEMI = ST-segment elevation myocardial infarction; SVG = saphenous venous grafts; TIMI = Thrombolysis In Myocardial Infarction; TVR = target vessel revascularization.

[b]ARCTIC = Assessment by a double Randomisation of a Conventional antiplatelet strategy versus a monitoring-guided strategy for drug-eluting stent implantation and of Treatment Interruption versus Continuation 1 year after stenting; DAPT = Dual Antiplatelet Therapy Study; DES-LATE = Optimal Duration of Clopidogrel Therapy With DES to Reduce Late Coronary Arterial Thrombotic Event; 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; 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.

TABLE 2. Baseline Patient Characteristics in the 8 Studies Included in the Analysis[a]

Study[b]	Patients (No.)			Follow-up (mo)	Age (y)	Male sex (%)	HTN (%)	HLD (%)	DM (%)	Previous MI (%)	Second-generation stent (%)
	Total	ACS	Non-ACS								
RESET	2117	3 mo=301 12 mo=300	3 mo=758 12 mo=758	12	62	64	62	59	28	2	85
OPTIMIZE	3119	3 mo=496 12 mo=504	3 mo=1067 12 mo=1052	12	62	63	87	64	35	35	100
ISAR-SAFE	3995	6 mo=794 12 mo=807	6 mo=1200 12 mo=1194	9	67	81	90	87	25	25	89
PRODIGY	1970	6 mo=733 24 mo=732	6 mo=250 24 mo=255	24	68	77	72	55	24	27	50
ITALIC	1822	6 mo=395 24 mo=397	6 mo=517 24 mo=513	12	61	80	65	67	37	15	100
ARCTIC	1259	12 mo=167 18 mo=156	12 mo=457 18 mo=459	17	64	80	60	67	34	30	63
DES-LATE	5045	12 mo=1551 30 mo=1512	12 mo=963 30 mo=1019	24	62	69	57	NA	28	4	36
DAPT	11,648	12 mo=1771 30 mo=1805	12 mo=4015 30 mo=4057	18	62	75	75	NA	30	22	61

[a]ACS = acute coronary syndrome; DM = diabetes mellitus; HLD = hyperlipidemia; HTN = hypertension; MI = myocardial infarction; NA = not available.
[b]See Table 1 for expansions of the study names.

were only 4 events in patients with ACS (OR, 1.01; 95% CI, 0.14-7.17) and 6 events in patients without ACS (OR, 1.99; 95% CI, 0.36-10.92). In the RESET (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation) study, there were only 6 events in patients without ACS (OR, 0.50; 95% CI, 0.09-2.73) and no events in the ACS group; therefore, the point estimates for the ORs and 95% CIs could not be estimated.

Stent Thrombosis. A total of 105 ST events were reported in 15,587 patients (44 in 4969 patients with ACS and 229 in 10,618 patients without ACS) in 3 studies. Most of the events were derived from the Dual Antiplatelet Therapy Study (97 of 105), in which, compared with L-DAPT, S-DAPT was associated with an increase in ST in patients with ACS (OR, 3.67; 95% CI, 1.75-7.72) and patients without ACS (OR, 3.05; 95% CI, 1.66-5.60). In the ITALIC study, there were only 2 events in patients with ACS (OR, 5.05; 95% CI, 0.24-105.54) and 1 event in patients without ACS (OR, 2.98; 95% CI, 0.12-73.79). In the RESET study, there was only 1 event in patients with ACS (OR, 3.0; 95% CI,

TABLE 3. Risk-of-Bias Assessments for the 8 Included Randomized Clinical Trials

Study[a]	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of patients and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Selective reporting (reporting bias)	Other bias
RESET	Low	Low	Open label	Low	Low	Low
OPTIMIZE	Low	Low	Open label	Low	Low	Low
ISAR-SAFE	Low	Low	Double blind	Low	Low	Low
PRODIGY	Low	Low	Open label	Low	Low	Low
ITALIC	Low	Low	Open label	Low	Low	Low
ARCTIC-Interruption	Low	Low	Open label	Low	Low	Low
DES-LATE	Low	Low	Open label	Low	Low	Low
DAPT	Low	Low	Double blind	Low	Low	Low

[a]See Table 1 for expansions of the study names.

