Dual antiplatelet therapy duration after percutaneous coronary intervention using drug eluting stents in high bleeding risk patients: A systematic review and meta-analysis

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Abstract

Background Optimal dual antiplatelet therapy (DAPT) duration in patients at high bleeding risk (HBR) is not fully defined. We aimed to compare the safety and effectiveness of short-term DAPT (S-DAPT) with longer duration DAPT (L-DAPT) after percutaneous coronary intervention (PCI) with drug eluting stents (DES) in patients at HBR.

Methods We searched for studies comparing S-DAPT (≤3 months) followed by aspirin or P2Y 12 inhibitor monotherapy against L-DAPT (6-12 months) after PCI in HBR patients. Primary end points of interest were major bleeding and myocardial infarction (MI). Random-effects meta-analyses were performed to calculate odds ratios with 95% CIs.

Results Six randomized trials and 3 propensity-matched studies (n = 16,848) were included in the primary analysis. Compared with L-DAPT (n = 8,422), major bleeding was lower with S-DAPT (n = 8,426) [OR 0.68; 95% CI 0.51-0.89] whereas MI did not differ significantly between the 2 groups [1.16; 0.94-1.44]. There were no significant differences in risks of death, stroke or stent thrombosis (ST) between S-DAPT and L-DAPT groups. These findings were consistent when propensity-matched studies were analysed separately. Finally, there was a numerically higher, albeit statistically non-significant, ST in the S-DAPT arm of patients without an indication for OAC [1.98; 0.86-4.58].

Conclusions Among HBR patients undergoing current generation DES implantation, S-DAPT reduces bleeding without an increased risk of death or MI compared with L-DAPT. More research is needed to (1) evaluate risks of late ST after 1 to 3 months DAPT among patients with high ischemic and bleeding risks, (2) defining the SAPT of choice after 1 to 3 months DAPT. (Am Heart J 2022;250:1–10.)

Introduction

Dual antiplatelet therapy (DAPT) with aspirin (ASA) and a $P2Y_{12}$ inhibitor is recommended for 6 to 12 months after percutaneous coronary intervention (PCI) in all-comers to reduce risks of recurrent ischemic events.[1,2] Although guidelines further provision the use of 1 to

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

Condensed abstract

We aimed to compare short-term dual antiplatelet therapy (S-DAPT) with longer duration DAPT (L-DAPT) after drug eluting stents (DES) implantation in patients at high bleeding risk (HBR). Compared with L-DAPT, the odds of major bleeding were lower with S-DAPT [OR 0.63; 95% CI 0.44-0.90] whereas MI did not differ significantly between the 2 groups [1.31; 0.96-1.80]. There were no significant differences in risks of all-cause death, CV death or MI between S-DAPT and L-DAPT. In conclusion, among HBR patients undergoing current generation DES implantation, S-DAPT reduces bleeding without an increased risk of death or MI compared with L-DAPT.

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6 months DAPT in selected patients at high bleeding risk (HBR), these recommendations are based on expert consensus or observational data rather than dedicated, prospective randomized controlled trials (RCTs).[2] Therefore, the optimal duration of DAPT to prevent ischemic events while limiting bleeding in patients at HBR is not fully defined.

Recent trials have tested a strategy of shorter DAPT duration (1-3 months; S-DAPT) to mitigate the risk of bleeding after PCI with newer generation drug eluting stents (DES).[3-8] Although the results are promising, patients at HBR were frequently excluded or under-represented in these trials of short DAPT regimens.[3-6] Nevertheless, limited data in HBR patients has suggested comparable anti-thrombotic efficacy and lower incidence of bleeding with S-DAPT as compared with longer DAPT (L-DAPT) durations.[9-12] More recently, MASTER DAPT study specifically evaluating 1-month DAPT in HBR patients has shown non-inferiority with regards to composite ischemic end point but superiority for bleeding when compared with standard DAPT durations.[13] However, the individual trials have limitations given the non-inferiority design, lower than anticipated event rate and low statistical power to assess important individual ischemic end points.[14] Therefore, we performed this systematic review and meta-analysis of available studies to examine the aggregate data for comparison of S-DAPT (1-3 months) vs L-DAPT (6-12 months) on individual ischemic and bleeding end points in patients at HBR.

