Comparison of the safety and efficacy of between second-generation and first-generation drug eluting stents in patients with left main coronary artery stenosis: A systematic review and meta-analysis

Running title: Safety and efficacy of second-generation drug-eluting stents in left main stenosis.

Xiao-Fei Gao [1], Mei-Jun Liu[1], Yi-Zhou Xu*

[1] Department of Cardiology, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, 261# Huansha Road, Hangzhou, Zhejiang, China 310006.

*Correspondence to: Yi-Zhou Xu, Department of Cardiology, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, 261# Huansha Road, Hangzhou, Zhejiang, China 310006. E-mail: hzsykyzsci@163.com.

Xiao-Fei Gao and Mei-Jun Liu contributed equally to this work and are co-first authors.

Disclosure

Funding: This work was supported by Zhejiang Provincial Traditional Chinese Medicine Science and Technology Project under grant numbers 2017ZQ021

Conflicts of interest: The authors have no conflicts of interest to declare.

Ethics approval: Ethics approval will not be required because all analyses in the present study will be performed based on data from published studies.

Total words: 4081 words

Abstract

Objective:

The aim of this meta-analysis was to compare the safety and efficacy of second-generation and first-generation drug eluting stents (DES) for the treatment of left main coronary artery (LMCA) stenosis.

Methods:

PubMed, EmBase and Cochrane Library were searched to identify eligible studies comparing the safety and efficacy of second-generation DES and first-generation DES for the treatment of LMCA stenosis. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to summary the estimates.

Results:

We identified 11 studies (1 was RCTs and 10 were observational studies) involving 4345 LMCA patients who treated with second-generation and first-generation DES. Second-generation DES had lower risk of MACE (15.4% vs.18.5%; OR 0.69 (0.52, 0.91); *P*=0.009), stent thrombosis (1.1% vs.2.4%; OR 0.46 (0.28, 0.74); *P* = 0.001) , TVR (6.8% vs.13.4%; OR 0.48 (0.35, 0.66); *P* < 0.0001) , and MI (1.6% vs.3.5%; OR 0.58 (0.35, 0.94); P=0.03) compared with first-generation DES. There were no differences in the risks of all-cause mortality (6.8% vs.7.9%; OR 0.88 (0.68, 1.15); *P*=0.36), cardiac mortality (3.4% vs.4.5%; OR 0.73 (0.51, 1.03); *P*=0.07), and TLR (8.7% vs.7.8%; OR 1.09 (0.86, 1.39); *P*=0.48) between second-generation and first-generation DES.

Conclusions:

In LCMA patients, compared with first-generation DES, second-generation DES was associated with lower risk of MACE, stent thrombosis, TVR, and MI. No differences were found with respect to all-cause death, cardiac death, and TLR.

Key words:

Second-generation stents; Drug-eluting stents; Percutaneous coronary intervention; Left main; Meta-analysis

What's known

Studies have evaluated the safety and efficacy of between second-generation and first-generation DES in

LMCA stenosis patients and the results of these studies were inconsistent.

What's new

Second-generation DES have advantages over first-generation DES in improving clinical safety and efficacy. However, to the best of our knowledge, it remains unclear whether second-generation DES are more effective than first-generation DES in LMCA disease patients. In our analysis, we found that second-generation DES was associated with a significant reduction in the risk of MACE, ST, TVR, and MI compared with first-generation DES

Introduction

At present, coronary artery bypass graft (CABG) is considered the gold standard treatment of unprotected left main coronary artery (ULMCA) stenosis. With the advent of the first-generation drug-eluting stents (DES), some randomized controlled trials (RCTs) have showed that percutaneous coronary

intervention (PCI) with first-generation DES had similar outcomes in left main coronary artery (LMCA) stenosis compared to CABG. In the PRECOMBAT trial(1), which was a randomized trial comparing bypass surgery versus angioplasty using sirolimus-eluting stent (SES) in patients with LMCA stenosis, Park, et al. found that PCI with SES was noninferior to CABG with respect to the risk of major adverse cardiac or cerebrovascular events (MACCE) at 1 year follow up. Moreover, a meta-analysis analysis of randomized clinical trials showed that PCI with first-generation DES was associated with similar rates of MACCE, death, and myocardial infarction, and even a lower risk of stroke at 1 year compared with CABG(2). These results suggested that PCI with first-generation DES could be considered an acceptable alternative to CABG in LMCA stenosis patients who are not at high risk.

