Efficacy and safety of short-term (≤6 months) duration of dual antiplatelet therapy after drug-eluting stents: a meta-analysis of randomized controlled trials

Chun-Lin Xiang, Yi-Zhen Gong*, Long-Jia Zeng**, Bei-Bei Luo, Jian Xu, Yan He

Departments of Geriatric Cardiology, *Evidence-based Medicine, **Obstetrics and Gynecology, the First Affiliated Hospital of Guangxi Medical University; Nanning, Guangxi-People’s Republic of China

ABSTRACT

Objective: Optimal duration of dual antiplatelet therapy (DAPT) after drug-eluting stent (DES) implantation remains controversial. The present study is an assessment of efficacy and safety of short-term (≤6 months) DAPT after DES implantation in patients with coronary artery disease, especially in important subgroups.

Methods: PubMed, Embase, and the Cochrane Central Register of Controlled Trials were searched for randomized, controlled trials comparing short-term and long-term (>6 months) DAPT after DES implantation. Primary efficacy outcome was stent thrombosis (ST). Primary safety outcome was major bleeding. Pooled relative risks (RRs) with 95% confidence interval (CI) were calculated using random- or fixed-effects models as appropriate.

Results: Total of 7 trials involving 15870 patients were included in the study. Short-term DAPT significantly reduced major bleeding by 49% compared with long-term DAPT (RR: 0.51; 95% CI: 0.32–0.80; p=0.003) without increasing risk of ST (RR: 1.28; 95% CI: 0.83–1.97; p=0.266). In addition, no differences were observed in all-cause mortality, myocardial infarction (MI), cardiac mortality, or cerebrovascular accidents. Moreover, no significant difference in composite of cardiovascular events, bleeding, and mortality was found in important clinical subgroups.

Conclusion: Short-term DAPT is associated with lower bleeding risk compared with long-term DAPT. Number of ST and MI was higher with short-term DAPT without reaching statistical significance. Comprehensive clinical judgment is necessary to weigh benefits and risks in the individual patient. (Anatol J Cardiol 2017; 17: 168-75)

Keywords: antiplatelet therapy, coronary artery disease, drug-eluting stent

Introduction

Dual antiplatelet therapy (DAPT) is the cornerstone for patients undergoing percutaneous coronary intervention (PCI) and can effectively reduce risk of stent thrombosis (ST) and ischemic events (1–3). This comes, however, at the expense of an increased risk of bleeding. To balance efficacy and safety of DAPT, the American Heart Association and American College of Cardiology guidelines recommend at least 12 months of DAPT after drug-eluting stent (DES) implantation (4, 5). This is based on support from observational and surveillance studies of first-generation DES. Subsequently, the European Society of Cardiology guidelines recommended 6 months of DAPT following implantation of second-generation or newer DES for stable coronary artery disease (6). Yet optimal duration of DAPT after DES implantation remains controversial.

Recently, 3 large, randomized, controlled trials [DAPT (7), ISAR-SAFE (8), and ITALIC (9)] have examined benefits and risks of DAPT treatment for up to 6 months or beyond 1 year. However, results were seemingly conflicting or heterogeneous. DAPT trial revealed extended DAPT significantly reduced risks of ST and major adverse cardiovascular and cerebrovascular events (MACCE), but was associated with increased risk of bleeding (7). In ITALIC trial, 6-month duration of DAPT showed similar benefit and risks of bleeding and thrombotic events compared with 24-month DAPT (9). Furthermore, recent results from ISAR-SAFE trial indicated that net clinical benefit of short-term and long-term DAPT (L-DAPT) was similar (8).

Several previous meta-analyses have assessed efficacy and safety of short-term DAPT (S-DAPT) after DES implantation...
(10–13); however, we noticed that statistical evaluations were all performed at population level. It is opinion of present study authors that since every individual has different risk of bleeding and ST, enhancing precision in assessment of S-DAPT in important subgroups is more important than statistical approach performed at an overall level. Therefore, we sought to identify relative benefits and risks of S-DAPT in key clinical subgroups and offer clinicians a more comprehensive picture of S-DAPT based on current research evidence.