Methods

The current study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[15] Medline, Cochrane and Embase databases were searched for RCTs or sub-analyses of RCTs comparing different durations of DAPT after PCI with DES implantation in HBR patients. We also searched for propensity matched studies comparing DAPT durations with newer generation stents. Following key words were used for database search in different combinations: "dual antiplatelet therapy", "DAPT", "drug eluting stents", "DES" and "high bleeding risk". Inclusion criteria were RCTs and propensity matched studies that compared ≤3 months DAPT (S-DAPT) vs L-DAPT (6-12 months) after newer generation DES implantation and reported data on patients at HBR. We excluded studies that used bare metal stents.

Two authors (A.G. and A.R.) independently screened and reviewed the studies for inclusion and exclusion criteria. Primary end points included major bleeding defined by BARC 3 or 5 bleeding, and myocardial infarction (MI). Secondary end points were major adverse cardiac and cerebrovascular events (MACCE), all-cause death, cardiovascular (CV) death, stroke and stent thrombosis (ST). End points were defined as per individual trial protocol.

We used random effects meta-analysis with Mantel-Haenszel method to study comparisons of S-DAPT and L-DAPT regimens. Odds ratios and 95% confidence intervals (CI) were calculated and graphed as forest plots for individual end points. Heterogeneity was calculated using I^2 statistic and was considered significant if I^2 >50%. In case of significant heterogeneity, sensitivity analyses were performed by excluding 1 study at a time to explore the influence of single trials. We also performed sensitivity analyses for major bleeding, MI and ST according to the presence or absence of an indication for oral anticoagulation (OAC). Meta-regression analyses were used to explore the influence of selected patient characteristics [age, gender, chronic kidney disease, prior MI and acute coronary syndrome (ACS)] on the treatment effect of DAPT for the primary study end points. Finally, publication bias was assessed using funnel plot graphs. All data was analyzed using Cochrane Review Manager, version 5.3. No extramural funding was used to support this work.

Results

Initial database search resulted in 932 studies, out of which 6 RCTs (n = 8,895) and 3 propensity matched studies (n = 7,953) were identified comparing S-DAPT and L-DAPT after DES implantation in HBR patients (Supplementary Figure 1).[9-11,16-20] Four RCTs included patients without indication for OAC (n = 6,407)[9-11,18] whereas 3 RCTs included patients with an indication for OAC (n = 2,488).[16-18] WOEST and AUGUSTUS trials were excluded from the current analysis since the studies did not compare durations of DAPT in patients undergoing PCI.[21,22]

Trial design, inclusion criteria, and baseline characteristics of patients are described in Tables I and II. Out of 9 studies, 3 mandated $P2Y_{12}$ monotherapy for the study period in S-DAPT arm,[9-11] 5 involved ASA monotherapy[16,17,19,20] and 1 trial allowed either ASA or $P2Y_{12}$ monotherapy.[18] Amongst the 6 RCTs, the clinical presentation was ACS in 4,790 (53.8%) patients and stable CAD in 4,105 (46.2%) patients.

All studies reported rates of major bleeding (Figure 1). The overall incidence of major bleeding was 2.6% in S-DAPT arm compared with 3.8% in L-DAPT arm [OR 0.68; 95% CI 0.51-0.89; absolute risk difference -1.2%]. There was moderate heterogeneity among studies (I^2 = 53%). In the leave-one-out sensitivity analysis, no single study influenced the risk estimates for major bleeding. These results were consistent when stratified according to indication for OAC ([0.50; 0.28-0.91] for patients without indication for OAC and [0.78; 0.52-1.17] for patients on OAC) with no significant interaction (P = .23) (Supplementary Figure 2A).

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Table I. Trial design, major inclusion criteria and primary end point of individual studies

