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Short-term dual antiplatelet therapy for 1–3 months after percutaneous coronary intervention using drug eluting stents: A systematic review and meta-analysis of randomized clinical trials

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Abstract

Background: The optimal dual antiplatelet therapy (DAPT) duration and regimen in patients undergoing percutaneous coronary intervention (PCI) using current generation drug eluting stents (DES) is still unclear.

Aims: To compare the safety and efficacy of short-term DAPT (S-DAPT) with longer duration DAPT (L-DAPT) after contemporary PCI.

Methods: We searched for studies comparing S-DAPT (≤3 months) followed by single antiplatelet therapy (SAPT) with aspirin or a $P2Y_{12}$ inhibitor against L-DAPT (6–12 months) after PCI with current generation DES. Primary end-points of interest were major bleeding and stent thrombosis (ST) at 1 year. Random-effects meta-analyses were performed to calculate odds ratios with 95% CIs.

Results: Eleven RCTs ($n = 48{,}946$) were included in the primary analysis. Major bleeding was significantly lower with S-DAPT ($n = 24{,}424$) (odd ratio [OR 0.65; 95% confidence interval, CI 0.52–0.80]) compared with L-DAPT ($n = 24{,}486$). There were no differences in ST between the two groups [OR 1.26; 95% CI 0.97–1.63]. There were no significant differences in risks of all-cause death, cardiovascular death or myocardial infarction between S-DAPT and L-DAPT groups. In a subgroup analysis, there was borderline significantly higher ST with 1 month S-DAPT [1.39; 1.0–1.92], but not with 3 months S-DAPT [1.07; 0.70–1.64], when compared to L-DAPT. Finally, there were no significant treatment interactions observed when trials using SAPT with aspirin were compared with those using $P2Y_{12}$ inhibitor monotherapy.

Conclusion: Among patients undergoing current generation DES implantation, S-DAPT for 1–3 months reduces major bleeding without an increase in ischemic events compared with L-DAPT. Three months S-DAPT might provide a better risk-benefit profile based on current analysis. Further study is needed to define the SAPT of choice after 1–3 months DAPT.

Abbreviations: ACS, acute coronary syndrome; ASA, aspirin; CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; DAPT, dual antiplatelet therapy; DES, drug eluting stent; HBR, high bleeding risk; L-DAPT, long dual antiplatelet therapy; MI, myocardial infarction; NACE, net adverse cardiac events; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; ST, stent thrombosis; S-DAPT, short dual antiplatelet therapy.

KEYWORDS
aspirin, drug eluting stents, dual antiplatelet therapy, $P2Y_{12}$ inhibitor, percutaneous coronary intervention

1 | INTRODUCTION

Current guidelines recommend 6–12 months of dual antiplatelet therapy (DAPT) with aspirin (ASA) and a $P2Y_{12}$ inhibitor after percutaneous coronary intervention (PCI) using drug eluting stents (DES).[1,2] While DAPT is aimed to reduce atherothrombotic events after PCI, there is an inherent risk of increased bleeding particularly with prolonged DAPT.[1–3] Accordingly, in line with improvements in DES designs and pharmacotherapy, several RCTs have tested the strategy of shortened DAPT (S-DAPT) for 1–3 months after second or current generation DES implantation.[4–8] Traditionally, S-DAPT regimens have involved discontinuation of $P2Y_{12}$ inhibitor,[4–6] whereas more recently, withdrawal of ASA has been proposed.[7,8] Both strategies have been compared against longer DAPT (L-DAPT) in randomized controlled trials (RCTs), however, the optimal duration and regimen of S-DAPT is still debated. Therefore, we performed an updated meta-analysis of all available RCTs in an attempt to examine the efficacy and safety of S-DAPT in comparison with L-DAPT after contemporary PCI.

2 | METHODS

This meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[9] We systematically searched Medline, Cochrane and Embase databases for RCTs or sub-analyses of RCTs comparing different durations of DAPT after PCI. Trials were also searched in presentations at major international cardiology meetings. Following key words were used in different combinations: "dual antiplatelet therapy," "DAPT," "drug eluting stents," "DES," and "Percutaneous coronary intervention."

Inclusion criteria were RCTs that (1) compared outcomes with ≤3 months DAPT (S-DAPT) versus 6–12 months DAPT (L-DAPT) after PCI, (2) used current generation DES. We excluded studies that (1) used first generation DES or bare metal stents, (2) compared 6 months DAPT with ≥12 months DAPT.

Primary end points of interest were major bleeding and stent thrombosis (ST) at 1-year follow-up. Secondary end points included all-cause death, cardiovascular (CV) death and myocardial infarction (MI). Major bleeding was defined as BARC 3 or 5 bleeding (when reported) or TIMI major bleeding. Other end points were defined as per individual trial protocol.

Statistical analyses were performed according to recommendations of Cochrane collaboration using the Cochrane Review Manager, version 5.4. A random effects meta-analysis model with Mantel–Haenszel method was used to calculate odds ratios (ORs) and 95% confidence intervals (CI). Forest plots were generated to observe aggregate effect size and intervals for individual end-points. Heterogeneity among trials was measured using I^2 statistic, and was classified as significant if $I^2 > 50\%$. We also performed following subgroup analyses: (1) comparison of trials according to S-DAPT duration (1 month vs. 3 months), (2) stratification of trials based on type of single antiplatelet therapy (SAPT) (ASA vs. $P2Y_{12}$ inhibitor).

