Curr Cardiol Rep (2016) 18: 8
DOI 10.1007/s11886-015-0683-8

The Tradeoff Between Shorter and Longer Courses of Dual Antiplatelet Therapy After Implantation of Newer Generation Drug-Eluting Stents

John A. Bittl[1]

Published online: 5 January 2016

Abstract The benefit of prolonged dual antiplatelet therapy (DAPT) after implantation of drug-eluting stents (DESs) remains uncertain. In 10 randomized controlled trials (RCTs) of 31,666 predominantly low-risk patients undergoing DES implantation, shorter courses (3–12 months) of DAPT resulted in lower mortality (odds ratio [OR] 0.83, 95 % confidence interval [CI] 0.69–0.98) and major hemorrhage (OR 0.60, 95 % CI 0.48–0.75) but increased myocardial infarction (MI, OR 1.34, 95 % CI 1.04–1.73) and stent thrombosis (ST, OR 1.75, 95 % CI 1.08–2.82) than did longer courses (12–36 months) of DAPT. A risk-benefit analysis identified 3 fewer deaths and 5 fewer bleeds but 4 more MIs and 3 more STs annually for every 1000 patients treated with the shorter courses. In the predominantly low-risk population enrolled in RCTs, limiting DAPT to 3 to 12 months after DES implantation saved lives and prevented bleeding at the expense of increased ST and MI.

Keywords Antiplatelet therapy · Percutaneous coronary intervention · Hemorrhage · Randomized controlled trials

Introduction

Drug-eluting stents (DESs) have been a major advance in the treatment of patients with obstructive coronary artery disease, but their use has been associated with stent thrombosis (ST) and myocardial infarction (MI). Stent thrombosis after bare-metal stent (BMS) implantation typically occurs within 30 days, but it can occur later [1]. Stent thrombosis may occur years after implantation of drug-eluting stents (DESs), but the lifetime risk of ST for a first-generation DES does not seem to be higher than that for a BMS [2].

Dual antiplatelet therapy (DAPT), which is defined as the combination of aspirin and a platelet P2Y12 receptor antagonist, reduces ST after implantation of BMSs by 85 % (relative risk 0.15, 95 % confidence interval [CI] 0.05–0.43), as compared with aspirin alone [3]. Based on the findings in two randomized controlled trials (RCTs), namely PCI-CURE (a substudy of the Clopidogrel in Unstable angina to prevent Recurrent Events trial) [4] and CREDO (Clopidogrel for the Reduction of Events During Observation) study [5], and in observational studies reporting a persistent risk of ST risk beyond 6 months after stent implantation [6, 7], particularly in the context of DAPT cessation [8], the 2011 American College of Cardiology/American Heart Association guideline recommended a minimum duration of DAPT of at least 12 months after DES implantation [9]. In PCI-CURE, however, stenting comprised 80 % of the cases, and all stents were BMS. Similarly, in the CREDO trial, all implanted stents were BMS and only 63 % of patients assigned to clopidogrel completed 1 year of therapy [5].

After the publication of the 2011 guideline [9], 10 new RCTs have compared shorter courses (3–12 months) with longer courses (12–36 months) of DAPT in patients receiving newer generation DESs [10–19, 20•, 21•]. In order to identify the risks and benefits of prolonged DAPT in the 10 RCTs, the current analysis was performed to answer the question: As compared with 12–36 months of DAPT, did 3–12 months of DAPT after implantation of newer generation DESs result in differences in (1) mortality, (2) major hemorrhage, (3) MI, and (4) ST?

This article is part of the Topical Collection on *Ischemic Heart Disease*

✉ John A. Bittl
jabittl@mac.com

[1] Munroe Heart and Vascular Institute, Munroe Regional Medical Center, 1221 SE 5th Street, Ocala, FL 34471, USA

Methods

Aggregate data from 10 RCTs of patients undergoing newer generation DES implantation and randomized to either shorter or longer courses of DAPT [10–19, 20•, 21•] comprised the evidence base for the analysis (Table 1). Summary data from each trial were abstracted in triplicate and validated against published reports [21•, 22•]. Whenever possible, DES-enriched data sets [20•, 21•] were preferred over data sets from the same trials containing subjects treated with both BMSs and DESs [12, 23].