Study(Follow up)	*N* patients	Study design &Randomization	Major inclusion criteria	High bleeding risk criteria	Primary end point
MASTER DAPT (12 mo)	1 M DAPT *N* = 2295 3 or 6 M DAPT *N* = 2284	RCT Non-Inferiority; At 1 mo after index procedure	ACS or Stable CAD, PCI with biodegradable-polymer SES, & free from ischemic & bleeding events for 1 M	Use of OAC, <12 M bleeding, age ≥75, hematological disorders, stroke or TIA in last 6 M, PRECISE-DAPT score ≥25	Composite of death, MI, stroke, Major (BARC 3-5) or clinically relevant non major bleeding (BARC 2-5)
TWILIGHT-HBR (15 mo)	3 M DAPT *N* = 521 15 M DAPT *N* = 543	RCT Non-Inferiority; At 3 mo after PCI	ACS or Stable CAD, underwent PCI & free of ischemic events between for 3 mo	ARC-HBR criteria	BARC 2-5 bleeding
TICO (12 mo)	3 M DAPT *N* = 682 12 M DAPT *N* = 694	RCT Non-Inferiority; During index procedure	ACS, underwent successful PCI with ultrathin bioresorbable polymer SES	Low body weight, anemia, & chronic kidney disease	Composite of major bleeding, death, MI, ST, stroke, or TVR
STOPDAPT-2 (12 mo)	1 M DAPT *N* = 496 12 M DAPT *N* = 558	RCT Non-Inferiority; During index procedure	ACS or Stable CAD, underwent PCI with cobalt chromium EES	ARC-HBR criteria	Composite of cardiovascular (CV death, MI, definite ST, stroke) & bleeding outcomes (TIMI major or minor)
ISAR TRIPLE (9 mo)	1.5 M DAPT *N* = 307 6 M DAPT *N* = 307	RCT Superiority; During index procedure	ACS or Stable CAD, underwent PCI with DES, on OAC for at least 12 mo	Use of OAC	Composite of death, MI, definite ST, stroke, or TIMI major bleeding
SAFE A (12 mo)	1 M DAPT *N* = 102 6 M DAPT *N* = 106	RCT Superiority; During index procedure	ACS or Stable CAD, underwent PCI with DES, nonvalvular Atrial Fibrillation	Use of OAC	Incidence of any bleeding events (TIMI, BARC or bleeding requiring blood transfusion)
EVOLVE Short DAPT (15 mo)	3 M DAPT *N* = 1487 12 M DAPT *N* = 1948	Prospective Propensity Matched Non-Inferiority.	Unstable Angina or Stable CAD, underwent PCI with SYNERGY-EES & free of ischemic events between for 3 M	Use of OAC, <12 M bleeding, age ≥75, hematological disorders, stroke, renal insufficiency	Death/MI & Definite/probable ST
XIENCE 90 (12 mo)	3 M DAPT *N* = 1693 12 M DAPT *N* = 1280	Prospective Propensity Matched Non-Inferiority	Successful PCI exclusively with fluoropolymer-based cobalt chromium EES (XIENCE)	Use of OAC, <12 M bleeding, age ≥75, hematological disorders, stroke, renal insufficiency	Composite of death, MI
XIENCE 28 (12 mo)	1 M DAPT *N* = 1392 6 M DAPT *N* = 1411	Prospective Propensity Matched Non-Inferiority	Successful PCI exclusively with fluoropolymer-based cobalt chromium EES (XIENCE)	Use of OAC, <12 M bleeding, age ≥75, hematological disorders, stroke, renal insufficiency	Composite of death, MI

MASTER DAPT: Management of high bleeding risk patients post bioresorbable polymer coated stent implantation with an abbreviated vs standard DAPT regimen; TWILIGHT: ticagrelor with or without aspirin in high-risk patients after PCI; TICO: ticagrelor monotherapy after 3-mo in patients treated with a new generation sirolimus-eluting stent for acute coronary syndrome; STOPDAPT-2: effect of 1-mo dual antiplatelet therapy followed by clopidogrel vs 12-mo dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI; ISAR-TRIPLE: triple therapy in patients on oral anticoagulation after drug eluting stent implantation; SAFE-A: short-duration triple antithrombotic therapy for atrial fibrillation patients who require coronary stenting; EVOLVE Short DAPT: evaluation of 3-mo dual antiplatelet therapy in high bleeding risk patients treated with a bioabsorbable polymer-coated everolimus-eluting stent; XIENCE 90/XIENCE 28: 3- or 1-mo dapt in patients at high bleeding risk undergoing everolimus-eluting stent implantation.

ACS, acute coronary syndrome, ARC-HBR, academic research consortium for high bleeding risk; BARC, bleeding academic research consortium, CAD, coronary artery disease; CV, cardiovascular; DAPT, dual antiplatelet therapy; DES, drug eluting stent; EES, everolimus eluting stent; M, month(s), MI, myocardial infarction, MACE, major adverse cardiovascular events, OAC, oral anticgoagulation; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; ST, stent thrombosis; SES, sirolimus eluting stent; TIMI, thrombolysis in myocardial infarction, TIA, transient ischemic attack; TVR, target vessel revascularization.