**Methods**

**Data sources and search strategy**

Records of PubMed, Embase, and the Cochrane Central Register of Controlled Trials databases dating from inception to September 2015 were comprehensively and systematically searched without language restriction. Search was limited to randomized controlled trials (RCTs) that compared S-DAPT to L-DAPT after DES implantation. Search terms included “drug eluting stent” and “dual antiplatelet.” In order to acquire additional potentially eligible trials, reference lists of articles chosen for inclusion and recent reviews were manually screened.

**Study selection and eligibility criteria**

The following inclusion criteria were applied in PICOS order: (1) population: patients received DAPT after DES implantation; (2) intervention and comparison: duration of DAPT ≤6 months versus >6 months. DAPTs used were aspirin and clopidogrel; (3) availability of complete clinical data; and (4) study design, RCT.

**Data extraction and quality assessment**

Two independent reviewers (CL Xiang and LJ Zeng) performed data abstraction. Discrepancies were resolved through discussion between the 2 investigators. For each study, first author, year of publication, sample size, population characteristics, stent type, duration of follow-up, and outcome data were recorded. Primary efficacy outcome was ST. ST was defined as definite or probable ST according to the Academic Research Consortium classification (14). Primary safety outcome was major bleeding, based on one of the following definitions: (1) TIMI, Thrombolysis in Myocardial Infarction; (2) REPLACE-2, Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events; (3) GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; or (4) BARC, Bleeding Academic Research Consortium (15) (Table 1). Secondary outcomes of interest were all-cause mortality, myocardial infarction (MI), cardiac mortality, cerebrovascular accidents. Cochrane Collaboration’s tool was used to assess methodological quality of selected RCTs (16). Two investigators (CL Xiang and LJ Zeng) reviewed all studies and assigned a value of “low,” “high,” or “unclear” to the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting or other bias (16).

**Statistical analysis**

Relative risk (RR) with 95% confidence intervals (CI) for dichotomous outcomes was calculated. I2 statistic was used to test heterogeneity between studies. I2 statistic of <25%, 25% to 50%, and >50% indicated low heterogeneity, moderate heterogeneity, and high heterogeneity, respectively (17). Outcomes were then pooled and compared with fixed-effects models (I2<50%) or random-effects models (I2≥50%) (17–19). P value <0.05 was considered statistically significant. All statistical analyses were performed using STATA software, version 12.0 (Stata Corp., College Station, TX, USA).

According to implanted stent type, sensitivity analysis was performed to detect heterogeneity or investigate possible influence of use of different type of stent in some clinical trials (20). Pre-specified subgroup analysis was also performed to assess relative benefit and risks of S-DAPT in important clinical subgroups: age (years <65 or ≥65 years), sex, history of diabetes, renal function (creatinine clearance ≤60 mL/min or >60 mL/min), left ventricular ejection fraction (LVEF) (<50% or ≥50%), acute coronary syndrome (ACS)/unstable coronary disease, bifurcation, multi-stent, simple or complex lesion(s). Pooled RRs were calculated using inverse variance method.

**Results**

**Literature search and study characteristics**

Study selection process is illustrated in Figure 1 (21). Initial search yielded 2342 relevant publications, from which 2335 were excluded due to duplicate studies or other reasons (non-RCT, review, editorial, study design, ongoing trails, or no original data). Finally, 7 RCTs with total of 15870 participants were included in this meta-analysis (8, 9, 22–26). Major characteristics (duration of DAPT, stent type, follow-up, percentage of male participants and those with diabetes, hypertension, or dyslipidemia) of the 7 RCTs included are presented in Table 1. Trials were published between 2012 and 2015. Sample size ranged from 1399 to 4000. Average age of the patients was similar between trials, while median follow-up period for outcome evaluation was of significant difference (range: 1–3 years). Majority of stents used in included trials were second-generation DES (proportion >86%; Table 1). Composite of cardiovascular events, bleeding, and mortality was evaluated as primary outcome in all trials.