Despite these results, safety issues regarding the increased late and very late stent thrombosis following the first-generation DES implantation have caused concern. In a large cohort of unselected patients undergoing PCI, first-generation DES was associated with a significantly higher risk of stent thrombosis compared with bare-metal stents (BMS) at 3 years(3). A collaborative network meta-analysis of randomized controlled trials indicated that compared to BMS, paclitaxel-eluting stents (PES) was associated with a higher risk of late definite stent thrombosis(4). Additionally, a pooled patient-level meta-analysis of randomized trials demonstrated that among acute ST-segment elevation myocardial infarction (STEMI) patients undergoing PCI, the incidence of very late reinfarction and stent thrombosis was increased with SES and PES implantation(5). Therefore, second-generation DES was designed with the goal of improving clinical safety and efficacy. In the LEMAX Pilot study, Salvatella, et al. found that unprotected left main stenting using EES is safe and effective in the midterm, with a 15.1% MACCE rate and a 0.6% stent thrombosis rate at one year(6). Simard, et al. found that the treatment of left main coronary stenoses with zotarolimus-drug eluting stents had better clinical results with only a 7.5% in-stent restenosis (ISR)/TLR rate and a 15% MACE rate at an average 12.4 months follow-up(7).

Based on the above evidence, second-generation DES have advantages over first-generation DES in improving clinical safety and efficacy. However, to the best of our knowledge, it remains unclear whether second-generation DES are more effective than first-generation DES in LMCA disease patients. We therefore performed a meta-analysis on the basis of the available data to compare the safety and efficacy of

second-generation DES and first-generation DES for the treatment of LMCA stenosis.

Materials and methods

Search strategy

The Electronic database PubMed, EMBASE, and the Cochrane Library were searched for eligible studies from their date of inception up to February 2019. The following terms were used: “drug eluting stent”, “DES”, “everolimus”, “zotarolimus”, “biolimus”, “rapamycin”, “left main”. In addition, to retrieve all the eligible studies, we manually screened all relevant publications and also scanned the reference lists of included studies. The language and publication status of the research papers were restricted to English and published paper, respectively.

Inclusion and Exclusion Criteria

Studies that met the following criteria were considered for inclusion in this meta-analysis: (1) studies which enrolled LMCA stenosis patients undergoing PCI; (2) studies with comparisons between second-generation DES and first-generation DES; (3) studies which had availability of clinical outcomes, including major adverse cardiac events, all-cause mortality, cardiac mortality, myocardial infarction, target vessel revascularization, target lesion revascularization, and stent thrombosis; (4) studies which were observational trial or RCTs; (5) full-text article. The following ineligible studies were excluded from this meta-analysis: (1) studies which included non- LMCA stenosis patients; (2) studies without control group; (3) studies which have no available clinical outcomes; (4) duplicate publications; (5) conference abstract, reviews, commentaries, meta-analysis, editorials, and letters.

Clinical Outcomes and Definitions

The primary efficacy endpoint was major adverse cardiac events (MACE), which was defined by each study. Although the definition of MACE differed between studies, the MACE definition of each individual study was accepted. The primary safety endpoint was stent thrombosis (definite, probable, or possible ST) according to the definition criteria of the Academic Research Consortium (ARC). Secondary outcomes were all-cause death, cardiac death, target vessel revascularization (TVR), target lesion revascularization (TLR), and myocardial infarction (MI). TVR/TLR was defined as any percutaneous or surgical revascularization procedure of the target vessel/ lesion.

Data Extraction

Data was extracted independently by two investigators. The following data were abstracted from each study: the first author's surname, year of publication, country, ethnicities of the patients, type of study, duration of follow-up, MACE definition, stent type, sample size, mean age, male, diabetes mellitus, hypertension, dyslipidemia, previous MI, previous PCI, previous CABG. Any discrepancies about the extracted data were resolved by consensus or a third author adjudication. The quality of the included studies was assessed using the Jadad scale for randomized controlled studies and Newcastle-Ottawa Quality scale (NOS) for observational studies.

Statistical Analysis

Propensity score matching data was used for the meta-analysis unless they were unavailable. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to summary the estimates. The heterogeneity between studies was assessed using the chi-square-based Cochran Q test and I^2 statistic, which was considered significant when $P < 0.10$ in the Q test, or $I^2 > 50\%$. In this analysis, the fixed-effects model was used to calculate the pooled ORs when $I^2 < 50\%$; otherwise, a random-effects model (DerSimonian and Laird) was used. Subgroup analyses was performed to explore potential sources of heterogeneity according to follow-up duration (≥2 years and < 2 years) and different ethnicity (Caucasian and Asian populations). Sensitivity analysis was carried out by omitting each individual study in turn to evaluate the influence of each study on the overall estimate. Finally, funnel plots was constructed to visually assess the potential publication bias. All *P* values were two sided, and a p-value <0.05 was considered statistically significant. All statistical analyses were performed by using RevMan statistical software (Review Manager 5.3, The Cochrane Collaboration, Copenhagen, Denmark).