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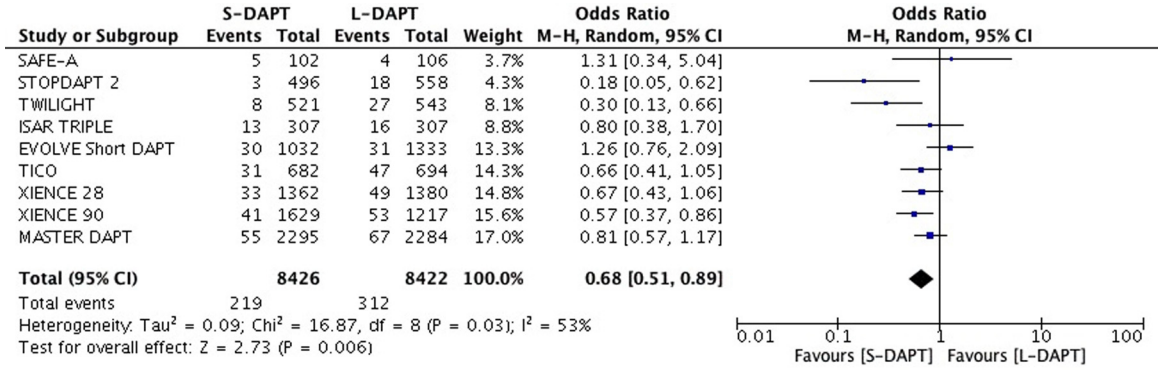
Table II. Clinical characteristics of patients enrolled in the studies included in the meta-analysis

Study	DAPT	Mean Age (Y)	Male (%)	HTN (%)	DM (%)	HLD (%)	CKD (%)	Prior MI (%)	ACS (%)	Stent type	P2Y12 Inhibitor
MASTER DAPT	1 M 6 M	76 76	69 69	77 78	33 34	67 68	18 20	19 19	49 47	Biodegradable-polymer SES	Clopidogrel, Prasugrel, Ticagrelor
TWILIGHT-HBR	3 M 15 M	72	67	-	47	-	-	29	62	Any DES	Ticagrelor
TICO	3 M 12 M	-	-	-	-	-	-	-	100 100	Bioresorbable polymer- SES	Ticagrelor
STOPDAPT-2	1 M 12 M	76	70	81	44	73	72	16	29	CoCr-EES	Clopidogrel
ISAR TRIPLE	1.5 M 6 M	74 73	75 79	77 76	28 24	74 75		29 25	33 32	Any DES	Clopidogrel
Safe A	1 M 6 M	73 72	78 80	75 65	46 45	77 80	10 16	9 19	17 17	Any DES	Clopidogrel, Prasugrel
EVOLVE Short DAPT	3 M	76	66	88	36	80	10	19	26	Synergy-EES	Clopidogrel, Prasugrel, Ticagrelor
XIENCE 90	3 M 12 M	75 73	65 59	90 92	39 43	83 91	40 44	16 30	35 34	CoCr-EES	Clopidogrel, Prasugrel, Ticagrelor
XIENCE 28	1 M 6 M	76 73	67 59	85 92	37 42	68 91	47 44	16 30	34 36	CoCr-EES	Clopidogrel, Prasugrel, Ticagrelor

ACS, acute coronary syndrome; CKD, chronic kidney disease; CoCr-EES, cobalt-chromium everolimus eluting stent; DAPT, dual anti-platelet therapy; DM, diabetes mellitus; DES, drug eluting stent; HTN, hypertension; HLD, hyperlipidemia; M, month(s); Y, years; Synergy-EES, synergy- everolimus eluting stent; SES, sirolimus eluting stent.

Figure 1



Forest plot illustrating odds ratio of major bleeding. CI, confidence intervals; DAPT, dual antiplatelet therapy; L, long; S, short.

MI was reported in 5 RCTs and 3 propensity-matched studies (Figure 2). There was no significant difference in incidence of MI between S-DAPT group and L-DAPT group (2.3% vs 2%) [OR 1.16; 95% CI 0.94-1.44]. There was no significant heterogeneity among studies. Estimates were consistent among patients with [1.23; 0.65-2.61] or without [1.34; 0.94-1.93] an indication for OAC (Supplementary Figure 2B).

Rates of ST were reported in 5 RCTs and 3 propensity-matched studies (Figure 3). Overall, the frequency of ST was low (0.42%) [OR for S-DAPT vs L-DAPT 1.33; 95% CI 0.79-2.23]. ST was numerically higher in S-DAPT arm as compared with L-DAPT in the sub-group without an indication for OAC [OR 1.98; 95% CI 0.86-4.58], however this did not reach statistical significance ($P = .10$) (Supplementary Figure 2C). This effect was not seen in the sub-group with indication for OAC [1.24; 0.36-4.30].