Quality assessment of selected RCTs is provided in Figure 2 in the supplemental material. Although most of the studies were open-label, randomized trials, blinded adverse events adjudication was implemented. As adverse events are clearly defined and blinded outcome adjudication was implemented, it was decided that open-label design was not significant source of bias. Publication bias was not assessed because pooled estimate included fewer than 10 trials (27).
Table 1. Characteristics of included randomized studies

|                | Gwon et al., 2012 (EXCELLENT) (22) | Valgimigli et al., 2012 (PRODIGY) (24) | Kim et al., 2012 (RESET) (23) | Feres et al., 2013 (OPTIMIZE) (25) | Gilard et al., 2015 (ITALIC) (9) | Colombo et al., 2014 (SECURITY) (26) | Schulz-Schüpke et al., 2015 (ISAR-SAFE) (8) |
|----------------|-----------------------------------|----------------------------------------|-------------------------------|-----------------------------------|-----------------------------------|----------------------------------------|---------------------------------------------|
|                | S-DAPT | L-DAPT | S-DAPT | L-DAPT | S-DAPT | L-DAPT | S-DAPT | L-DAPT | S-DAPT | L-DAPT | S-DAPT | L-DAPT | S-DAPT | L-DAPT |
| Duration, months | 6 | 12 | 6 | 24 | 3 | 12 | 3 | 12 | 6 | 12 | 6 | 12 | 6 | 12 |
| Patients, n | 722 | 721 | 983 | 987 | 1059 | 1058 | 1563 | 1566 | 912 | 910 | 682 | 717 | 1997 | 2003 |
| Age, years mean* | 63.0±9.6 | 62.4±10.4 | 67.9±11 | 67.8±11 | 62.4±9.4 | 62.4±9.8 | 61.3±10.4 | 61.9±10.6 | 61.7±10.9 | 61.5±11.1 | 64.9±10.2 | 65.5±10.1 | 67.2 (59.3–73.3) | 67.2 (59.1–73.7) |
| Male gender | 65% | 64% | 76% | 77% | 64% | 63% | 64% | 63% | 81% | 79% | 78% | 77% | 81% | 81% |
| Diabetes | 38% | 39% | 24% | 25% | 30% | 29% | 35% | 35% | 36% | 38% | 30% | 31% | 25% | 24% |
| Hypertension | 73% | 74% | 70% | 73% | 62% | 61% | 86% | 88% | 65% | 65% | 75% | 71% | 90% | 92% |
| Dyslipidemia | 75% | 76% | 53% | 56% | 58% | 60% | 63% | 64% | 67% | 67% | 65% | 61% | 88% | 87% |
| Stent type | | | | | | | | | | | | | |
| BMS | 0% | 0% | 25% | 25% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0.4% | 0.3% |
| 1st-gen. DES | 25% | 25% | 25% | 25% | 0% | 28% | 0% | 0% | 0% | 0% | 0% | 0% | 11% | 10% |
| 2nd-gen. DES | 75% | 75% | 50% | 50% | 100% | 72% | 100% | 100% | 100% | 100% | 100% | 88% | 89% |
| Follow-up (months) | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 36 | 36 | 24 | 24 | 15 | 15 |
| MB criteria | TIMI | TIMI | TIMI | TIMI | TIMI | TIMI | REPLACE-2, TIMI | REPLACE-2, GUSTO | TIMI | TIMI | BARC | BARC | TIMI | TIMI |
| Primary Endpoint | Composite of cardiac death, MI, or TVR during 1-year period after randomization. | Incidence of death from any cause, nonfatal MI, or cerebrovascular accident at 2 years | Composite of cardiovascular death, MI, ST, TVR, or bleeding at 1 year | Composite of death from any cause MI, stroke, or MI at 1 year | Composite of death, MI, emergency TVR, stroke, or MB within 12 months after stenting | Composite of cardiac death, MI, stroke, ST, or type 3 or 5 bleeding at 12 months | Composite of death MI, ST, stroke, or MB at 9 months after randomization |

