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Meta-analysis of duration of dual antiplatelet therapy in patients with acute coronary syndrome after percutaneous coronary intervention

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The residual risk for secondary cardiovascular events is highest during the first 12 months after acute coronary syndrome (ACS).[1] Dual antiplatelet therapy (DAPT) is the cornerstone of treatment to encounter this high thrombotic risk after ACS.[1] While long-term aspirin monotherapy is considered a standard approach for the secondary prevention of major adverse cardiovascular events (MACEs) in patients with coronary artery disease, the duration of DAPT in ACS remains a debatable topic.[1] The current professional guidelines recommend DAPT for 12 months in the setting of low bleeding risk and for 6 months with high bleeding risk after ACS;[2] however, recent data have shown conflicting evidence regarding the duration of DAPT.[3,4] The preliminary results of DAPT STEMI favored 6 months therapy for having comparable results to 12 months DAPT in ACS cohorts.[3] Conversely, the SMART DATE endorsed 12 months or longer DAPT for better protection against MACEs.[4] To address this controversy, we conducted a meta-analysis of randomized

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Author contribution

SUK contributed to the conception and design of the work. IBR, HR, ANL, MR, MSK and AR contributed to the data acquisition, analysis, and interpretation of data for the work. SUK drafted the manuscript. EK critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

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controlled trials (RCTs) comparing the duration of DAPT (3–6 months vs. ≥12 months) in ACS patients treated with newer generation drug-eluting stents (DESs).

A comprehensive search strategy was devised using MEDLINE, EMBASE and CENTRAL (inception to 20 March 2018) to identify published RCTs. The outcomes from each trial were selected to most closely approximate the primary and secondary composite endpoints in ACS cohorts. The primary endpoint was MACEs (composite of myocardial infarction, stroke, revascularization, stent thrombosis and death) and the secondary endpoint was an expanded MACE (composite of myocardial infarction, stroke, stent thrombosis, death and major bleeding). Quality assessment of each trial was performed using the Cochrane risk of bias tool. The literature search, data extraction and bias risk assessment were performed by two authors (ANL and HR) independently. Estimates were pooled using a generic invariance random effects model and reported as hazard ratio (HR) with 95% confidence interval (CI). Heterogeneity was quantified by I^2 with values greater than 75% consistent with high grade heterogeneity. If HRs were not available, risk ratios were pooled as HRs if the risk of the event did not vary over time. Publication bias was assessed using Egger's regression test. Analyses were conducted at 5% significance. Comprehensive Meta-Analysis (version 3) was used for meta-analysis.

Eight RCTs (10,130 patients)[4–11] were included in this meta-analyses (Table 1). MACEs were extracted from four trials (6242 patients) and expanded MACEs were reported in four trials (3888 patients). There was no significant difference between both groups in terms of MACEs (HR 1.03, 95% CI 0.83–1.29; $P = 0.78$, $I^2 = 0$) or expanded MACE (HR 1.06, 95% CI 0.77–1.47; $P = 0.72$, $I^2 = 0$) (Figure 1). The out-comes had low statistical heterogeneity and Egger's regression test did not detect publication bias (intercept −0.39, 95% CI − 2.06–1.26; $P = 0.58$).

This meta-analysis suggests that there were no significant differences between 3–6 months versus 12 months of longer of DAPT in terms of MACEs or expanded MACEs among ACS subjects treated with DESs. The prolonged DAPT requires a trade-off between protection against ischemic endpoints and an increased risk of hemorrhage.[1] The enhanced bleeding risk has the potential to generate higher mortality rates by increasing non-cardiac mortality, which was not offset by a reduction in cardiac mortality in the published literature.[2, 4–11] The expanded DAPT may reduce the ischemic endpoints but overall protective impact on mortality declines over time. While the mortality rate is approximately 50% for acute and subacute stent thrombosis, late stent thrombosis is associated with approximately 10% mortality rates.[4, 6,10] Because the bleeding risk remains constant and the ischemic risk declines over time, DAPT for longer than 6 months might not influence mortality in patients with ACS.