MACCE was not significantly different between S-DAPT and L-DAPT [OR 0.99; 95% CI 0.75-1.30] (Figure 4). Similarly, stroke did not differ between the 2 DAPT arms

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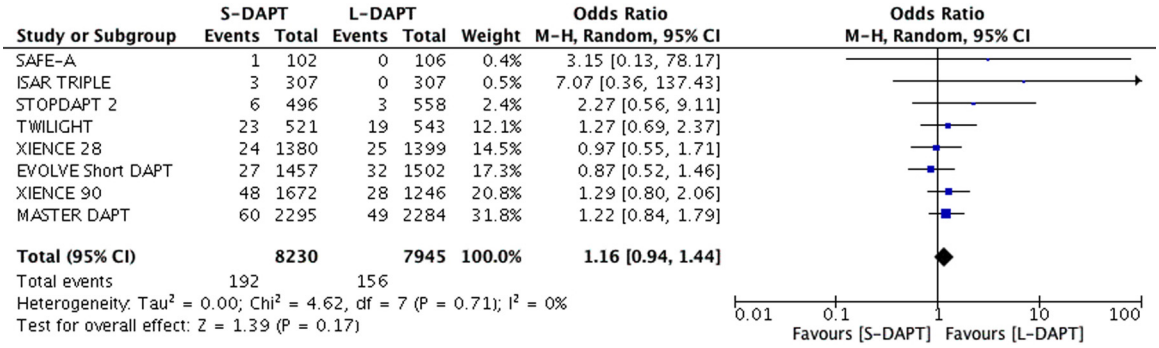
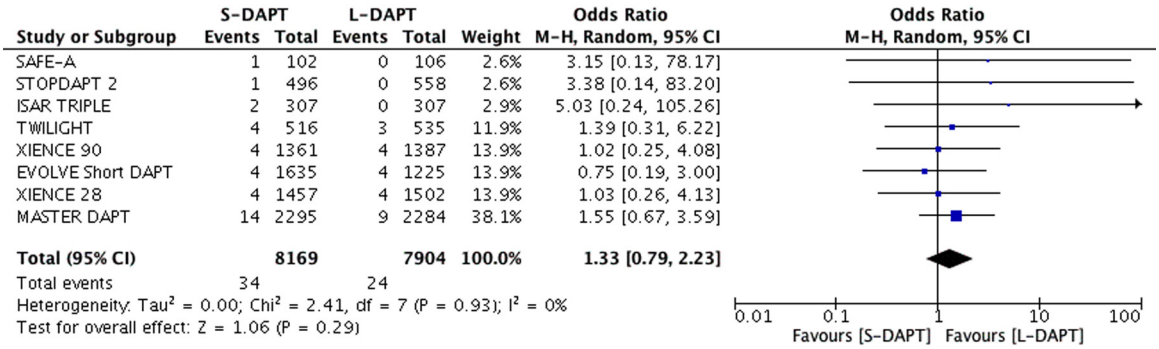
Figure 2



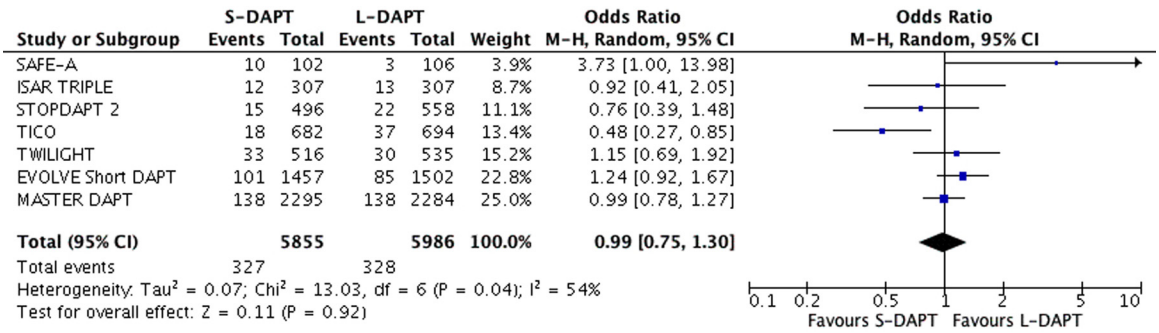
Forest plot illustrating odds ratio of myocardial infarction. CI, confidence intervals; DAPT, dual antiplatelet therapy; L, long; S, short.

Figure 3



Forest plot illustrating odds ratio of stent thrombosis. CI, confidence intervals; DAPT, dual antiplatelet therapy; L, long; S, short.

Figure 4



Forest plot illustrating odds ratio of major adverse cardiac and cerebrovascular events. CI, confidence intervals; DAPT, dual antiplatelet therapy; L, long; S, short.