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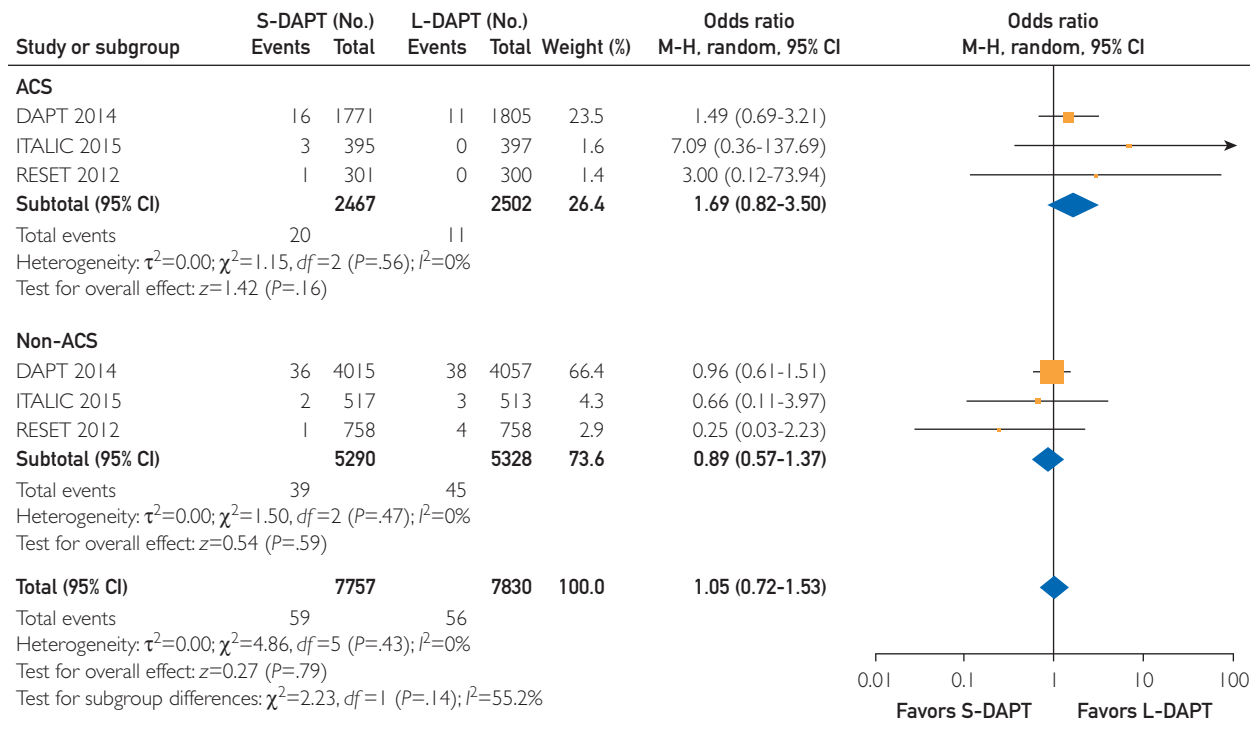

FIGURE 2. Forest plot for cardiovascular mortality for patients with and without acute coronary syndrome (ACS). DAPT = Dual Antiplatelet Therapy Study; ITALIC = Is There A LIfe for DES After Discontinuation of Clopidogrel; L-DAPT = long-duration dual antiplatelet therapy; M-H = Mantel-Haenszel; RESET = REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation; S-DAPT = short-duration dual antiplatelet therapy.

0.12-73.94) and 4 events in patients without ACS (OR, 0.33; 95% CI, 0.03-3.20).

Target Vessel Revascularization. Target vessel revascularization was reported in 3939 patients (1393 with ACS and 2546 without ACS). Short-duration DAPT was associated with an increase in TVR in patients with ACS, but the difference was not significant for patients without ACS (OR, 5.04 [95% CI, 1.28-19.76]; and OR, 0.89 [95% CI, 0.51-1.55], respectively) (Figure 3).