Compliance with medical therapy (statins, beta-blockers, angiotensin-converting enzyme inhibitors, etc.) and comprehensive modification of risk factors can provide desired cardiovascular benefits with a shorter duration of DAPT. In a recent study, 135 ACS patients were enrolled to receive either a complex cardiac rehabilitation program (physiotherapy, strict diet, stress management and life style counseling) or traditional cardiac rehabilitation.[12] At 3 months follow-up, parameters of platelet aggregation and hyperactivity were

significantly reduced in patients with complex cardiac rehabilitation compared with traditional rehabilitation. This highlights the importance of effective medical therapy and modification of cardiovascular risk factors besides DAPT.

This is the largest meta-analysis to our knowledge on this issue. That said, this report has shortcomings such as heterogeneity in baseline comorbidities of the patients, type of DESs and P2Y12 inhibitors used. We could not analyze individual components of key endpoints or types of ACS due to paucity of data among ACS cohorts in the trials. In conclusion, due to the persistent bleeding risk with prolonged DAPT, clinicians should consider a shorter duration of DAPT combined with effective medical management and modification of risk factors to prevent MACEs.

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References

1. Lettino M, Leonardi S, De Maria E, et al. Antiplatelet and antithrombotic treatment for secondary prevention in ischaemic heart disease. Eur J Prev Cardiol 2017; 24: 61–70. [PubMed: 28618904]
2. Schiele F, Ecarnot F and Chopard R. Coronary artery disease: risk stratification and patient selection for more aggressive secondary prevention. Eur J Prev Cardiol 2017; 24: 88–100. [PubMed: 28618915]
3. Kedhi E DAPT STEMI: a randomized trial of 6-month vs. 12-month DAPT after DES implantation in STEMI. TCTMD 2017.
4. Hahn J-Y, Song YB, Oh J-H, et al. 6-Month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, non-inferiority trial. Lancet 2018; 391: 1274–1284. [PubMed: 29544699]
5. Feres F, Costa RA, Abizaid A, et al. Three vs. twelve months of dual antiplatelet therapy after zotarolimuseluting stents: the OPTIMIZE randomized trial. JAMA 2013; 310: 2510–2522. [PubMed: 24177257]
6. 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. [PubMed: 22179532]
7. Han Y, Xu B, Xu K, et al. Six versus 12 months of dual antiplatelet therapy after implantation of biodegradable polymer sirolimus-eluting stent: randomized substudy of the I-LOVE-IT 2 Trial. Circ Cardiovasc Interv 2016; 9: e003145. [PubMed: 26858080]
8. Hong SJ, Shin DH, Kim JS, et al. 6-Month versus 12-month dual-antiplatelet therapy following long ever-olimus-eluting stent implantation: the IVUS-XPL Randomized Clinical Trial. JACC Cardiovasc Interv 2016; 9: 1438–1446. [PubMed: 27212028]
9. Kim BK, Hong MK, Shin DH, et al. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). JACC 2012; 60: 1340–1348. [PubMed: 22999717]
10. Schulz-Schupke 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. [PubMed: 25616646]

11. Valgimigli M, Campo G, Monti M, et al. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. Circulation 2012; 125: 2015–2026. [PubMed: 22438530]

12. Toth-Zsamboki E, Horvath Z, Hajtman L, et al. Cardiac rehabilitation programme as a non-pharmacological platelet inhibitory tool in acute coronary syndrome survivors. Eur J Prev Cardio 2017; 24: 1148–1156.