3 | RESULTS

Initial database search resulted in 1519 studies, out of which 21 RCTs were identified comparing S-DAPT and L-DAPT after DES implantation. After application of inclusion and exclusion criteria, 11 RCTs were selected (Supporting Information: Figure 1).[4–8,10–15] Trial data was censored at 12 months. In the MASTER DAPT trial, subgroup data for patients on oral anticoagulation was excluded because DAPT duration was only 3 months in the control group.[14]

Trial design, inclusion criteria, and baseline characteristics of patients are described in Tables 1 and 2. Out of the 11 included studies, four RCTs involved SAPT with ASA after 1–3 months DAPT,[4–6,15] 6 trials mandated $P2Y_{12}$ inhibitor monotherapy,[7,8,10–13] and 1 trial allowed either ASA or $P2Y_{12}$ monotherapy.[14] The clinical presentation was acute coronary syndrome (ACS) in 62.2% patients and stable coronary artery disease (CAD) in 37.8% patients.

All 11 RCTs reported rates of major bleeding (Figure 1). The overall incidence of major bleeding was 1.2% in S-DAPT arm compared with 1.8% in L-DAPT arm (odd ratio [Odds Ratio, OR 0.65; 95% confidence interval, CI 0.52–0.80]). There was moderate heterogeneity among studies ($I^2 = 36\%$). These results were consistent when stratified according to type of SAPT {[OR 0.71; 95% CI 0.51–0.99] for patients on ASA and [OR 0.57; 95% CI 0.41–0.80] for patients on a $P2Y_{12}$ inhibitor} (Supporting Information: Figure 2).

Rates of ST were reported in 11 RCTs (Figure 2). Overall, the frequency of ST was low (0.49%) and similar between S-DAPT compared to L-DAPT [OR 1.26; 95% CI 0.97–1.63].

In a subgroup analysis, ST was higher in S-DAPT for 1 month as compared with L-DAPT [OR 1.39; 95% CI 1.0–1.92], however this effect was not seen with 3-month DAPT [OR 1.07; 95% CI 0.70–1.64] (Figure 3). No significant treatment interaction was noted between type of SAPT used and risk of ST (Supporting Information: Figure 3).

There was no significant difference in incidence of MI between S-DAPT group and L-DAPT group (1.9% vs. 1.7%) [OR 1.10; 95% CI 0.96–1.26] (Figure 4). There was no significant heterogeneity among studies. Estimates were consistent among patients on SAPT with ASA

TABLE 1 Trial design, major inclusion criteria and primary outcomes of individual studies

Study, follow-up	Design	*N* patients	Major inclusion criteria	Primary endpoint
RESET 2012, 1 Year	3 M DAPT > ASA 12 M DAPT, Non-inferiority	*N* = 1059 *N* = 1058	Angina or acute MI, >50% diameter stenosis	Composite of death from CV cause, MI, ST, ischemia driven TVR, or bleeding
OPTIMIZE 2013, 1 Year	3 M DAPT > ASA 12 M DAPT, Non-inferiority	*N* = 1563 *N* = 1556	Stable angina or silent ischemia or low-risk ACS, elevated biomarker levels	NACCE composite of death from any cause, MI, stroke, or major bleeding
GLOBAL LEADERS 2018, 2 Years	1 M DAPT > Ticagrelor 12 M DAPT > ASA, Superiority	*N* = 7980 *N* = 7988	Any indication for PCI	Composite of all-cause death or new Q-wave myocardial infarction
REDUCE 2019, 2 Years	3 M DAPT > ASA 12 M DAPT, Noninferiority	*N* = 751 *N* = 745	STEMI, NSTEMI or UA	Composite of all-cause mortality, MI, ST, stroke, TVR, or bleeding
SMART CHOICE 2019, 1 Year	3 M DAPT > P2Y12 Inhibitor 12 M DAPT, Noninferiority	*N* = 1495 *N* = 1498	One or more coronary artery > 50% stenosis	MACE composite of all-cause death, MI, stroke
STOP DAPT 2 2019, 1 Year	1 M DAPT > P2Y12 Inhibitor 12 M DAPT, Non-inferiority	*N* = 1500 *N* = 1509	Underwent successful PCI with CoCr-EES	Composite of cardiovascular & bleeding events, cardiovascular death, MI, ST, ischemic or hemorrhagic stroke, or TIMI major or minor bleeding
TWILIGHT 2019, 1 Year	3 M DAPT > Ticagrelor 12 M DAPT, Superiority	*N* = 3555 *N* = 3564	PCI with DES, high risk of ischemic or bleeding events	BARC type 2, 3, or 5 bleeding
TICO 2020, 1 Year	3 M DAPT > Ticagrelor 12 M DAPT, Non-Inferiority	*N* = 1527 *N* = 1529	ACS, underwent PCI with bioresorbable polymer SES	TIMI Major Bleeding, BARC 3-5 bleeding, MACCE composite of death, MI, stent thrombosis, stroke, or target-vessel revascularization,
1-month DAPT 2021, 1 year	1 M DAPT > ASA 6-12 M DAPT, Non-Inferiority	*N* = 1507 *N* = 1513	Nonemergent PCI for CAD 1 M group: polymer-free drug-coated stent, 6-12 M group: biodegradable-polymer DES	Composite outcome of cardiac death, nonfatal MI, target vessel revascularization, stroke, or major bleeding
STOP DAPT 2 ACS 2021, 1 Year	1 M DAPT > P2Y12 Inhibitor 12 M DAPT, Non-inferiority	*N* = 2058 *N* = 2078	PCI for ACS with cobalt-chromium EES	Composite of cardiovascular death, MI, stroke, stent thrombosis, TIMI major or minor bleeding
MASTER DAPT 2021, 1 Year	1 M DAPT > P2Y12 Inhibitor 12 M DAPT, Non-inferiority	*N* = 1447 *N* = 1466	ACS or Stable CAD, PCI with biodegradable-polymer SES	MACCE composite of death, MI, stroke, NACE (MACE + Major Bleeding), Major bleeding or clinically relevant non major bleeding