The primary outcomes of the present analysis were all-cause mortality, major hemorrhage, MI, and definite or probable ST. Newer generation DESs were defined as everolimus-eluting stents (EESs), zotarolimus-eluting stents, and biolimus-eluting stents with biodegradeable polymers [24•].

Forest plots were created to convey the relative effectiveness of shorter versus longer durations of DAPT. A random-effects model was preferred to acknowledge the variations in study design, duration of treatment and differences in follow-up among the 10 RCTs. All analyses were intention-to-treat. Original meta-analyses were created with [R] 3.0.2 [25••] and library package meta 3.8–0 [26••]. Effect-size estimates and numbers needed to treat (NNTs) were calculated from the random-effects models using study weights, odds ratios (ORs), and 95 % CIs, using standard methods [27].

Results

The 10 RCTs [10–19, 20•] enrolled 31,666 patients, of whom 523 (1.7 %) died, 338 (1.1 %) had major hemorrhage, 597 (1.9 %) had an MI, and 177 (0.6 %) had definite or probable ST. The RCTs generally enrolled low-risk patients. Eight of 10 trials found lower than expected event rates (Table 1). The proportion of patients in each trial with prior MI ranged from 1.7 to 34.7 % (Table 1), and the overall pooled proportion of patients with prior MI was 20.0 %. However, the trials were judged to be of high quality with at least moderate freedom from bias and to have intermediate to high grades for relevance and fidelity [22•].

Relative Differences Between Shorter and Longer Durations of DAPT

A systematic analysis of the 10 RCTs suggested that shorter courses of DAPT of 3–6 months duration were associated with lower mortality (OR 0.83, 95 % CI 0.69–0.98) and major hemorrhage (OR 0.60, 95 % CI 0.48–0.75) but increased rates of MI (OR 1.34, 95 % CI 1.04–1.73) and ST (OR 1.75, 95 % CI 1.08–2.82) than were longer courses of 12–36 months duration (Fig. 1).

Absolute Differences

A weighted analysis of the 10 RCTs suggested that shorter courses of DAPT of 3–6 months duration were associated with significantly lower annual rates of all-cause mortality (1.57 vs. 1.88 % [95 % CI 1.60–2.26 %]) and major hemorrhage (0.76 vs. 1.26 % [95 % CI 1.01–1.57 %]) but higher annual rates of MI (1.94 vs. 1.46 % [95 % CI 1.13–1.86 %]) and ST (0.59 vs. 0.34 % [95 % CI 0.21–0.55 %]) than were longer courses of DAPT of 12–36 months duration.

After shorter courses of DAPT, 16 patients per 1000 died annually compared with 19 (95 % CI 16–23) patients per 1000 who died in the same period of follow-up while being treated with longer courses of DAPT. After shorter courses of DAPT, 8 patients per 1000 had major hemorrhage annually compared with 13 (95 % CI 10–16) patients per 1000 who had hemorrhage annually during longer courses of DAPT. On the other hand, after shorter courses of DAPT, 19 patients per 1000 had MI annually compared with 15 (95 % CI 11–19) patients per 1000 who had MI annually with longer courses of DAPT, and 6 patients per 1000 had ST annually compared with 3 (95 % CI 2–5) patients per 1000 who had ST annually while under treatment with longer courses of DAPT during the same period of follow-up.

The NNT with shorter courses of DAPT to prevent 1 death was 325 (95 % CI 145–3237). The NNT with shorter courses of DAPT to prevent 1 major bleed was 199 (95 % CI 124–403). On the other hand, the NNT with longer courses of DAPT to prevent 1 MI was 210 (95 % CI 125–1314), and the NNT with prolonged courses of DAPT to prevent 1 ST was 396 (95 % CI 262–2435).

