

Duration of dual antiplatelet therapy in patients with acute coronary syndrome undergoing drug-eluting stent implantation: A meta-analysis

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Abstract

Objective: This meta-analysis was performed to evaluate the optimal discontinuation of dual antiplatelet therapy (DAPT) after drug-eluting stent (DES) implantation in acute coronary syndrome (ACS) patients.

Methods: A systematic search was conducted without language restrictions using PubMed, the Cochrane Library, and Clinical Trials.gov from January 2008 to July 2019. Studies that met the following criteria were included: (1) randomized trials that compared DAPT durations of < 12 months (“short DAPT”) or ≥ 12 months (“long DAPT”); (2) studies that included data on patients with ACS; and (3) studies that included data on outcomes. The outcomes were pooled using the Mantel–Haenszel model, generating relative risk (RR) and 95% confidence intervals (CI). Statistical heterogeneity was evaluated using the Cochrane Q statistic *P*-value and I^2 value. Publication bias was assessed by visually inspecting the funnel plots.

Results: Eight studies comprising 10,537 participants were included in the analysis. The primary endpoint was not different between short-term and long-term DAPT (RR, 1.11; 95% CI, 0.92–1.34).

Conclusion: A meta-analysis of the available evidence suggests that DAPT can be reduced to 3 or 6 months without increasing the risk of cardiovascular and cerebrovascular events in patients with ACS who are undergoing DES implantation.

Keywords

Dual antiplatelet therapy, drug-eluting stents, acute coronary syndromes, percutaneous coronary intervention, coronary artery disease, acute coronary syndrome, cardiovascular, cerebrovascular

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Introduction

Millions of patients worldwide with coronary artery disease receive percutaneous coronary intervention (PCI) yearly to treat ischemic events.¹ In contrast to bare metal stents, drug-eluting stents (DESs) have been shown to cause a remarkable reduction in repeated revascularization.² However, several observational studies have confirmed that the risk of death or myocardial infarction (MI) remains after DES implantation.³ Dual antiplatelet therapy (DAPT), which is a P2Y12 inhibitor, has been perceived as a way to prevent thrombus formation. Current guidelines suggest that the DAPT duration in patients with stable coronary artery disease is 6 months or less.⁴ ESC/EACTS Guidelines on Myocardial Revascularization⁵ recommend that in patients with ACS who are treated with coronary stent implantation, DAPT with a P2Y12 inhibitor in addition to aspirin should be used for 12 months unless there are contraindications such as an excessive risk of bleeding. In patients with ACS and stent implantation who have a high risk of bleeding, discontinuation of P2Y12 inhibitor therapy after 6 months should be considered. The guidance is based on the conclusions of the SMART-DATE trial.⁶ However, the optimal discontinuation of DAPT after DES implantation for ACS patients remains controversial.⁷⁻⁹

Methods

A systematic search was conducted without language restriction in PubMed, the Cochrane Library, and Clinical Trials.gov from January 2008 to July 2019. Search keywords were “dual antiplatelet therapy, drug-eluting stents.” These studies were included when the following criteria were met: (1) randomized trials that compared DAPT durations of <12 months (“short DAPT”) or ≥ 12 months (“long DAPT”);

(2) studies that included data on patients with ACS; and (3) studies that included data on outcomes. The quality of the involved studies and assessment of trial bias risk were determined for the domains suggested by the Cochrane collaboration,^{10,11} emphasizing sequence generation, allocation concealment, blinding, outcomes assessment, and selectivity. The optimal time of dual antiplatelet therapy was determined by comparing the statistical differences based on the primary endpoint. The relative risk (RR) with 95% confidence interval (CI) for the outcome in each study was determined. Fixed- or random-effects models were with the Mantel–Haenszel method to incorporate the RR from the trials involved, when appropriate. A test of heterogeneity was conducted, and the Q statistic was acquired. The I^2 index was used to summarize the proportion of the total variability in the estimates. Publication bias was assessed by visually inspecting the funnel plots. A two-tailed $P \leq 0.05$ was considered to be statistically significant. Data were analyzed using Review Manager (RevMan) 5 (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

As shown in Figure 1, nine randomized controlled trials^{6,12-19} that comprised 10,537 enrolled patients were factored into the final analysis.^{10,11} The major characteristics of the included trials are presented in Table 1. All trials were rated as 5 to 7, or high quality studies, according to the Jadad score standard.