Abbreviations: ASA, Aspirin; CAD, Coronary Artery Disease; DAPT, Dual Antiplatelet Therapy; GLOBAL LEADERS, Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months versus aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent; M, Months; MACCE, Major Adverse Cardiac or Cerebrovascular Event; MASTER DAPT, Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Prolonged DAPT Regimen; NACE, Net Adverse Clinical Event; OPTIMIZE, Optimized Duration of Clopidogrel Therapy Following Treatment With the Endeavor Zotarolimus—Eluting Stent in the Real World Clinical Practice; PCI, Percutaneous Coronary Intervention; REDUCE, Randomized Evaluation of short-term DUal antiplatelet therapy in patients with acute Coronary syndromE treated with a new generation stent; RESET, REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation; SMART-CHOICE, Effect of P2Y12 Inhibitor Monotherapy versus Dual Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention; STOP DAPT-2, Effect of 1-Month Dual Antiplatelet Therapy Followed by Clopidogrel versus 12-Month Dual Antiplatelet Therapy on Cardiovascular and Bleeding Events in Patients Receiving PCI; STOP DAPT-2 ACS, Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2 Acute Coronary Syndrome; TICO, Ticagrelor Monotherapy versus Ticagrelor With Aspirin and Adverse Events in Acute Coronary Syndrome; TWILIGHT, Ticagrelor with or without Aspirin in High-Risk Patients after PCI; 1-Month DAPT, A Randomized Controlled Comparison Between One Versus More Than 6 Months of Dual Antiplatelet Therapy After Biolimus A9-Eluting Stent Implantation.

TABLE 2 Clinical characteristics of patients enrolled in the randomized controlled trials included in the meta-analysis

Trial		Mean Age (y)	Female (%)	HTN (%)	DM (%)	HLD (%)	Smoker (%)	Prior MI (%)	ACS (%)	Stent Type	P2Y12 Inhibitor
RESET	3 M	62	36	62	30	58	25	2	56	ZES, EES, SEZ, ZES	Clopidogrel
	1 M	62	37	61	29	60	23	2	54		
OPTIMIZE	3 M	61.3	37	86	35	63	19	35	32	ZES, SES, EES, ZES	Clopidogrel
	12 M	62	37	88	35	64	17	35	32		
GLOBAL LEADERS	1 M	65	23	74	26	69	26	23	47	BES	Ticagrelor
	24 M	65	24	73	25	70	26	24	47		
REDUCE	3 M	61	17	51	22	46	42	13	100	New Generation DES	Clopidogrel, Prasugrel, Ticagrelor
	12 M	60	23	51	20	45	43	12	100		
SMART CHOICE	3 M	65	27	62	38	45	28	4	58	EES, ZES, SES	Clopidogrel, Prasugrel, Ticagrelor
	12 M	64	26	61	37	46	29	4	58		
STOP DAPT 2	1 M	68	21	74	39	74	27	14	38	EES	Clopidogrel, Prasugrel
	12 M	69	24	73	38	75	21	13	39		
TWILIGHT	3 M	65	24	73	37	61	20	29	64	DES	Ticagrelor
	12 M	65	24	72	37	60	23	29	66		
TICO	3 M	61	21	50	27	61	36	4	100	BP SES	Ticagrelor
	1 M	61	20	51	27	60	38	3	100		
1-month DAPT	1 M	67	31	67	37	81	17	4	38	PF DCS	Clopidogrel
	6–12 M	67	31	66	38	82	16	4	41	BP DES	
STOP DPAT 2 ACS	1 M	67	21	68	30	67	35	6	100	CoCr-EES	Clopidogrel, Prasugrel
	12 M	67	21	68	30	67	34	5	100		
MASTER DAPT	1 M	78	34	76	33	66	46	18	51	BP SES	Clopidogrel, Prasugrel, Ticagrelor
	6 M	78	34	77	34	68	43	18	52		

Abbreviations: ACS, Acute Coronary Syndrome; BMS, Bare-Metal Stent; BES, Biolimus Eluting Stent; BP SES, Biodegradable Sirolimus Eluting Stent; CoCr-EES, cobalt-chromium everolimus-eluting stent DES, Drug Eluting Stent; DAPT, Dual Antiplatelet Therapy; DM, Diabetes Mellitus; EES, Everolimus Eluting Stent; GLOBAL LEADERS, Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months versus aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent; HLD, Hyperlipidemia; HTN, Hypertension; MASTER DAPT, Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Prolonged DAPT Regimen; MI, Myocardial Infarction; OPTIMIZE, Optimized Duration of Clopidogrel Therapy Following Treatment With the Endeavor Zotarolimus—Eluting Stent in the Real World Clinical Practice; PES, Paclitaxel Eluting Stent; PF DCS, Polymer Free Drug Coated Stent; RESET, REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation; REDUCE, Randomized Evaluation of short-term DUal antiplatelet therapy in patients with acute Coronary syndromE treated with a new generation stent; SES, Sirolimus Eluting Stent; SMART-CHOICE, Effect of P2Y12 Inhibitor Monotherapy versus Dual Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention; STOP DAPT-2, Effect of 1-Month Dual Antiplatelet Therapy Followed by Clopidogrel versus 12-Month Dual Antiplatelet Therapy on Cardiovascular and Bleeding Events in Patients Receiving PCI; STOP DAPT-2 ACS, Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2 Acute Coronary Syndrome; TWILIGHT, Ticagrelor with or without Aspirin in High-Risk Patients after PCI; TICO, Ticagrelor Monotherapy versus Ticagrelor With Aspirin and Adverse Events in Acute Coronary Syndrome; 1-Month DAPT, A Randomized Controlled Comparison Between One Versus More Than 6 Months of Dual Antiplatelet Therapy After Biolimus A9-Eluting Stent Implantation; y, Years; ZES, Zotarolimus Eluting Stent.