*Age data of ISAR-SAFE are shown as median (interquartile range). BARC - Bleeding Academic Research Consortium; BMS - bare metal stent; DAPT - dual antiplatelet therapy; DES - drug-eluting stent; GUSTO - Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; L-DAPT - long-term (>6 months) duration of DAPT after drug-eluting stent; MB - major bleeding; MI - myocardial infarction; PCI - percutaneous coronary intervention; REPLACE-2 - Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events; S-DAPT - short-term (≤6 months) duration of DAPT after drug-eluting stent; ST - stent thrombosis; TIMI - thrombolysis in myocardial infarction; TVR - target vessel revascularization.
Primary outcomes

ST
All RCTs reported ST (8, 9, 22–26). Outcomes of ST were pooled and compared with fixed-effects model (Fig. 3). There was no significant difference in ST according to duration of S-DAPT and L-DAPT (RR: 1.28; 95% CI: 0.83–1.97; p=0.266), and there was low heterogeneity among studies (I²=0.0%; p=0.608). Sensitivity analysis excluding trials containing bare metal stent (BMS) or including only trials containing second-generation DES did not appreciably alter findings (Table 2).

Major bleeding
All RCTs reported major bleeding (8, 9, 22–26). Outcomes of major bleeding were pooled and compared with fixed-effects model (Fig. 3). Risk of major bleeding was significantly reduced in S-DAPT when compared with control group (RR: 0.51; 95% CI: 0.32–0.80; p=0.003), and there was low heterogeneity among studies (I²=0.0%; p=0.868). Sensitivity analysis excluding trials containing BMS did not appreciably alter findings (RR: 0.53; 95% CI: 0.30–1.09; p=0.092) (Table 2).

Secondary outcomes

All-cause mortality
All RCTs reported all-cause mortality (8, 9, 22–26). Outcomes of all-cause mortality were pooled and compared with fixed-effects model (Fig. 4). No significant difference in all-cause mortality was found between short and long DAPT when only trials containing second-generation DES were analyzed (RR: 0.58; 95% CI: 0.30–1.09; p=0.092) (Table 2).

Secondary outcomes

All-cause mortality
All RCTs reported all-cause mortality (8, 9, 22–26). Outcomes of all-cause mortality were pooled and compared with fixed-effects model (Fig. 4). No significant difference in all-cause mortality was found between short and long DAPT when only trials containing second-generation DES were analyzed (RR: 0.58; 95% CI: 0.30–1.09; p=0.092) (Table 2).
Table 2. Sensitivity analysis according to type of stent implanted

| Secondary outcomes | Excluding trials with BMS | Excluding trials with BMS and first-generation DES |
|--------------------|---------------------------|-----------------------------------------------|
|                    | (RR: 1.36; 95% CI: 0.76-2.44; P=0.299) | (RR: 1.20; 95% CI: 0.61-2.35; P=0.598) |
|                    | (RR: 0.86; 95% CI: 0.57-1.30) | (RR: 0.88; 95% CI: 0.30-1.08; P=0.092) |

Outcomes were pooled and compared with fixed-effects models. BMS - bare metal stent; CI - confidence interval; DES - drug-eluting stent; RR - relative risk

Figure 4. Forest plot for secondary efficacy and safety outcomes. Data are n/N. Heterogeneity: all-cause mortality I2=0.0%; P=0.835; myocardial infarction I2=0.0%; P=0.859; cardiac mortality I2=0.0%; P=0.835; cerebrovascular accidents I2=0.0%; P=0.417. DAPT - dual antiplatelet therapy; L-DAPT - duration of DAPT >6 months; S-DAPT - duration of DAPT ≤6 months. Outcomes were pooled and compared with fixed-effects models.

Cardiac mortality
Six RCTs reported cardiac mortality (9, 22–26). Outcomes of cardiac mortality were pooled and compared with fixed-effects model (Fig. 4). There was no significant difference seen in cardiac mortality between S-DAPT and L-DAPT (RR: 0.99; 95% CI: 0.89–1.43; p=0.327), and there was low heterogeneity among studies (I2=0.0%, p=0.859). Sensitivity analysis excluding trials containing BMS or including only trials containing second-generation DES did not appreciably alter findings (Table 2).