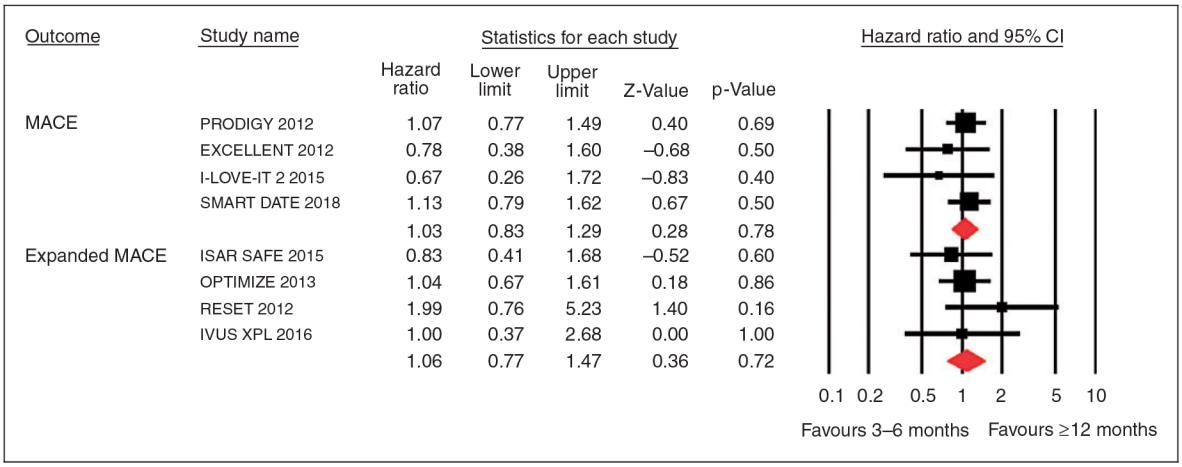

Figure 1.

Forest plot comparing 3–6 months versus 12 months or longer duration of dual antiplatelet therapy in acute coronary syndrome patients treated with drug-eluting stents. MACEs: major adverse cardiovascular events.

Table 1.

Study characteristics.

Studies	ACS patients	Duration of DAPT (months)	Time of randomization	Definition of MACE	Follow-up (months)	CRoB scale[a]
PRODIGY 2012[11]	1456	6 vs. 24	1 Month after index PCI	All-cause death, MI, or cerebrovascular accident	24	*****
EXCELLENT 2012[6]	744	6 vs. 12	Index PCI	All-cause death, MI, stroke, ST (definite or probable), or TIMI-major bleeding	12	*****
RESET 2012[9]	601	3 vs. 12	Index PCI	Cardiovascular death, MI, ST (definite or probable), ischemia-driven target-vessel revascularization, or TIMI-major bleeding	12	*****
OPTIMIZE 2013[5]	1000	3 vs. 12	Index PCI	All-cause death, MI, stroke, major bleeding based on GUSTO/ REPLACE-2	12	*****
I-LOVE-IT 2 2015[7]	1330	6 vs. 12	Index PCI	All-cause death, MI, CVA, major bleeding BARC≥3	18	*****
ISAR SAFE 2015[10]	1601	6 vs. 12	6 Months after PCI	All-cause death, MI, ST(definite or probable), stroke, TIMI major bleeding	15	******
IVUS XPL 2016[8]	686	6 vs. 12	Index PCI	Cardiac death, MI, stroke, or TIMI major bleeding	12	*****
SMART DATE 2018[4]	2712	6 vs. ≥12	Index PCI	All-cause death, MI, or stroke	18	*****

ACS: acute coronary syndrome; BARC: Bleeding Academic Research Consortium; DAPT: dual antiplatelet therapy; CRoB scale: Cochrane risk of bias scale; EXCELLENT: Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; GUSTO: Global Utilization of Streptokinase and Tpa for Occluded Arteries; I-LOVE-IT: Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary Revascularization; ISAR SAFE: Intracoronary Stenting and Antithrombotic Regimen: Safety And Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting; IVUS-XPL: Impact of Intravascular Ultrasound Guidance on Outcomes of XIENCE PRIME Stents in Long Lesions; MACE: major adverse cardiovascular event; MI: myocardial infarction; 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; PCI: percutaneous coronary intervention; REPLACE 2: Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events 2; RESET: REal Safety and Efficacy of a 3-month dual antiplatelet Therapy following E-ZES implantation; ST: stent thrombosis; TIMI: thrombolysis in myocardial infarction; SMART-DATE: 6-month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome.

[a]Scale consists of seven domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete data reporting (attrition bias), selective reporting (reporting bias) and other bias. Each domain carries one star and 5 or more stars represents good quality.

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