All studies^{6,12-19} provided data for the primary endpoint. The test of heterogeneity indicated that the homogeneity was good. The RR was incorporated in the fixed-effects model. The visual inspection of the funnel plot did not indicate publication

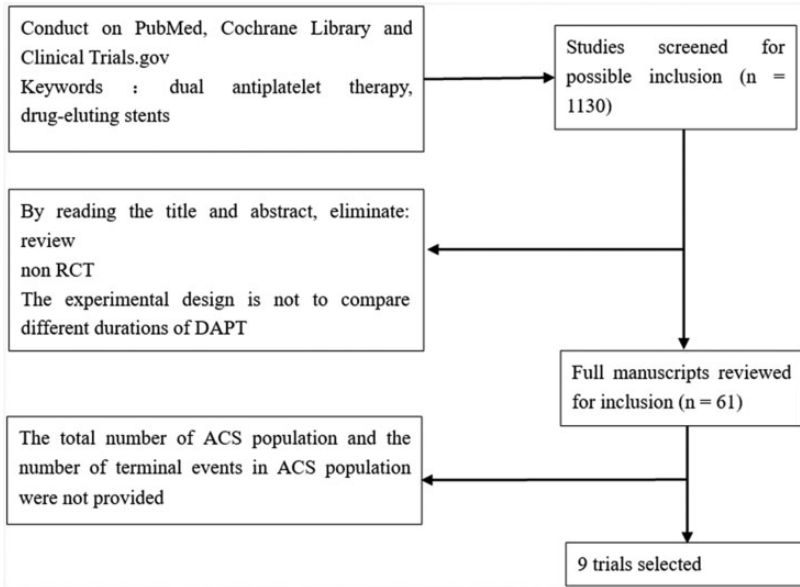


Figure 1. Study flow diagram.

bias. The short-term and long-term DAPT were not different based on the primary endpoint (RR, 1.11; 95% CI, 0.92–1.34; Figure 2).

The sensitivity analysis using the random-effects model yielded significantly similar results. The exclusion of any trial yielded similar results for the short-term DAPT group compared with the long-term DAPT group (Table 2).

Given the different definition of the end event for each test, the greatest risk of double antiplatelet therapy was bleeding.²⁰ The increased risk of bleeding was associated with prolonged DAPT.²¹ This may mask the benefits of dual antiplatelet therapy in reducing the incidence of redevelopment and cardiac infarction. Thus, a subgroup analysis was performed. The end event of subgroup 1^{6,13,14} did not include bleeding events, while the end event of subgroup 2^{12,15–19} included bleeding events. Neither subgroup 1 (RR, 1.07; 95% CI, 0.84–1.36) nor subgroup 2 (RR, 1.17; 95% CI,

0.87–1.57) was markedly different based on the primary endpoint (Table 3).

Each trial had a different definition for a short course of antiplatelet therapy, which might have affected the outcome. Two trials had a short-term DAPT of 3 months, while six other trials had a short-term DAPT of 6 months. A subgroup analysis was performed based on the short duration of antiplatelet therapy. Subgroup 3^{18,19} had a 3-month short course of antiplatelet therapy, while subgroup 4^{6,12–17} had a 6-month short course of antiplatelet therapy. Neither subgroup 3 (RR, 1.13; 95% CI, 0.76–1.68) nor subgroup 4 (RR, 1.10; 95% CI, 0.89–1.36) was significantly different based on the primary endpoint (Table 3).

Discussion

Currently, the optimal discontinuation of DAPT after DES implantation for ACS patients remains controversial.^{7,8} Most guidelines recommend that ACS patients

Table 1. Characteristics of included trials.

Name of trial	Year	The type of stent	Group		Primary Endpoint definition
			S-DAPT	L-DAPT	
EXCELLENT	2008/7 to 2009/7	Everolimus-eluting stents were used in three-quarters of patients and sirolimus-eluting stents were used in one-quarter of patients as a result of 3:1 randomization of stents.	6 months	12 months	Composite of cardiac death, MI, or TVR at 12 months after PCI
I-LOVE-IT	–	DES with biodegradable polymer	6 months	12 months	Composite of cardiac death, MI, or TVR at 12 months after PCI
ISAR-SAFE	2008/10 to 2014/4	New-generation DES	6 months	12 months	Composite of death, MI, stroke, stent thrombosis, or TIMI major bleeding at 15 months after PCI
ITALIC	2008/11 to 2010/12 2012/1 to 2013/11	At least one Xience V	6 months	12 months	Composite of death, MI, repeat TVR, stroke, or TIMI major bleeding
IVUS-XPL	2010/10 to 2014/7	Everolimus-eluting stent	6 months	12 months	Composite of cardiac death, MI, stroke, or TIMI major bleeding
NIPPON	2011/12 to 2015/6	DES	6 months	18 months	All-cause mortality, MI, stroke, and major bleeding
OPTIMIZE	2010/4 to 2012/3	Zotarolimus-eluting stents	3 months	12 months	All-cause mortality, MI, stroke, and major bleeding
RESET	2009/4 to 2010/12	Zotarolimus-eluting stent implantation	3 months	12 months	Composite of cardiac death, MI, stent thrombosis, ischemia-driven TVR, or bleeding at 12 months after PCI
SMART-DATE	2012/9 to 2015/12	–	6 months	12 months	Composite of major adverse cardiac and cerebrovascular events, defined as a composite of all-cause mortality, myocardial infarction, or stroke at 18 months after the index procedure