Cerebrovascular accidents
All RCTs reported cerebrovascular accidents (8, 9, 22–26).
were calculated using inverse variance method. For subgroups of age (<65 or ≥65 years), sex, history of diabetes, renal function (creatinine clearance ≤60 mL/min or >60 mL/min), LVEF (<50% or ≥50%), ACS/ unstable coronary disease, bifurcation, multi-stent, simple or complex lesion(s)

**Figure 6.** Forest plot for composite of cardiovascular events, bleeding, and mortality in important clinical subgroups. Data available from Schulz-Schüpke et al., 2015; Gwon et al., 2012; Feres et al., 2013. Evidences from subgroups (Fig. 5, 6). No significant difference in composite of cardiovascular events, bleeding, and mortality was found between S-DAPT and L-DAPT for subgroups of age (year <65 or ≥65 years), sex, history of diabetes, renal function (creatinine clearance ≤60 mL/min or >60 mL/min), LVEF (<50% or ≥50%), ACS/ unstable coronary disease, bifurcation, multi-stent, simple or complex lesion(s).”

**Discussion**

The present study is meta-analysis of 7 large RCTs to evaluate efficacy and safety of S-DAPT for patients undergoing PCI. Results demonstrate that S-DAPT significantly reduced major bleeding by 49% compared with L-DAPT (RR: 0.51; 95% CI: 0.32–0.80; p=0.003) without increasing risk of ST (RR: 1.28; 95% CI: 0.83–1.97; p=0.266). On the other hand, S-DAPT was non-inferior to L-DAPT in reducing risk of all-cause mortality, MI, cardiovascular mortality, or cerebrovascular accidents. Sensitivity analysis showed that data from a few patients treated with BMS or first-generation DES did not appreciably alter findings. Results of this meta-analysis are robust.

However, current meta-analysis differs from current guidelines’ recommendation of 6 to 12 months. This can be explained by the following factors. It’s worth noting that currently recommended duration of DAPT is based on observational and surveillance studies of first-generation DES. In contrast, majority of stent types used in current RCTs included in this meta-analysis were second-generation DES (Table 1). Strong evidence has demonstrated that second-generation DES are safer with lower ST risk compared with first-generation DES (28). They were also associated with reduction in target vessel MI and target lesion revascularization (29).

Since every individual has different risk of bleeding and ST, enhancing precision in assessment of S-DAPT in important subgroups is more important than statistical approach performed at overall level. For example, bleeding risk is driven by elderly age (≥75 years), history of bleeding (e.g., gastrointestinal), history of stroke or TIA, low body weight, or disease of liver or kidney (30). Patients with ACS, lesion complexity, diabetes, hypertension, or dyslipidemia have increased risk of ST (30). These patients are often underrepresented in trials. For this reason, relative benefits and risks of S-DAPT in important clinical subgroups were investigated. Our subgroup analysis didn’t demonstrate any impact due to age (<65 or ≥65 years), sex, history of diabetes, renal function (creatinine clearance ≤60 mL/min or >60 mL/min), LVEF (<50% or ≥50%), ACS/unstable coronary disease, bifurcation, multi-stent, simple or complex lesion(s) on composite of cardiovascular events, bleeding, and mortality. These results may benefit from improved biocompatibility and decreased thrombogenicity. Previous evidence reveals that second-generation DES has significant risk reduction in late and very late ST compared with earlier-generation DES (31, 32). However, caution should be used before generalizing subgroup analysis results for individual patients for several reasons. First, definitions of composite primary endpoint of included trials were heterogeneous, which may affect statistical power of the evidence. At the same time, we have also taken note that due to lack of patient-level data of each component of composite events (e.g., ST and MI), subgroup analysis was based on composite events of cardiovascular events, bleeding, and mortality. Therefore, though there was no distinct risk difference in these events, it’s not surprising that there are no significant differences in these events between S-DAPT and L-DAPT.
significant difference seen in risk of composite events between S-DAPT and L-DAPT, risk of ST and MI of key subgroup under DAPT treatment for up to 6 months remains uncertain. More evidence is needed to clarify benefits of S-DAPT with respect to ST and MI. Nonetheless, these subgroup analysis findings do provide clinical reference for individualized DAPT management.