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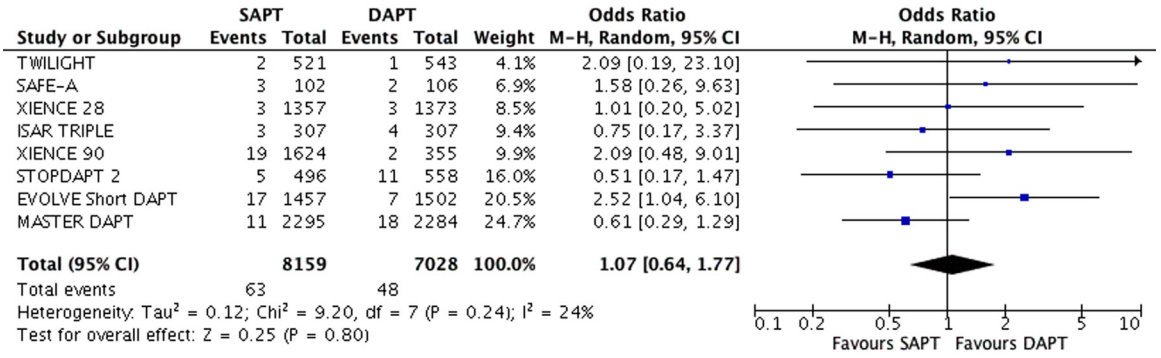
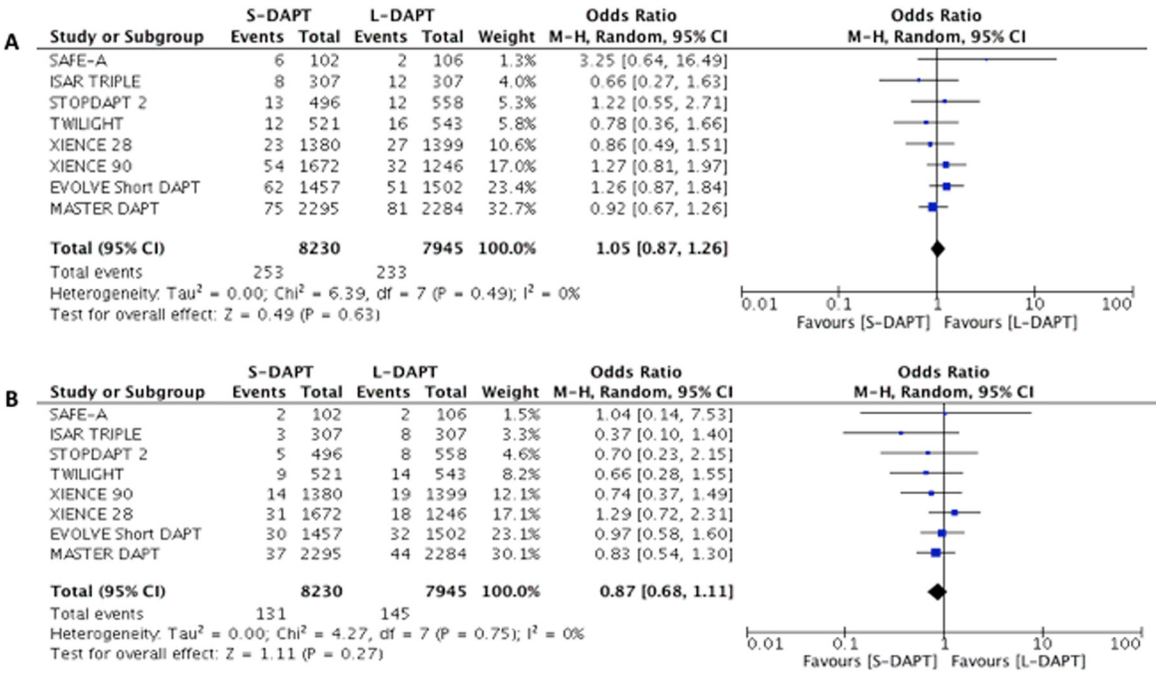
Figure 5



Forest plot illustrating odds ratio of stroke. CI, confidence intervals; DAPT, dual antiplatelet therapy; L, long; S, short.

Figure 6



Forest plot illustrating odds ratio of (A) all-cause death, (B) cardiovascular death. CI, confidence intervals; DAPT, dual antiplatelet therapy; L, long; S, short.

[OR 1.07; 95% CI 0.64-1.77] (Figure 5). Finally, among 5 RCTs and 2 propensity-matched studies reporting mortality (Figure 6), there were no differences in all-cause death [OR 1.05; 95% CI 0.87-1.26] or CV death [0.87; 0.68-1.11] between S-DAPT and L-DAPT groups.