[1.04; 0.76–1.41] and SAPT with $P2Y_{12}$ inhibitor [1.08; 0.85–1.36] (Supporting Information: Figure 4).

Finally, there were no differences in all-cause death [OR 0.92; 95% CI 0.78–1.08] or CV death [OR 0.83; 95% CI 0.65–1.05] between S-DAPT and L-DAPT groups (Figures 5 and 6). These findings were observed regardless of whether ASA or $P2Y_{12}$ inhibitor were used as SAPT (Supporting Information: Figure 5–6).

4 | DISCUSSION

In this study of 48,946 patients pooled from 11 RCTs, the main findings are as follows:

(1) S-DAPT for 1–3 months significantly reduces risk of major bleeding compared with L-DAPT.

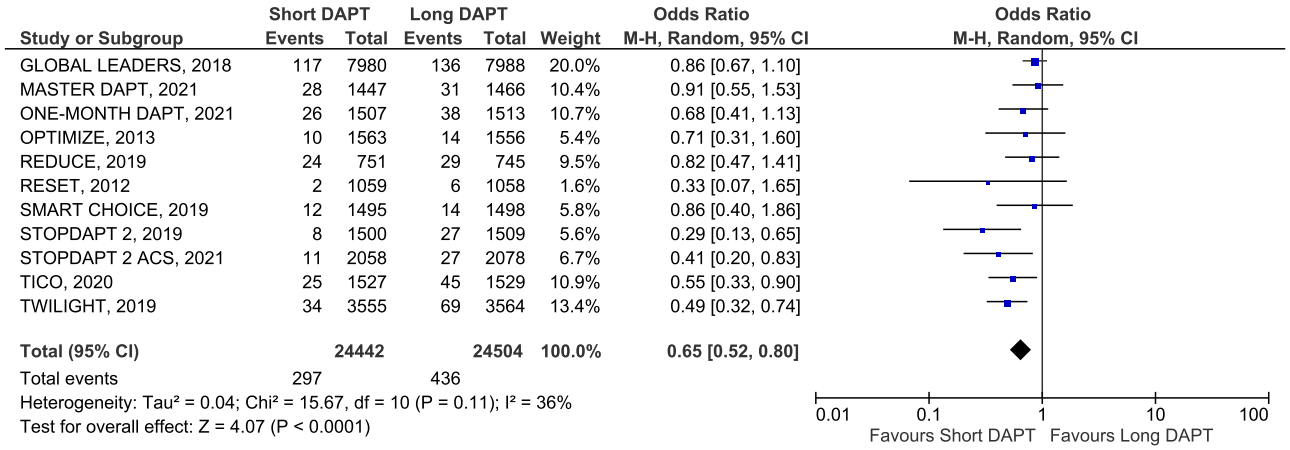

FIGURE 1 Forest plot illustrating odds ratio of major bleeding. CI, confidence intervals; DAPT, Dual antiplatelet therapy. [Color figure can be viewed at wileyonlinelibrary.com]

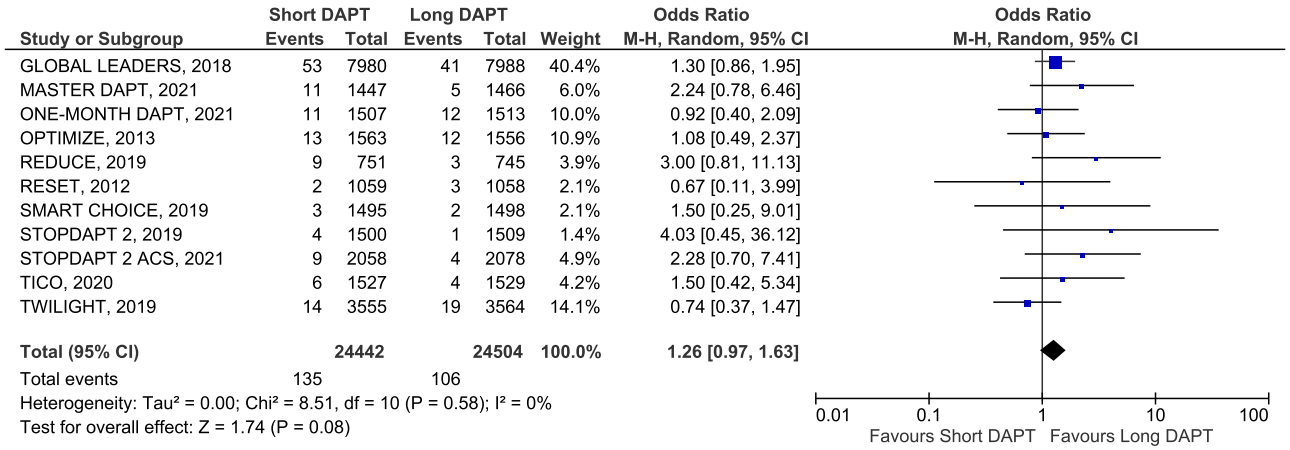

FIGURE 2 Forest plot illustrating odds ratio of stent thrombosis. CI, Confidence Intervals; DAPT, Dual antiplatelet therapy. [Color figure can be viewed at wileyonlinelibrary.com]