Major Bleeding. Major bleeding with S-DAPT and L-DAPT in patients with and without ACS was reported according to the Thrombolysis In Myocardial Infarction criteria in the ITALIC trial[17] and according to the Global Utilization of Streptokinase and TPA for Occluded Arteries in the Dual Antiplatelet Therapy Study.[20] There were no significant differences in major bleeding with S-DAPT and L-DAPT in patients with and without ACS in both studies.[17,20]

Stroke. Stroke (defined as new acute neurologic deficit that lasts for >24 hours or results in death) with S-DAPT and L-DAPT in patients with and without ACS was reported in the ITALIC study, in which there was no significant difference in stroke with S-DAPT and L-DAPT in patients with ACS (OR, 0.33; 95% CI, 0.01-8.23) and patients without ACS (OR, 0.14; 95% CI, 0.01-2.74).[17]

NACE Composite. The NACE was reported in 19,327 patients (8845 with and 10,482 without ACS). However, because the definition of this composite end point varies from study to study, we did not pool this end point to perform a meta-analysis.

No publication bias was observed with the funnel plots or the Egger regression test (P=.75 for cardiac mortality and P=.23 for TVR) (Supplemental Figures 1 and 2, respectively [available online at http://www.mayoclinicproceedings.org]).

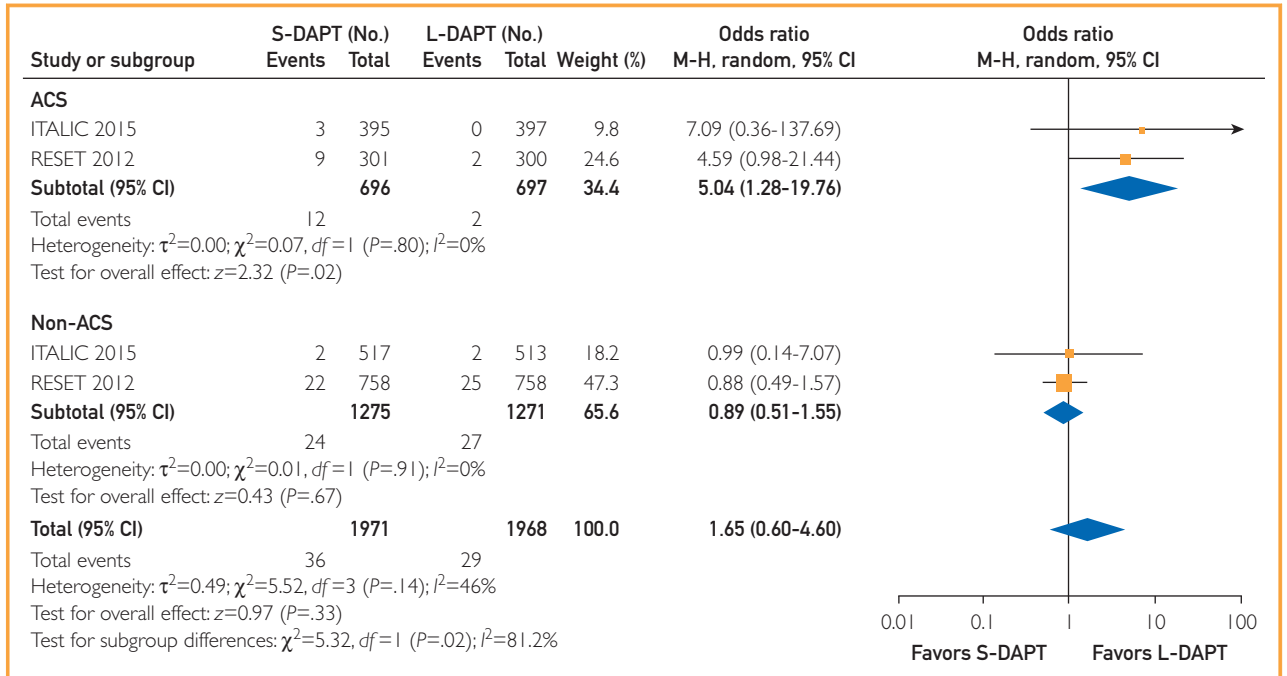

FIGURE 3. Forest plot for target vessel revascularization for patients with and without acute coronary syndrome (ACS). ITALIC = Is There A LIfe for DES After Discontinuation of Clopidogrel; L-DAPT = long-duration dual antiplatelet therapy; M-H = Mantel-Haenszel; RESET = REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation; S-DAPT = short-duration dual antiplatelet therapy.