Discussion

This systematic review evaluated the outcomes in patients enrolled in 10 RCTs [10–19, 20•, 21•] after implantation of newer generation DESs and identified a tradeoff between shorter and longer courses of DAPT. Shorter courses (3–12 months) of DAPT resulted in lower mortality and major bleeding but caused more MIs and STs than did longer courses (12–36 months) of DAPT.

Mortality

The finding of decreased mortality with shorter courses of DAPT is consistent with results of other analyses [21•, 22•, 28•, 29•] but seems counterintuitive given that prolonged

Table 1 Randomized controlled trials of dual antiplatelet therapy duration after implantation of drug-eluting stents

Study (Comparison)	Year[a]	Trial completion	Primary study endpoint	Trial design and outcome	Expected event rate in control group (%)	Observed event rate in control (%)	Proportion with prior MI (%)
DES-LATE (12 vs. 36 months) [11]	2010	Extension of ZEST-LATE and REAL-LATE [10]	Cardiac death, MI or stroke <24 h	Superiority not shown	2.7	2.6	3.9
PRODIGY (6 vs. 24 months) [12, 21•]	2012	Enrollment completed	Death, MI or stroke	Superiority not shown	8.0	10.1	26.7
EXCELLENT (6 vs. 12 months) [13]	2012	Enrollment completed	Cardiac death, MI, or ischemia-driven TVR	Noninferiority confirmed	10.0	4.5	4.4
RESET (3 vs. 12 months) [14]	2012	Enrollment completed	Cardiac death, MI, ST, revasc, or bleeding	Noninferiority confirmed	10.5	4.7	1.7
OPTIMIZE (3 vs. 12 months) [15]	2013	Enrollment completed	NACCE–death, MI, stroke, or bleed	Noninferiority confirmed	9.0	6.0	34.7
ARCTIC (12 vs. 18 months) [16]	2014	Extension of ARCTIC trial [16]	Death, MI, ST, stroke, or urgent TVR	Superiority not shown	6.0	4.0	30.4
SECURITY (6 vs. 12 months) [17]	2014	Stopped after 1399 of 2740 planned	Cardiac death, MI, ST, or stroke	Noninferiority confirmed	4.5	4.5	20.7
ITALIC (6 vs. 24 months) [18]	2015	Stopped after 2031 of 2475 planned	Death, MI, urgent TVR, stroke, or major bleeding	Noninferiority confirmed	3.0	1.5	15.1
ISAR-SAFE (6 vs. 12 months) [19]	2015	Stopped after 4005 of 6000 planned	Death, MI, ST, stroke, or TIMI major bleed	Noninferiority confirmed	10.0	1.5	25.2
DAPT (12 vs. 30 month) [20•]	2015	Enrollment completed	Coprimary: ST and MACCE	Superiority shown	0.5/2.9	0.5/2.4	21.6

Abbreviations: *ARCTIC*, double randomization of a monitoring adjusted antiplatelet treatment versus a common antiplatelet treatment for DES implantation, and interruption versus continuation of double antiplatelet therapy, *DAPT* dual antiplatelet therapy or dual antiplatelet trial, *EXCELLENT* comparison of the efficacy of everolimus- eluting versus sirolimus-eluting stent for coronary lesions, *ISAR-SAFE* safety and efficacy of 6 months dual antiplatelet therapy after drug-eluting stenting, *ITALIC* is there a LIFe for DES after discontinuation of clopidogrel, *MACCE* major adverse cardiac and cerebrovascular events (death, myocardial infarction, or stroke), *MACE* major adverse cardiac event(s), *MI* myocardial infarction, *mos* months, *NACCE* net adverse cardiac and cerebrovascular events (death, MI, stroke, or major bleeding), *OPTIMIZE* optimized duration of clopidogrel therapy following treatment with the endeavor zotarolimus- eluting stent in the real world clinical practice, *PRODIGY* PROlonging dual antiplatelet treatment in patients with coronary artery disease after graded stent-induced intimal hyperplasia study, *REAL-LATE* correlation of clopidogrel therapy discontinuation in real world patients treated with drug-eluting stent implantation and late coronary arterial thrombotic events, *RESET* real safety and efficacy of a 3-month dual antiplatelet therapy following zotarolimus-eluting stents implantation, *SECURITY* second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy, *ST* stent thrombosis, *TVF* target vessel failure, *TVR* target vessel revascularization, *ZEST-LATE* evaluation of the long-term safety after zotarolimus-eluting stent, sirolimus-eluting stent, or paclitaxel-eluting stent implantation for coronary lesions and late coronary arterial thrombotic events