(2) There were no significant differences in risks of death or MI between the two DAPT durations at 12 months.
(3) In a subgroup analysis, ST was borderline significantly higher with 1 month, but not 3 months DAPT, when compared with L-DAPT.
(4) Finally, there were no significant differences in ischemic end-points between trials of S-DAPT followed by ASA monotherapy and S-DAPT followed by $P2Y_{12}$ monotherapy as compared to L-DAPT.

Several RCTs and their meta-analyses have shown similar anti-ischemic efficacy and reduced bleeding risks with ≤6 months DAPT compared to 12 months or longer DAPT atleast in low-risk PCI patients.[4–6,16–18] Based on these findings, American and European guidelines updated recommendations for mandated DAPT durations after PCI to 6 months in stable CAD.[1,2] While, three months DAPT was examined in only 3 trials at the time of 2017 guideline updates,[4–6] more recently, new trials have been published further testing the S-DAPT regimens of 1–3 months duration in comparison with 6–12 months DAPT.[7,8,10–15] However, individual RCTs suffer from limitations with respect to their non-inferiority design and low statistical power to derive conclusions on individual ischemic end-points. Moreover, some of these trials differ from previous DAPT duration trials with regard to a strategy of continuing SAPT with a $P2Y_{12}$ inhibitor with early discontinuation of ASA.[7,8,10–13] Although theoretically appealing, the concept of "aspirin-free" regimen with $P2Y_{12}$ inhibitor remains debated given the lack of head-to-head comparison against SAPT with ASA in prospective randomized trials.[19] Therefore, the optimal duration and regimen of S-DAPT among patients undergoing contemporary PCI remains unclear.

The present analysis aimed to consolidate the findings of all available trials comparing S-DAPT (1–3 months) with L-DAPT after current generation DES implantation. In the RESET, OPTIMIZE, and REDUCE trials, S-DAPT followed by ASA monotherapy was noninferior to 12 months DAPT for a composite end-point of net adverse cardiac events (NACE).[4–6] In the GLOBAL LEADERS trial, besides observing similar rates of all cause death or new Q-wave MI with ticagrelor monotherapy after 1-month DAPT, the bleeding rates did not differ in comparison to conventional 12 months DAPT.[8]

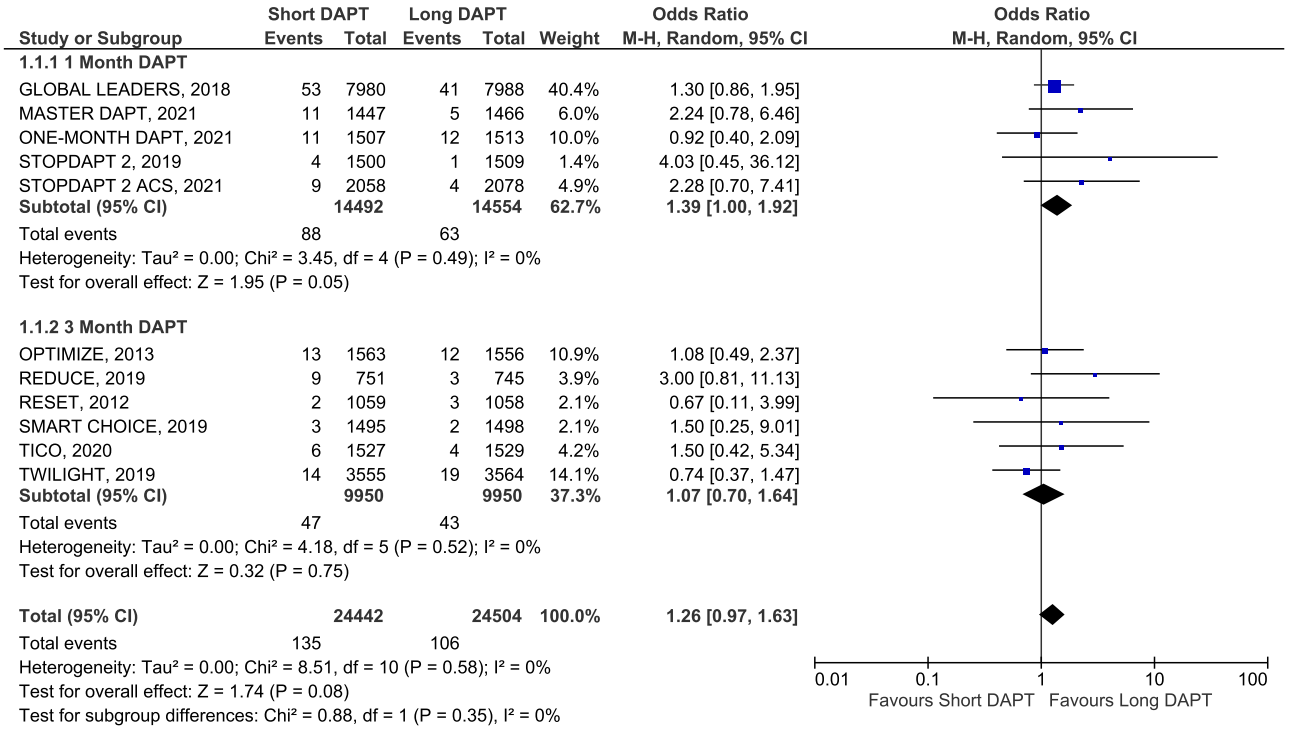

FIGURE 3 Forest plot illustrating odds ratio of stent thrombosis according to duration of S-DAPT. CI, Confidence Intervals; DAPT, Dual antiplatelet therapy. [Color figure can be viewed at wileyonlinelibrary.com]