DES, drug eluting coronary stents; S-DAPT, dual antiplatelet therapy durations of <12 months; L-DAPT, dual antiplatelet therapy durations of ≥12 months; TVR, target vessel revascularization; PCI, percutaneous coronary intervention; MI, myocardial infarction; TIMI, thrombolysis in myocardial infarction.

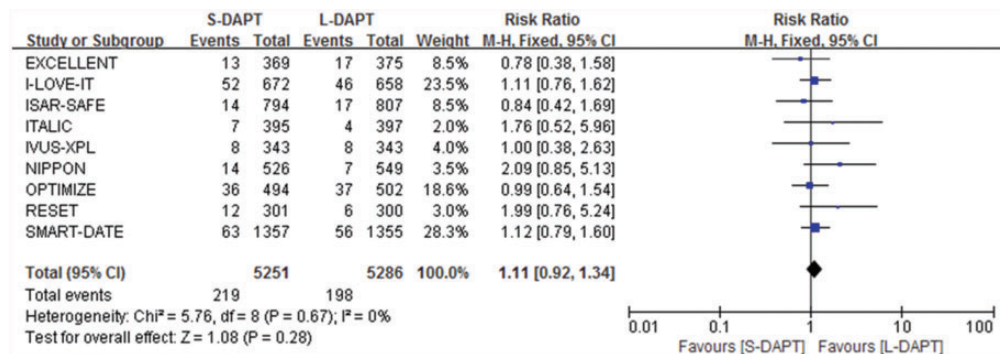


Figure 2. Meta-analysis results of the primary endpoint for patients with ACS.

Table 2. Sensitivity analysis.

Trial excluded	Fixed-effects model	Random-effects model
–	1.11 (0.92 to 1.34)	1.10 (0.91 to 1.33)
EXCELLENT	1.14 (0.94 to 1.38)	1.13 (0.93 to 1.38)
I-LOVE-IT	1.11 (0.89 to 1.37)	1.10 (0.89 to 1.37)
ISAR-SAFE	1.13 (0.93 to 1.38)	1.13 (0.93 to 1.37)
ITALIC	1.09 (0.91 to 1.32)	1.09 (0.90 to 1.32)
IVUS-XPL	1.11 (0.92 to 1.35)	1.11 (0.91 to 1.34)
NIPPON	1.07 (0.89 to 1.30)	1.07 (0.88 to 1.30)
OPTIMIZE	1.14 (0.92 to 1.40)	1.13 (0.92 to 1.39)
RESET	1.08 (0.89 to 1.31)	1.08 (0.89 to 1.30)
SMART-DATE	1.10 (0.88 to 1.38)	1.09 (0.87 to 1.37)

Table 3. Subgroup analysis.

Subgroup	Trial number	Fixed-effects model	Random-effects model
1	3	1.07 (0.84 to 1.36)	1.07 (0.84 to 1.36)
2	6	1.17 (0.87 to 1.57)	1.15 (0.86 to 1.56)
3	2	1.13 (0.76 to 1.68)	1.22 (0.65 to 2.31)
4	7	1.10 (0.89 to 1.36)	1.10 (0.89 to 1.36)

with PCI should undergo postoperative double antiplatelet therapy for at least 1 year.⁴ As indicated in the meta-analysis, the difference in endpoint events between ≤ 6 -month DAPT and ≥ 12 -month DAPT was not statistically significant. However, the increased risk of bleeding with DAPT remains controversial.^{20–22} This may mask the benefits of DAPT in reducing the

incidence of redevelopement and cardiac infarction.²² However, the meta-analysis revealed that the difference in endpoint events (prognosis and bleeding) between ≤ 6 -month DAPT and ≥ 12 -month DAPT was not statistically significant. It was also indicated by the subgroup analysis that both 6-month and 3-month DAPT were not markedly different compared with

≥12-month DAPT in terms of a statistical benefit. For ACS patients with drug-coated stent implantation, this can shorten the duration of DAPT for 6 months or even 3 months without increasing the risk of cardiovascular and cerebrovascular events in patients.