DISCUSSION

In the present systematic review and analysis of RCTs in which patients were analyzed according to clinical syndrome acuity, S-DAPT was associated with higher rates of ST, MI, and TVR without a significant reduction in bleeding risk compared with L-DAPT in patients with ACS. In patients without ACS, S-DAPT was associated with an increased risk of MI but overall lower all-cause mortality.

Current guidelines for the duration of DAPT after DES implantation in patients with and without ACS are mainly based on evidence from the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events), substudy CURE-PCI, and CLARITY (Addition of Clopidogrel to Aspirin and Fibrinolytic Therapy for Myocardial Infarction) trials, which have shown improved clinical outcomes with the addition of clopidogrel to aspirin in patients with ACS.[1,2,21-24] However, bare metal stents were used in these studies, and they do not reflect current-day practice wherein various DESs have largely replaced bare metal stents.[21-24]

Apparent benefits of extended-duration DAPT after DES implantation in the setting of ACS could have several possible explanations. Formation of a platelet-rich thrombus and platelet hyperactivity play a critical role in ACS; the latter has also been correlated with prognosis in patients with ACS.[25] Furthermore, patients with ACS have been shown to have increased platelet reactivity compared with patients without ACS.[26] Results from the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study have shown that approximately 20% of patients with ACS who underwent percutaneous coronary intervention had recurrent major adverse cardiovascular events within 3 years of the index event. These events were equally distributed between recurrence at the culprit lesion and lesions, which were labeled nonculprit during angiography after the index ACS.[27] Dual antiplatelet therapy is protective for both stent- and non–stent-related atherothrombotic events.[2-4,11] Moreover, premature discontinuation of clopidogrel therapy after ACS has been shown to be associated with an increase in all-

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cause mortality and risk of recurrent MI.[28-30] D'Ascenzo and colleagues[31] have reported a significant increase in the risk of adverse events (death or recurrent ACS) after interruption of DAPT more than 12 months after ACS. This was independent of the hospital admitting diagnosis (unstable angina, non-STEMI, or STEMI), and results remain significant even after adjustment for age, sex, and kind of stent.[31] Such increased risk was observed only in patients treated with percutaneous transluminal coronary angioplasty and not in patients who were treated only medically.[31] These adverse outcomes could be partly attributed to an increased platelet reactivity leading to a state of rebound hyperthrombosis after clopidogrel discontinuation.[28,29] Similarly, in a subgroup analysis of the PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study) at 2 years, Costa et al[32] reported that L-DAPT was associated with an increased risk of bleeding without any significant difference in the primary end point (a composite of all-cause mortality, MI, or cerebrovascular accident) in the non-ACS setting.

Recently, in a post hoc analysis of the Dual Antiplatelet Therapy Study, Yeh et al[33] proposed a DAPT score to identify patients who might benefit from L-DAPT after percutaneous coronary intervention. In this scoring system, ACS at the time of presentation was given 1 point, and L-DAPT was associated with a favorable benefit-risk ratio in patients who have a total DAPT score of 2 or more. The DAPT score has been shown to improve prediction of expected treatment benefit vs harm of L-DAPT beyond assessment of MI history alone.[34] However, caution should be exercised until prospective validation of this prediction rule has been performed because the DAPT score was designed for patients who do not have events for the first 12 months while receiving DAPT and have no contraindications for more prolonged DAPT and are tolerating this therapy.