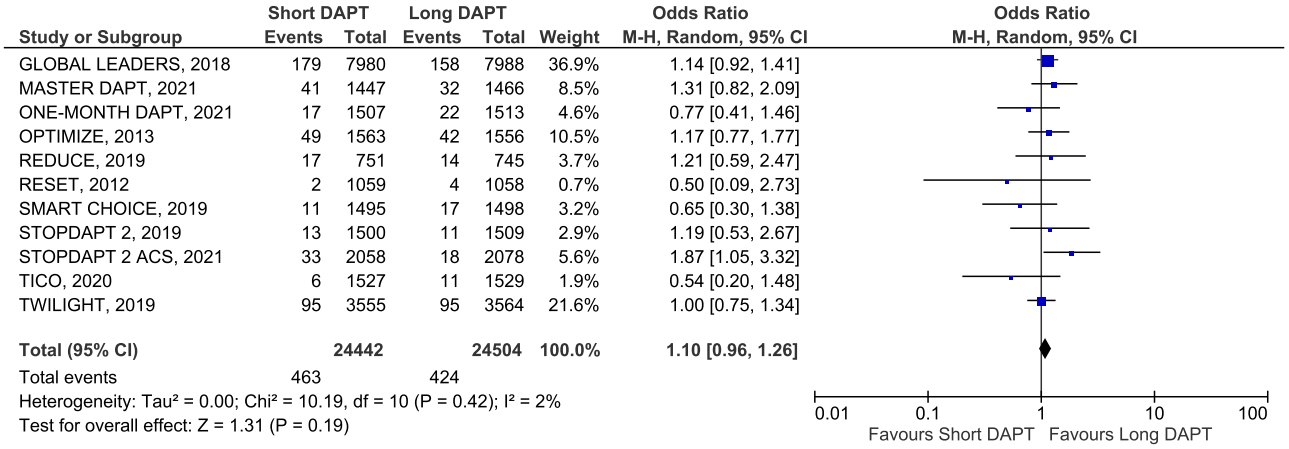

FIGURE 4 Forest plot illustrating odds ratio of myocardial infarction. CI, Confidence Intervals; DAPT, Dual antiplatelet therapy. [Color figure can be viewed at wileyonlinelibrary.com]

Conversely, TWILIGHT and TICO trials comparing 3-months DAPT followed by ticagrelor monotherapy with 12 months DAPT showed reduced rates of major bleeding without an increase in ischemic events.[7,13] Even more recently, MASTER DAPT and 1-month DAPT trials reported that among patients undergoing PCI using newer generation DES, 1-month DAPT was noninferior to 6–12 months DAPT in terms of NACE.[14,15] It should be noted that the risk estimates of major bleeding with S-DAPT compared to L-DAPT have been inconsistent between these individual trials.

Our findings reconcile the somewhat contrasting results of individual trials. Major bleeding was significantly decreased with a relative risk reduction of 35% in the S-DAPT arm compared with L-DAPT in our pooled analysis. As it relates to ST, we observed no significant differences in overall risks between the S-DAPT and L-DAPT regimens. However, 1-month DAPT was associated with borderline significantly higher ST as compared with L-DAPT. These findings are clinically relevant since the individual trials have been underpowered to detect important differences in rates of infrequent ischemic end-points such as ST.[20] Nevertheless, ST is potentially fatal and associated with worse outcomes even with current generation DES.[21] On the contrary, our findings suggest that 3 months DAPT might be sufficient in terms of ST risk compared with L-DAPT.

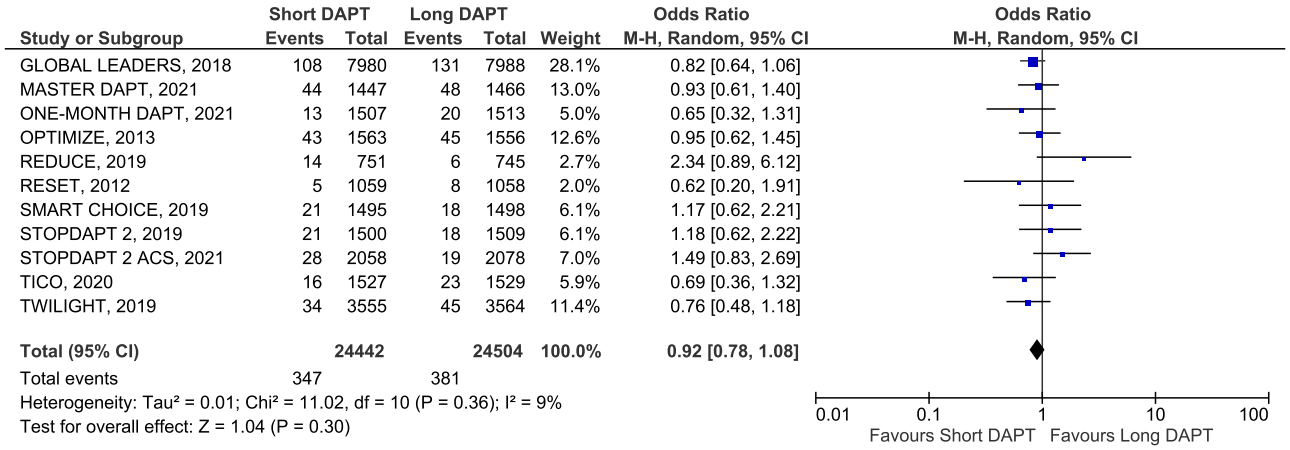

FIGURE 5 Forest plot illustrating odds ratio of all-cause death. CI, Confidence Intervals; DAPT, Dual antiplatelet therapy. [Color figure can be viewed at wileyonlinelibrary.com]