The meta-analyses performed by Bavishi⁷ also had similar conclusions. However, the risk of cerebrovascular disease and shorter antiplatelet therapy sessions were not considered. Fewer tests were also conducted. The meta-analyses performed by Palmerini⁹ also had similar conclusions. However, this article is a network meta-analysis. It is uncertain whether the results were obtained from a direct comparison or indirect comparison. The sample size of ACS patients and the credibility of the results are also uncertain.

The present meta-analysis had some limitations. The sample size was small, and the inclusion test did not describe the criteria for evaluating ACS patients. However, this study provides comprehensive evidence for a future study on DAPT in patients with ACS who are undergoing DES implantation. All involved trials were rated as high quality studies based on the Jadad score standard. The heterogeneity test revealed high homogeneity, and the sensitivity analysis and subgroup analysis revealed good stability. Thus, the meta-analysis was highly reliable.

Conclusion

Overall, the ≤6-month and ≥12-month DAPT were not different among patients with ACS based on the primary endpoint. DAPT could be reduced to 6 months or even 3 months without increasing the risk of cardiovascular and cerebrovascular events in patients with ACS who are undergoing DES implantation.


Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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References [AQ1]

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics-2016 update: A report from the American Heart Association. *Circulation* 2016; 133: e38–e360.
2. El-Mokadem M, El-Ramly M, Hassan A, et al. Comparison between catheter-based delivery of paclitaxel after bare-metal stenting and drug-eluting stents in coronary artery disease patients at high risk for in-stent restenosis. *Cardiovasc Revasc Med* 2017; 8: 596–600.
3. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: Data from a large two-institutional cohort study. *Lancet* 2007; 369: 667–678.
4. 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 Thorac Cardiovasc Surg* 2016; 152: 1243–1275.
5. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019; 40: 87–165.
6. Hahn JY, Song YB, Oh JH, 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.
7. Bavishi C, Trivedi V, Singh M, et al. Duration of dual antiplatelet therapy in patients with an acute coronary syndrome undergoing percutaneous coronary intervention. *Am J Med* 2017; 130: 1325.e1–1325.e12.
 8. Zwart B and Ten BJM. Dual antiplatelet therapy duration in patients following percutaneous coronary intervention or after acute coronary syndrome: one size does not fit all. *Future Cardiol* 2017; 13: 199–201.
 9. Palmerini T, Della Riva D, Benedetto U, et al. Three, six, or twelve months of dual antiplatelet therapy after DES implantation in patients with or without acute coronary syndromes: An individual patient data pairwise and network meta-analysis of six randomized trials and 11473 patients. *Eur Heart J* 2017; 38: 1034–1043.
 10. Methley AM, Campbell S, Chew-Graham C, et al. PICO, PICOS and SPIDER: A comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. *BMC Health Serv Res* 2014; 14: 579.
 11. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. *Open Med* 2009; 3: e123–e130.
 12. Hong SJ, Shin DH, Kim JS, et al. 6-month versus 12-month dual-antiplatelet therapy following long everolimus-eluting stent implantation: The IVUS-XPL randomized clinical trial. *JACC Cardiovasc Interv* 2016; 9: 1438–1446.
 13. 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.
 14. 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 sub-study of the I-LOVE-IT 2 trial. *Circ Cardiovasc Interv* 2016; 9: e003145.
 15. Schulz-Schüpke S, Byrne RA, Ten BJM, 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: e1252–1263.
 16. Gilard M, Barragan P, Noryani AA, et al. 6-versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: The randomized, multicenter ITALIC trial. *J Am Coll Cardiol* 2015; 65: 777–786.
 17. Nakamura M, Iijima R, Ako J, et al. Dual antiplatelet therapy for 6 versus 18 months after biodegradable polymer drug-eluting stent implantation. *JACC Cardiovasc Interv* 2017; 10: 1189–1198.
 18. 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.
 19. Kim BK, Hong MK, Shin DH, et al. A new strategy for discontinuation of dual antiplatelet therapy: The RESET trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). *J Am Coll Cardiol* 2012; 60: 1340–1348.
 20. Miyazaki Y, Suwannasom P, Sotomi Y, et al. Single or dual antiplatelet therapy after PCI. *Nat Rev Cardiol* 2017; 14: 294–303.
 21. Zhang L, Lu J, Dong W, et al. Meta-analysis of comparison of the newer P2Y12 inhibitors (oral preparation or intravenous) to clopidogrel in patients with acute coronary syndrome. *J Cardiovasc Pharmacol* 2017; 69: 147–155.
 22. Palmerini T, Sangiorgi D, Valgimigli M, et al. Short- versus long-term dual antiplatelet therapy after drug-eluting stent implantation: An individual patient data pairwise and network meta-analysis. *J Am Coll Cardiol* 2015; 65: 1092–1102.