Present meta-analysis supports recent findings of studies reporting that S-DAPT significantly reduced major bleeding events without increasing risk of ST, all-cause mortality, MI, cardiac mortality, or cerebrovascular accidents (8, 9, 22–26, 33, 34). While L-DAPT effectively reduced risk of ST and ischemic events, risk of bleeding increases with longer duration of treatment. Thus, maintaining balance between efficacy and safety for optimal DAPT duration for patients undergoing PCI is the key point. Although a recent study found that CHA2DS2-VASc and HAS-BLED scores have some reference value for MACCEs and prediction regarding major bleeding after stent placement, there is currently still no gold standard for evaluation of ischemic and bleeding risk after PCI (35–37).

As a clinician, comprehensive clinical judgment is necessary to weigh benefits and risks in the individual patient based on risk factors for bleeding and ST after DES placement. Present study results provide evidence supporting S-DAPT for patients with low risk of ischemic events or high risk of bleeding. S-DAPT should be considered in those patients to increase clinical benefit. But what is the solution for patients with DES who are at high risk of ST or MI and low risk of bleeding? In this study, we found that S-DAPT tended to increase risk of ST and MI (combined RRs >1; Fig. 3, 4), though this trend was not statistically significant. In addition, since these high-risk patients were not represented in clinical studies, application of S-DAPT is not recommended for these patients. Studies of evidence-based medicine have demonstrated that extended DAPT (e.g. 30 months) could significantly reduce risk of ST, but this effect was significantly attenuated with use of second-generation DES and was accompanied by increased risk of bleeding (38). Extended DAPT duration should be considered for patients such as those with ACS, lesion complexity, diabetes, hypertension, or dyslipidemia.

**Study limitations**

The main limitations of present study are related to the following aspects. First, due to lack of patient-level data of each component of composite events, subgroup analysis was based on composite events of cardiovascular events, bleeding, and mortality. Although no significant difference in composite events was found in important clinical subgroups, risk of ST or major bleeding of key subgroup undergoing DAPT treatment for up to 6 months remains uncertain. Of the 3 trials containing 100% second-generation DES, only study of Feres et al. (25), in which short DAPT was defined as ≤3 months, was included in subgroup analysis, given lack of adequate data. Secondly, multiple types of stents were tested in individual trials. Although the majority of stents used in the included trials were second-generation DES, early stents were still used in about 13% of cases (BMS: 3.2%; first-generation DES: 9.9%). Sensitivity analysis can help mitigate potential effect of heterogeneity on validity of the results.

**Conclusions**

S-DAPT is associated with lower bleeding risk compared with L-DAPT. Instances of ST and MI were numerically higher with S-DAPT, yet without reaching statistical significance. Comprehensive clinical judgment is necessary to weigh benefits and risks for individual patient. S-DAPT is most likely to be of benefit for patients who are at high risk of bleeding but who are also at low risk for ischemic events.

**Funding sources:** None.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

**Authorship contributions:** Concept – C.L.X., Y.H.; Design – C.L.X., Y.Z.G.; Supervision – Y.H.; Funding – C.L.X., Y.H.; Materials – C.L.X., L.J.Z.; Data collection &/or processing – C.L.X., L.Z.; Analysis and/or interpretation – C.L.X., Y.Z.G.; Literature review – C.L.X., B.B.L.; Writing – C.L.X., Y.Z.G., L.J.Z.; Critical review – Y.H.

**References**

1. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001; 345: 494-502.
2. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007; 357: 2001-15.
3. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009; 361: 1045-57.
4. Pfisterer M, Brunner-La Rocca HP, Buser PT, Rickenbacher P, Hunziker P, Mueller C, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. J Am Coll Cardiol 2006; 48: 2584-91.
5. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline 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. J Am Coll Cardiol 2011; 58: e44-122.
6. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014; 35: 2541-619.
7. 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 2014; 371: 2155-66.
24. Valgimigli M, 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 vs. 12 months of clopidogrel therapy after drug-eluting stenting. Eur Heart J 2015; 36: 1252-63.