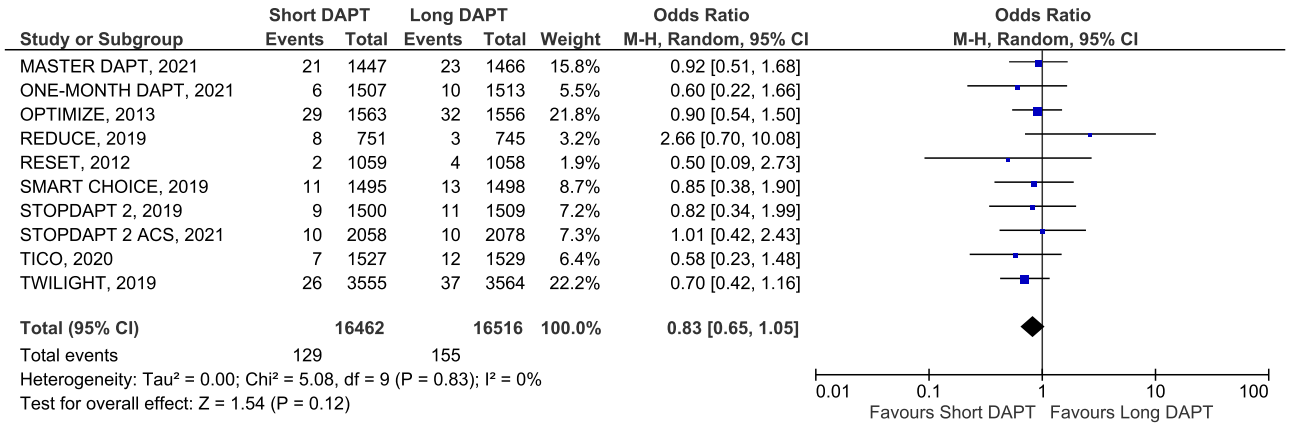

FIGURE 6 Forest plot illustrating odds ratio of cardiovascular death. CI, Confidence Intervals; DAPT, Dual antiplatelet therapy. [Color figure can be viewed at wileyonlinelibrary.com]

Consistent with the results of available RCTs, risks of death and MI were similar between S-DAPT and L-DAPT without between-trial heterogeneity in the present analysis. Furthermore, there were no significant differences in treatment effects when trials were stratified according to type of SAPT after abbreviated DAPT. These findings are in line with a prior meta-analysis that showed consistent summary estimates between trials employing SAPT with a $P2Y_{12}$ inhibitor and those employing SAPT with ASA.[22] However, this meta-analysis differs from prior analyses in stratifying risk estimates by different durations of S-DAPT (1 month vs. 3 months). Further, this is the largest analysis to date of all RCTs comparing 1–3 months DAPT versus L-DAPT after PCI.

These findings in aggregate have important clinical implications toward optimizing DAPT regimens. First, S-DAPT for 1–3 months duration might be associated with similar 1-year ischemic outcomes along with the benefit of decreased major bleeding as compared to L-DAPT in post-PCI patients who undergo current-generation DES implantation and remain event-free within the S-DAPT period. Noteworthy, as addressed in recent guidelines, these findings are particularly relevant for high-bleeding risk (HBR) patients who might not derive any ischemic benefit with prolonged DAPT.[23,24] Second, our findings reinforce the message of a tailored approach to DAPT duration based on an individual's ischemic and bleeding risks. While 1-month DAPT might be reasonable in a high bleeding risk patient, 3 months or longer DAPT might be the preferred approach in patients without HBR and/or with high-ischemic risk. Third, in regard to ACS, most trials enrolled low-risk patients as evident by the low event-rates and therefore, these findings might not be generalizable to high-ischemic risk patients such as those presenting with ST-elevation MI or undergoing multivessel PCI. Fourth, whether $P2Y_{12}$ inhibitor monotherapy provides superior ischemic protection against ASA monotherapy remains to be further investigated. In the absence of clear evidence, preference for $P2Y_{12}$ inhibitor might be influenced by risks of gastrointestinal bleeding or presence of high ischemic risk-factors such as ACS. Indeed, cumulative evidence regarding safety of $P2Y_{12}$ inhibitor monotherapy in ACS population is so-far reassuring.[20,25] Furthermore, the HOST-EXAM trial demonstrated superior efficacy and

safety of clopidogrel over ASA in the chronic maintenance phase (after 6–18 months DAPT) after PCI.[26]

Our study suffers from few limitations. First, individual RCTs have focused on composite end-points and lacked power for individual end-points such as ST. Therefore, our results for ST based on DAPT durations should be interpreted with caution. Second, there was some heterogeneity in terms of trial design (e.g., timing of randomization) and end-point definitions. However, we observed no significant heterogeneity for any of the individual end-points in our pooled analysis. Third, type of SAPT after S-DAPT differed between trials that is, ASA or $P2Y_{12}$ inhibitor monotherapy. To overcome this limitation, we performed sensitivity analysis based on trials of SAPT with ASA and trials of SAPT with $P2Y_{12}$ inhibitor versus L-DAPT whcih showed no difference in outcomes. Finally, although individual trials included ACS patients, certain high-risk subgroups were either underrepresented or excluded based on specific enrollment criteria. Thus, our findings might not be applicable to all patients undergoing PCI with current generation DES.