[a] Year of initial publication

courses of DAPT reduced both MI and ST. The mortality finding may reflect the interplay of several factors. First, newer generation DESs have a lower risk of ST than first-generation stents, which may have diminished the ability of longer courses of DAPT to protect against late thrombotic events related to the stent itself. In support of this, Baber and colleagues [30] reported that the risk of ST after implantation of newer generation EESs was almost 50 % lower than that for first-generation DESs (OR 0.55 95 % CI 0.38–0.78), similar to the reduction in risk of ST for EESs compared with other stent types reported in the DAPT appendix [20•]. Second, the risk of a fatal outcome from ST declines over time. Whereas acute and subacute ST are associated with mortality rates approaching 50 %, late and very late ST are associated with mortality rates of about 10 % [31, 32]. Third, bleeding early after percutaneous coronary intervention (PCI) probably has a larger effect on late mortality than do ischemic complications [33, 34]. Emerging evidence suggests that giving transfusions after PCI strongly increases the risk of dying during follow-up [35], which may be mediated by transfusion-related lung injury, volume overload, systemic inflammation, platelet activation, microvascular plugging and reduced nitric oxide availability in the presence of aging erythrocytes. Thus, the overall survival advantage seen with shorter courses of DAPT may be explained by a declining risk of ST and MI associated with the use of newer generation DESs counterbalanced by a uniform risk of bleeding and its life-threatening consequences associated with longer courses of DAPT.

Clinical Implications

All antithrombotic regimens involve a “fragile balance between efficacy and adverse events” [36]. Many physicians will use longer courses of DAPT in patients who have not