To our knowledge, this is the first systematic review in which efficacy and safety of S-DAPT and L-DAPT after DES implantation were analyzed according to clinical syndrome acuity. In the present analysis, we included data from RCTs only and evaluated the relationship of DAPT duration with different hard and soft clinical end points. However, this study has several limitations. First, covariate-adjusted analyses for possible confounders, such as location, extent and severity of MI, baseline patient and procedure variables (eg, the presence and severity of heart failure, diabetes, a history of bleeding, renal insufficiency, stroke, left main intervention, and length, number, and location of stents) could not be performed due to nonavailability of patient-level data. Studies included in the present meta-analysis have enrolled and randomized patients with various clinical presentations and characteristics, making it unlikely that these variables would have confounded the results due to selection bias; however, this cannot be completely excluded on the basis of the present analysis. Second, prasugrel and ticagrelor have been found to be superior to clopidogrel in the management of ACS.[1,3] However, guidelines on the optimum duration of DAPT after ACS are based on studies using clopidogrel as second agents.[1,3] Thus, the duration of DAPT using prasugrel and ticagrelor remains largely unknown. In the present study, we were unable to evaluate the duration of DAPT with prasugrel and ticagrelor because studies included in the present analysis did not compare duration of DAPT using these antiplatelets separately. However, such variations in DAPT reflect real-world clinical practice, where a different second antiplatelet is selected based on operator choices, clinical settings, and drug availability. Third, the trials included in this analysis were open label, and timing of randomization was not the same in all studies, with some variation in the definitions of various end points. This could dilute the difference between the S-DAPT and L-DAPT arms, especially if ischemic or bleeding events occurred before randomization or DAPT discontinuation. Owing to nonavailability of patient-level data, time-to-event analyses could not be performed to address this issue in this study. Fourth, owing to lack of patient-level information regarding the use of statins, β-blockers, or renin-angiotensin system blockers, we could not evaluate their effect on duration of DAPT. Fifth, duration of DAPT might be affected by type of stent implanted.[4] However, studies included in this analysis did not report outcomes in ACS and non-ACS settings separately for different generations of stents. Thus, we could not evaluate this relationship in this study. Finally, we could not analyze results separately for further breakdown of S-DAPT by time point (eg, <6 months, 6-12 months)

owing to lack of sufficient data to perform any meaningful analysis.

CONCLUSION

In the present analysis of RCTs in which patients were analyzed according to clinical syndrome acuity, S-DAPT was associated with higher rates of ST and MI, but there were nonsignificant differences in all-cause mortality, with no significant interactions according to ACS vs non-ACS. However, in patients without ACS, the benefit-risk profile may favor S-DAPT, with lower all-cause mortality, whereas the trends were reversed in ACS. Additional studies are required to determine whether the benefit-risk profile of S-DAPT vs L-DAPT varies according to clinical syndrome.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **ACC** = American College of Cardiology; **ACS** = acute coronary syndrome; **AHA** = American Heart Association; **BMS** = bare metal stent; **CI** = contraindication; **CKD** = chronic kidney disease; **CTO** = chronic total occlusion; **DAPT** = dual antiplatelet therapy; **DES** = drug-eluting stent; **DM** = diabetes mellitus; **ECG** = electrocardiogram; **FDA** = Food and Drug Administration; **GUSTO** = Global Utilization of Streptokinase and TPA for Occluded Arteries; **HLD** = hyperlipidemia; **HTN** = hypertension; **ICH** = intracranial hemorrhage; **ISR** = instent restenosis; **L-DAPT** = long-duration dual antiplatelet therapy; **LMA** = left main artery; **MACE** = major adverse cardiac event; **MI** = myocardial infarction; **NACE** = net adverse clinical events; **OAC** = oral anticoagulant; **OR** = odds ratio; **PCI** = percutaneous coronary intervention; **RCT** = randomized controlled trial; **S-DAPT** = short-duration dual antiplatelet therapy; **ST** = stent thrombosis; **STEMI** = ST-segment elevation myocardial infarction; **SVG** = saphenous venous grafts; **TIMI** = Thrombolysis In Myocardial Infarction; **TVR** = target vessel revascularization

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