5 | CONCLUSION

In this meta-analysis of 48,946 patients treated with DES, S-DAPT for 1–3 months was associated with reduced risk of major bleeding without an increase in MI and mortality compared with L-DAPT. Three months S-DAPT might provide a better risk profile based on current study in terms of ST. Risk of ST and choice of antiplatelet therapy after 1–3 months DAPT requires further investigation in future studies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are included within the articles.

ORCID

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REFERENCES

1. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American college of Cardiology/American heart association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2016;(68):1082-1115.
2. Valgimigli M, Bueno H, Byrne RA, et al. ESC scientific document group 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the european society of cardiology (ESC) and of the european association for Cardio-Thoracic surgery (EACTS). *Eur Heart J*. 2018;39:213-260.
3. 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;371:2155-2166.
4. Kim BK, Hong MK, Shin DH, et al. A new strategy for discontinuation of dual antiplatelet therapy. *J Am Coll Cardiol*. 2012;60:1340-1348.
5. 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;310:2510-2522.
6. De Luca G, Damen SA, Camaro C, Collaborators Final results of the randomised evaluation of short-term dual antiplatelet therapy in patients with acute coronary syndrome treated with a new-generation stent (REDUCE trial). *EuroIntervention*. 2019;Dec 6 15(11):e990-e998.
7. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med*. 2019;381:2032-2042.
8. Vranckx P, Valgimigli M, Jüni P, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet (London, England)*. 2018;392:940-949.
9. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4:1.
10. Hahn JY, Song YB, Oh JH, et al. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE randomized clinical trial. *JAMA*. 2019;321:2428-2437.
11. Watanabe H, Domei T, Morimoto T, et al. Effect of 1-Month dual antiplatelet therapy followed by clopidogrel vs. 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. *JAMA*. 2019;321:2414-2427.
12. Presented by Watanabe H, Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2 Acute Coronary Syndrome-STOPDAPT-2 ACS. European Society of Cardiology Virtual Congress. 2021.
13. Kim BK, Hong SJ, Cho YH, et al. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome: the TICO randomized clinical trial. *JAMA*. 2020;323(23):2407-2416.
14. Smits PC, Frigoli E, Tijssen J, et al. MASTER DAPT investigators. abbreviated antiplatelet therapy in patients at high bleeding risk with or without oral anticoagulant therapy after coronary stenting: an Open-Label, randomized, controlled trial. *Circulation*. 2021;144:1196-1211.
15. Hong SJ, Kim JS, Hong SJ, et al. 1-Month Dual-Antiplatelet therapy followed by aspirin monotherapy after polymer-free drug-coated stent implantation: one-month DAPT trial. *JACC. Cardiovasc interv*. 2021;14(16):1801-1811.
16. 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;125:505-513.
17. Schulz-Schüpke S, Byrne RA, Ten Berg JM, et al. ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting. *Eur Heart J*. 2015;36:1252-1263.
18. Sharma A, Agrawal S, Garg A, Vallakati A, Lavie CJ, Helft G. Duration of dual antiplatelet therapy following drug-eluting stent implantation: a systemic review and meta-analysis of randomized controlled

trials with longer follow up. *Catheter Cardiovasc Interv*. 2017;90:31-37.
19. Capodanno D, Mehran R, Valgimigli M, et al. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. *Nat Rev Cardiol*. 2018;15(8):480-496.
20. Garg A, Rout A, Sharma A, et al. Safety and efficacy of antiplatelet regimens after percutaneous coronary intervention using drug eluting stents: a network meta-analysis of randomized controlled trials. *Prog Cardiovasc Dis*. 2020;63(3):243-248.
21. Kuramitsu S, Ohya M, Shinozaki T, et al. Risk factors and long-term clinical outcomes of second-generation drug-eluting stent thrombosis. *Circulation: Cardiovasc Interv*. 2019;12(6):e007822.
22. Giacoppo D, Matsuda Y, Fovino LN, et al. Short dual antiplatelet therapy followed by P2Y12 inhibitor monotherapy vs. prolonged dual antiplatelet therapy after percutaneous coronary intervention with second-generation drug-eluting stents: a systematic review and meta-analysis of randomized clinical trials. *Eur Heart J*. 2021;42(4):308-319.
23. Collet JP, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42(14):1289-1367.
24. Costa F, Van Klaveren D, Feres F, et al. Dual antiplatelet therapy duration based on ischemic and bleeding risks after coronary stenting. *J Am Coll Cardiol*. 2019;73(7):741-754.
25. Valgimigli M, Gragnano F, Branca M, et al. P2Y12 inhibitor monotherapy or dual antiplatelet therapy after coronary revascularisation: individual patient level meta-analysis of randomised controlled trials. *BMJ*. 2021;373:n1332. doi:10.1136/bmj.n1332
26. Koo BK, Kang J, Park KW, et al. Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated, prospective, randomised, open-label, multicentre trial. *Lancet*. 2021;397(10293):2487-2496.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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