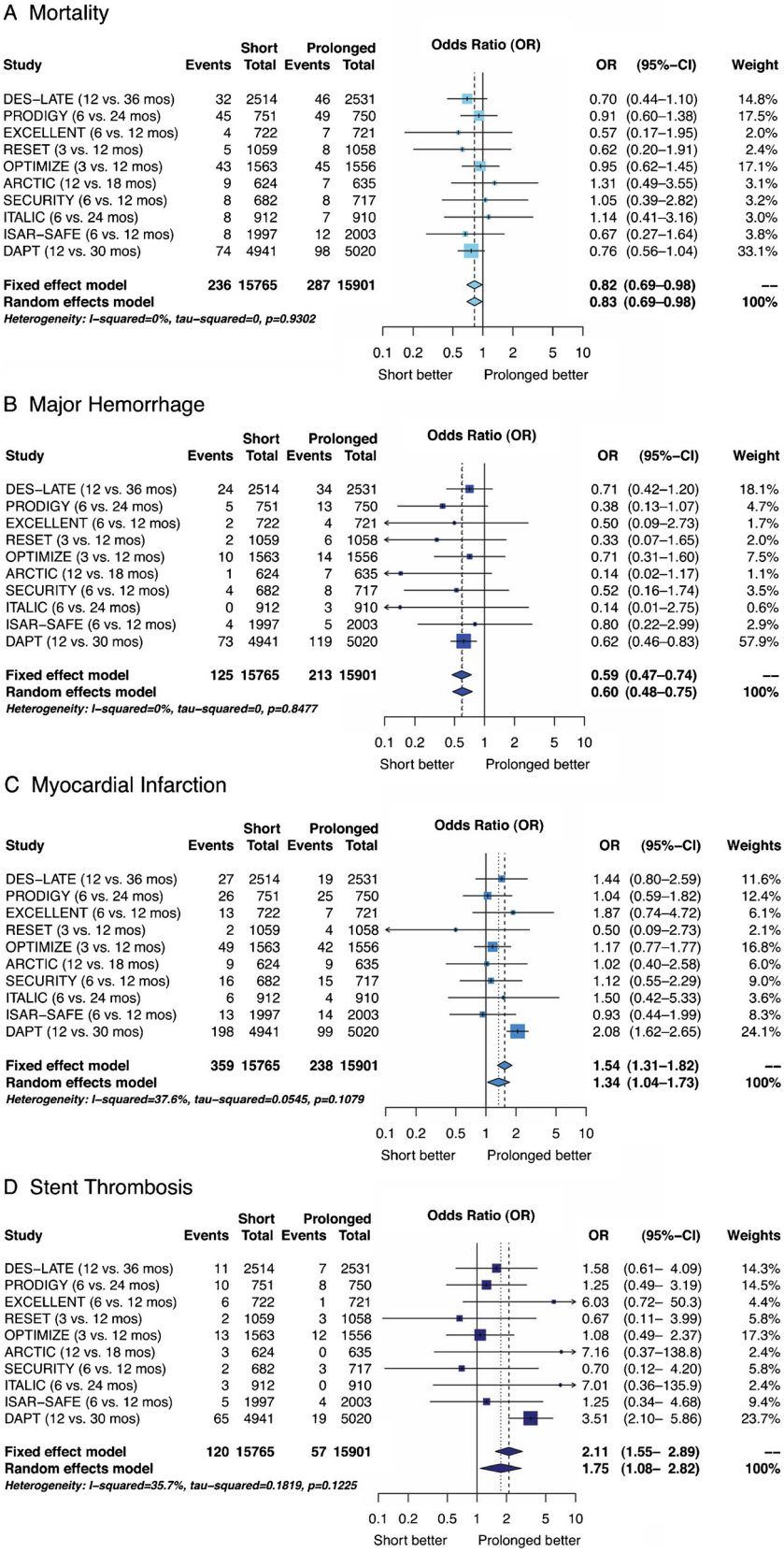

Fig. 1 Forest plot of mortality rates (**a**), major hemorrhage (**b**), myocardial infarction (**c**), and definite or probable stent thrombosis (**d**) after shorter courses (3–12 months) or longer courses (12–36 months) of dual antiplatelet therapy for drug-eluting stent implantation. *CI* confidence interval, *OR* odds ratio

had a bleeding complication on DAPT and have an increased systemic risk of atherothrombotic events or increased risk of late ST. In selected patients with prior MI, longer courses of DAPT may be reasonable regardless of whether coronary

stenting was used [37•]. In patients with high-risk angiographic findings such as multiple or overlapping stents, implantation of first-generation paclitaxel-eluting or sirolimus-eluting stents, prior stent thrombosis or impaired left ventricular function [38], longer courses of DAPT may be weighed as an option to prevent late ischemic events.

Conclusions

The findings in the current analysis may apply to populations similar to those enrolled in the RCTs [10–19, 20•, 21•] comparing shorter with longer durations of DAPT after implantation of predominantly newer generation DESs. In low-risk patients who have undergone newer generation DES implantation, a minimum DAPT duration of 3–12 months may be sufficient to prevent early and largely stent-related thrombotic events. Extension of DAPT beyond 12 months after implantation of newer generation DES entails a tradeoff. Patients at very low risk of bleeding or high risk of thrombotic events may derive a benefit from extension of DAPT beyond 12 months, but the inability to predict future bleeding limits the appeal of prolonged therapy.