Meta-regression demonstrated a significant correlation between prevalence of CKD and treatment effect of different DAPT durations on major bleeding [coefficient -0.02 (95% CI -0.04 to -0.01)] (Supplementary Figure 3). There was no significant association between other variables and OR for major bleeding or MI. Funnel plots for different end points are included in Supplementary Figure 4.

Discussion

In this study of over 16,000 HBR patients pooled from 6 RCTs and 3 propensity matched studies, treatment

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with S-DAPT for 1 to 3 months significantly decreased risk of major bleeding compared with L-DAPT. Importantly, there were no significant differences in risks of MI, stroke, all-cause death, CV death, or MACCE between the 2 DAPT strategies. These findings were consistent between the groups with or without an indication for OAC. Finally, there was a numerically higher incidence of ST in the S-DAPT group among patients without an indication for OAC, however estimates did not reach statistical significance.

To our knowledge, this is the first meta-analysis evaluating the efficacy and safety of S-DAPT against L-DAPT post PCI in patients with HBR. Several RCTs and their pooled analyses have shown non-inferiority of ≤6 months DAPT compared to 12 months DAPT with regards to ischemic efficacy at least in stable low-risk patients.[23-25] Contrarily, prolonged DAPT duration (>12 months) was shown to decrease MI, however, at the cost of higher bleeding risk.[26,27] These findings led to the 2017 guidelines update that redefined mandated DAPT durations in patients undergoing PCI.[2] Nevertheless, previous trials did not evaluate patients at increased bleeding risk sufficiently, and therefore the optimal DAPT duration in patients at HBR is not fully defined.

Emerging data on relative effect sizes of ischemic and bleeding events on mortality among patients undergoing PCI has turned our attention on optimizing DAPT durations in patients at HBR.[28,29] Increasingly encountered in practice, HBR represents a heterogenous group of patients, criteria for whom have been recently proposed for a more standardized definition.[30] A pooled analysis of RCTs assessing different durations of DAPT had suggested that HBR patients treated with prolonged DAPT might not derive any ischemic benefit as opposed to non-HBR patients.[31] Further, improvements in stent technology and drug pharmacotherapy have significantly reduced late ST (>30 days to 1 year) rates.[32] Therefore, a strategy of abbreviated DAPT on background of newer generation stents to reduce risks of bleeding without increasing risk of ischemic events is particularly appealing in HBR patients. In this context, RCTs comparing newer generation DES against BMS on background of one-month DAPT found superior efficacy and safety of DES in patients at increased bleeding risk.[33,34] Although these trials did not compare different DAPT durations after DES implantation, they suggested that a short DAPT after PCI using newer generation DES might be safe in patients at HBR.

Our analysis aimed to reconcile the findings of recently published studies. Incidence of major bleeding in the control arm of our pooled analysis (~4%) was consistent with that endorsed by the academic research consortium (ARC) for HBR.[30] Despite conflicting data from different studies, our pooled analysis shows significantly lower major bleeding with absolute risk reduction of 1.2% in the S-DAPT group compared with L-DAPT group. We did not observe any significant increase in MI with S-DAPT strategy compared with L-DAPT in our pooled analysis. MASTER DAPT included 4,434 HBR patients who were event-free at 1 month after PCI using a biodegradable-polymer sirolimus eluting stent, and randomized them to single antiplatelet therapy or DAPT for a period of 3 to 6 months depending on whether there was an indication for long-term OAC or not.[13] In a pre-specified analysis of patients with vs without an indication for OAC, rates of composite ischemic end points did not differ between S-DAPT and standard DAPT arms in either group, whereas risk of bleeding was significantly reduced with S-DAPT in patients without an indication for OAC.[18] Recently reported sub-analysis of TWILIGHT study including 1,064 HBR patients showed similar results of decreased major bleeding without ischemic compromise with S-DAPT followed by ticagrelor monotherapy compared with L-DAPT.[10] We found a numerically higher incidence of ST with S-DAPT in the sub-group without indication for OAC, however this was only reported in 3 studies and primarily driven by MASTER DAPT trial.[11,18] Although sub-group analyses were not powered for ischemic end points in this trial, inclusion of patients with high ischemic burden might explain these findings.[13,18] On the contrary, present findings in OAC sub-group are consistent with the AUGUSTUS trial where an ischemic benefit of ASA was limited only to the first 30 days after PCI.[35] Nevertheless, risk of late ST with early DAPT discontinuation after DES implantation in HBR patients who also have high thrombotic risk needs to be further investigated.