23. Kim BK, Hong MK, Shin DH, Lee HJ, Ko YG, 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: 777-86.

22. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009; 339: b2535.

21. Zhang T, Shen L, Hu L, He B. Optimal duration of dual-antiplatelet therapy following drug-eluting stent implantation: a meta-analysis. J Clin Pharmacol 2013; 53: 345-51.

20. Phan K, Tian DH, Cao C, Black D, Yan TD. Systematic review and meta-analysis of the everolimus-eluting stent on stent thrombosis: a meta-analysis of 13 randomized trials. J Am Coll Cardiol 2011; 58: 1569-77.

19. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50: 1088-101.

18. Phan K, Tian DH, Cao C, Black D, Yan TD. Systematic review and meta-analysis: techniques and a guide for the academic surgeon. Ann Cardiothorac Surg 2015; 4: 112-22.

17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-60.

16. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011; 123: 2736-47.

15. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-60.

14. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van ES GA, et al. Clinical End Points in Coronary Stent Trials: A Case for Standardized Definitions. Circulation 2007; 115: 2344-51.

13. Ziada KM, Abdel-Latif A, Charnigo R, Moliterno DJ. Safety of an abbreviated duration of dual antiplatelet therapy (<=6 months) following second-generation drug-eluting stents for coronary artery disease: A systematic review and meta-analysis of randomized trials. Catheter Cardiovasc Interv 2016; 87: 722-32.

12. Tsoi MF, Cheung CL, Cheung TT, Wong IC, Kumana CR, Tse HF, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ 2011; 343: d5928.

11. Liou K, Nagaraja V, Jepson N, Ooi SY. Optimal duration of dual antiplatelet therapy following drug-eluting stents implantation: A meta-analysis of 7 randomised controlled trials. Int J Cardiol 2015; 201: 578-80.

10. Tsoi MF, Cheung CL, Cheung TT, Wong IC, Kumana CR, Tse HF, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ 2011; 343: d5928.

9. Gilard M, Barragan P, Noryani AA, Noor HA, Majwal T, Hovasse T, et al. Standardized Definitions. Circulation 2007; 115: 2344-51.

8. Schulz-Schüpfke 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 vs. 12 months of clopidogrel therapy after drug-eluting stenting. Eur Heart J 2015; 36: 1252-63.

7. Colombo A, Chieffi A, Frascheri A, Garbo R, Masotti-Centolo M, Salvatella N, et al. 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.

6. Colombo A, Chieffo A, Frascheri A, Garbo R, Masotti-Centolo M, Salvatella N, et al. 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.

5. Sorajja P, Stone GW, Serruys PW, et al. 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.

4. Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ. Publication and related biases. Health Technol Assess 2000; 4: 1-115.

3. Palmerini T, Biondi-Zoccai G, Della Riva D, Stettler C, Sangiorgi D, D’Ascenzo F, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet 2012; 379: 1393-402.

2. Kereiakes DJ, Sudhir K, Hermiller JB, Gordon PC, Ferguson J, Yaqub M, et al. Comparison of everolimus-eluting and paclitaxel-eluting coronary stents in patients undergoing multilesion and multivessel intervention: the SPIRIT III (A Clinical Evaluation of the Investigational Device XIENCE V Everolimus Eluting Coronary Stent System [EECSS] in the Treatment of Subjects With De Novo Native Coronary Artery Lesions) and SPIRIT IV (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Subjects With De Novo Native Coronary Artery Lesions) randomized trials. JACC Cardiovasc Interv 2010; 3: 1229-39.

1. Binder RK, Lüscher TF. Duration of dual antiplatelet therapy after coronary artery stenting: where is the sweet spot between ischemia and bleeding? Eur Heart J 2015; 36: 1207-11.