Compliance with Ethical Standards

Conflict of Interest John A. Bittl declares that he has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Doyle B, Rihal CS, O'Sullivan CJ, Lennon RJ, Wiste HJ, Bell M, et al. Outcomes of stent thrombosis and restenosis during extended follow-up of patients treated with bare-metal coronary stents. Circulation. 2007;116:2391–8.
2. Mauri L, Hsieh W-H, Massaro JM, Ho KKL, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl J Med. 2007;356:1020–9.
3. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KKL, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. N Engl J Med. 1998;339:1665–71.
4. Mehta SR, Yusuf S, Peters RJG, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet. 2001;358:527–33.
5. Steinhubl SR, Berger PB, Mann III JT, Fry ETA, DeLago A, Wilmer C, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA. 2002;288:2411–20.
6. Pfisterer M, Brunner-La Rocca HP, Buser PT, Rickenbacker P, Hunziker P, Mueller C, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observation study of drug-eluting versus bare-metal stents. J Am Coll Cardiol. 2006;48:2584–91.
7. Eisenstein EL, Anstrom KJ, Kong DF, Shaw LK, Tuttle RH, Mark DB, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. Jama. 2007;297(2):159–68.
8. Daemen J, Wenaseser P, Tsuchida K, Abrecht L, Vaina S, Morger C, 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;369:667–78.
9. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B et al. 2011 ACCF/AHA/SCAI guidelines for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. 2011.
10. Park S-J, Park D-W, Kim Y-H, Kang S-J, Lee S-W, Lee CW, et al. Duration of dual antiplatelet therapy after implantation of drug-eluting stents. N Engl J Med. 2010;362:1374–82.
11. Lee CW, Ahn J-M, Park D-W, Kang S-J, Lee S-W, Kim Y-H, et al. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation. Circulation. 2014;129:304–12.
12. Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, et al. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. Circulation. 2012;125:2015–26.
13. Gwon H-C, Hahn J-Y, Park KW, Song YB, Chae I-H, Lim D-S, 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;125:505–13.
14. Kim B-K, Hong J-K, Shin D-H, Nam C-M, Kim J-S, Ko Y-G, 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;60:1340–8.
15. Feres F, Costa RA, Abizaid A, Leon MB, Marin-Neto A, Botelho RV, et al. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. JAMA. 2013;310:2510–22.
16. Collet J-P, Silvain J, Barthélémy O, Rangé G, Cayla G, Van Belle E, et al. Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomised trial. Lancet. 2014;384:1577–85.
17. Colombo A, Chieffo A, Frasheri A, Garbo R, Masotti-Centol M, Salvatella N. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. J Am Coll Cardiol. 2014;64:2086–97.
18. Gilard M, Barragan P, Noryani AAL, Noor HA, Majwal T, Hovasse T, et al. 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stent in patients nonresistant to aspirin: the randomized, multicenter ITALIC Trial. J Am Coll Cardiol. 2015;65:777–86.
19. Schulz-Schüpke S, Byrne RA, ten Berg JM, Neumann F-J, Han Y, Adriaenssens T et al. ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 versus 12 months of clopidogrel therapy after drug-eluting stenting. Eur Heart J. 2015.

20.• Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, et al. Twelve or 30 months of dual-antiplatelet therapy after drug-eluting stents. N Engl J Med. 2015;371:2155–66. **This report describes a large RCT with high fidelity, relevance, and low risk of bias.**

21.• Palmerini T, Benedetto U, Bacchi-Reggiani L, Della Riva D, Biondi-Zoccai G, Feres F, et al. Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials. Lancet. 2015;385:2371–82. **This systematic overview includes pairwise and Bayesian network meta-analyses of RCTs of DAPT duration.**

22.• Bittl JA, Baber U, Bradley SM, Wijeysundera DN. Duration of dual antiplatelet therapy: a systematic review for the 2015 guideline update: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2016;67:in press. **This is the official report of the evidence review committee assigned by the American College of Cardiology and American Heart Association to inform guideline development. The report analyzes evidence for DAPT duration for secondary prevention post-MI and after DES implantation and includes traditional meta-analysis and Bayesian hierarchical and conjugate-normal meta-analyses of RCTs**.