Altogether, these findings highlight the importance of an individualized approach to DAPT regimens. Recently, there has been a paradigm shift towards early discontinuation of ASA while continuing $P2Y_{12}$ monotherapy instead within abbreviated DAPT regimens.[36,37] In meta-analyses of RCTs that have tested this strategy in either atrial fibrillation or patients without indication for OAC, reduction in bleeding without increase in ischemic events has been shown.[38,39] In line with this, a substantial percentage of patients within S-DAPT arm of the present meta-analysis were on $P2Y_{12}$ monotherapy. Yet, data from propensity matched studies with ASA continuation after DAPT for 1 to 3 months have shown non-inferior ischemic outcomes compared to 6 to 12 months DAPT, albeit in selected low-risk population.[19,20] Whether $P2Y_{12}$ inhibitor monotherapy would provide a more favorable balance between ischemic benefits and bleeding risks in selected HBR patients remains to be investigated. Finally, a tailored clinical approach based on integration of bleeding (eg, PRECISE-DAPT) and ischemic (eg, DAPT) risk scores might allow for a more optimal decision-making regarding DAPT duration for an individual patient.[40]

Our study has few limitations. First, HBR definition was heterogenous among different studies included in

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the current analysis. Although, standardized criteria for HBR have been recently defined per HBR-ARC consortium, not all studies used these criteria. Further, a number of studies excluded patients requiring long-term use of OAC. However, to overcome this limitation, we performed a separate analysis of DAPT regiments in patients with long-term indication for OAC. Second, there was some heterogeneity in type of antiplatelet agent used after mandated DAPT duration in the S-DAPT group; However, this variance in antiplatelet agent choice reflects real world practice. Third, as with any trial-level meta-analysis, there was some heterogeneity in terms of trial design (eg, timing of randomization) and end point definitions. Therefore, we studied individual end points instead of composite end points. Fourth, our study was not registered with PROSPERO database.

Conclusion

In the present meta-analysis of 16,848 HBR patients treated with DES, S-DAPT for 1 to 3 months was associated with reduced risk of major bleeding without an increase in MI, compared with L-DAPT. These findings reinforce that an individualized approach to DAPT in terms of both duration and choice of antiplatelet agent is particularly relevant in HBR patients. Risk of late ST and choice of SAPT after 1 to 3 months DAPT requires further investigation in future studies of HBR patients.

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None

Conflict of Interest

D.J.A. declares that he has received consulting fees or honoraria from Abbott, Amgen, Aralez, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, PhaseBio, PLx Pharma, Pfizer, Sanofi, and The Medicines Company and has received payments for participation in review activities from CeloNova and St Jude Medical, outside the present work. D.J.A. also declares that his institution has received research grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli Lilly, Gilead, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, Osprey Medical, Renal Guard Solutions and Scott R. MacKenzie Foundation.

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Cover letter

November 28th, 2021
Daniel B. Mark, MD, MPH
Editor-in-Chief,
American Heart Journal

Re: "Dual Antiplatelet Therapy Duration after Percutaneous Coronary Intervention using Drug Eluting Stents in High Bleeding Risk Patients: A Systematic Review and Meta-analysis"

Dear Dr Mark,

On behalf of my co-authors, I am delighted to submit our manuscript entitled "Dual Antiplatelet Therapy Duration after Percutaneous Coronary Intervention using Drug Eluting Stents in High Bleeding Risk Patients: A Systematic Review and Meta-analysis" for your kind consideration and publication in your esteemed journal.

Patients at high bleeding risk constitute a substantial proportion of PCIs encountered in current clinical practice. Although recent trials have shown safety and efficacy of 1 to 3 months DAPT in all-comers, patients at high bleeding risk were frequently excluded or underrepresented in such trials of short DAPT regimens. Further, besides showing conflicting results, individual trials have been underpowered to detect meaningful differences in important end points such as myocardial infarction, stent thrombosis and major bleeding. Therefore, we performed a systematic review and meta-analysis of all available studies comparing short term DAPT against longer duration DAPT among patients at high bleeding risk. To the best of our knowledge, our study including ~16000 patients is the first meta-analysis of high bleeding risk patients, and thus. provides timely and relevant evidence to guide DAPT durations amongst such patients.

Our manuscript is not under consideration elsewhere. None of the paper's contents have been published before. All authors listed have reviewed the manuscript and have contributed sufficiently to the study.

Sincerely,
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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2022.04.004.

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