23. Yeh RW, Kereiakes DJ, Steg PG, Windecker S, Rinaldi MJ, Gershlick AH et al. Benefits and risks of extended duration dual antiplatelet therapy after PCI in patients with and without acute myocardial infarction. J Am Coll Cardiol. 2015;65:221–21.

24.• Palmerini T, Biondi-Zoccai G, Della Riva D, Mariani A, Sabate M, Smits PC, et al. Clinical outcomes with bioabsorbable polymer-based versus durable polymer-based drug-eluting stents and bare metal stents: evidence from a comprehensive network meta-analysis. J Am Coll Cardiol. 2014;63:299–307. **This high-quality meta-analysis identified the signal of increased mortality with prolonged DAPT after DES implantation.**

25.•• R Core Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2013. **This open-source statistical software is flexible and incredibly powerful but has a steep and long learning curve.**

26.•• Schwarzer G. Package "meta". Freiburg, Germany: version 3.8-0; 2012. **This open-source statistical package demonstrates the graphical power of [R].**

27. Cates CJ. Simpson's paradox and calculation of number needed to treat from meta-analysis. BMC Med Res Methodol. 2002;2:1–4. (http://www.nntonline.net/visualrx/).

28.• Spencer FA, Prasad M, Vandvik PO, Chetan D, Zhou Q, Guyatt G. Longer versus shorter duration dual-antiplatelet therapy after drug-eluting stent placement. Ann Intern Med. 2015. doi:10.7326/M15-0083. **This report describes a useful analysis of the evidence for DAPT after DES implantation.**

29.• Navarese EP, Andreotti F, Schulze V, Kolodziejczak M, Buffon A, Brouwer M et al. Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents. BMJ. 2015;350. doi:10.1136/bmj.h1618. **This meta-analysis is a useful synthesis of the evidence of DAPT duration after DES implantation.**

30. Baber U, Mehran R, Sharma SK, Brar S, Yu J, Suh J-W, et al. Impact of the everolimus-eluting stent on stent thrombosis: a meta-analysis of 13 randomized trials. J Am Coll Cardiol. 2011;58:1569–77.

31. Claessen BE, Henriques JP, Jaffer FA, Mehran R, Piek JJ, Dangas GD. Stent thrombosis: a clinical perspective. J Am Coll Cardiol Intv. 2014;7:1081–92.

32. Lasala JM, Cox DM, Dobies D, Baran K, Bachinsky WB, Rogers EW, et al. Drug-eluting stent thrombosis in routine clinical practice. Circ Cardiovasc Interv. 2009;2:285–93.

33. Lincoff AM, Kleiman NS, Kereiakes DJ, Feit F, Bittl JA, Jackman JD, et al. Long-term efficacy of bivalirudin and provisional glycoprotein IIb/IIIa blockade vs heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization: REPLACE-2 randomized trial. JAMA. 2004;292:696–703.

34. Mehran R, Lansky AJ, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, et al. Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomised controlled trial. Lancet. 2009;374:1149–59.

35. Kwok CS, Sherwood MW, Watson SM, Nasir SB, Sperrin M, Nolan J, et al. Blood transfusion after percutaneous coronary intervention and risk of subsequent adverse outcomes: a systematic review and meta-analysis. Circ Cardiovasc Interv. 2015;8:436–46.

36. Keaney JF. Balancing the risks and benefits of dual antiplatelet inhibition. N Engl J Med. 2015;372:1854–6.

37.• Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med. 2015;372:1791–800. **This high-quality trial in patients with prior MI revealed that prolonged DAPT produced a tradeoff between reduced nonfatal MI and increased nonfatal bleeding and an overall small treatment benefit.**

38. Cayla G, Hulot JS, O'Connor SA, Pathak A, Scott SA, Gruel Y, et al. Clinical, angiographic and genetic factors associated with early stent thrombosis. JAMA. 2011;306:1765–74.