Results

Characteristics of the Included Studies

The flow diagram of the studies selection was presented in figure 1. 4345 articles were retrieved during the initial search process. After careful screening, 11 studies(8-18) comparing clinical outcomes of first-generation versus second-generation DES in patients with LMCA entered the meta-analysis. In total, our meta-analysis comprised a total of 5120 people. Out of these patients, 2588 were allocated to first-generation DES and 2532 to second-generation DES. Baseline characteristics and procedural outcomes are shown in Table 1-3. Of the 11 studies, only 1 study was RCTs and the others were observational study. 7

out of 11 studies were conducted in European and American countries, 1 study was carried out in Argentina, 2 were conducted in Korea, and the rest 1 study was performed in Italy and Japan. 4 studies had reported the propensity score matching data. As for MACE, 6 studies reported specific definitions of MACE. Definition of MACE included studies was defined as the composite of all-cause death/cardiac death, MI and TLR/TVR except for the Valenti trial (defined as cardiac death, MI, TVR, and stroke). In addition, two studies reported the composite endpoint of all-cause death, MI, TLR and one study reported the composite endpoint of cardiac death, MI, TLR, which all can be considered as MACE. Two studies reported the composite endpoint of MACCE (defined as cardiac death, MI, TVR, and stroke/CVA). The follow-up duration ranging from 250 days to 3 years. The mean age of included patients ranged from 62 years to 71 years.

Primary efficacy outcome (MACE)

All the 11 trials reported the incidence of MACE, the result showed that DES-2 was associated with a significant reduction in the risk of MACE compared with DES-1 [15.4% vs.18.5%; OR 0.69 (0.52, 0.91); *P*=0.009] with significant heterogeneity (I^2 = 57%; *P*= 0.009) (Figure 2a).

Primary safety outcome (stent thrombosis)

10 trials reported the incidence of stent thrombosis. In general, the results showed that DES-2 was associated with a lower risk of stent thrombosis compared with DES-1[1.1% vs.2.4%; OR 0.46 (0.28, 0.74); *P* = 0.001]. There was no heterogeneity across the enrolled trials (I^2 = 0%; *P* = 0.81) (Figure 2b).

Secondary outcomes

All-cause mortality/cardiac mortality

7 trials reported the incidence of all-cause mortality and 8 trials reported the incidence of cardiac mortality, respectively. The results showed that there were no between-group differences in the risks of all-cause mortality [6.8% vs.7.9%; OR 0.88 (0.68, 1.15); *P*=0.36] and cardiac mortality [3.4% vs.4.5%; OR 0.73 (0.51, 1.03); *P*=0.07] (Figure 2c).

Repeat revascularization TLR/TVR

8 trials reported the incidence of TLR and 6 trials reported the incidence of TVR, respectively. The results showed that there was no statistical difference in the risks of TLR between the DES-2 and DES-1 [8.7% vs.7.8%; OR 1.09 (0.86, 1.39); *P*=0.48]. DES-2 can significantly reduce the risk of TVR compared

with DES-1 [6.8% vs.13.4%; OR 0.48 (0.35, 0.66); $P < 0.0001$] with no significant heterogeneity (I^2 = 18%; $P = 0.30$) (Figure 2c).

Myocardial infarction

9 trials reported the incidence of MI. The result showed that the DES-2 provide a significant advantage over DES-1 in reducing the incidence of MI [1.6% vs.3.5%; OR 0.58 (0.35, 0.94); P=0.03] with no significant heterogeneity (I^2 = 28%; P = 0.19) (Figure 2c).

Heterogeneity Analysis

Significant heterogeneity was noted in our study with respect to the endpoint of MACE. Thus, subgroup analysis was conducted to explore potential sources of heterogeneity. The subgroup analysis according to follow-up duration and ethnicity showed that heterogeneity was still significant in studies with a follow-up duration of more than 2 years and in Caucasian populations; However, with no significance in studies with a follow-up duration of less than 2 years and in Asian populations.

Sensitivity Analysis

To assess the reliability of the results of the meta-analysis, sensitivity analysis was carried out. After omitting each individual study in sequence, the results showed that it did not essentially affect the summary OR, further indicating that these outcomes were stable and reliable

Publication bias

Funnel plots was constructed to visually evaluate whether publication bias affected the results of the studies. The funnel plot suggested that no significant publication bias across the studies with respect to each outcome (Figure 3).

Discussions

The main findings of this meta-analysis can be summarized as follows: (1) second-generation DES was associated with a significant reduction in the risk of MACE, ST, TVR, and MI compared with first-generation DES. (2) There were no between-group differences in the risks of all-cause mortality, cardiac mortality, and TLR.

Previous a number of RCTs have been performed to compare the clinical outcomes of first-generation DES versus second-generation DES. In the majority of these studies, second-generation DES provided an improvement in safety and efficacy compare with first-generation DES. In the large-scale, prospective,

multicenter, randomized SPIRIT IV trial, Stone, et al. found that compared to PES, EES can significantly reduce the risk of MI, stent thrombosis, TVR, TLR and MACE, without significant differences in all-cause or cardiac mortality(19). Similarly, in the randomized COMPARE trial, Smits, et al. found that second-generation EES still had a lower 2-year rate of MACE, MI, TVR, TLR and stent thrombosis compared with PES even after discontinuation, at 12 months, of dual antiplatelet therapy(20). In the present meta-analysis, the results indicated that second-generation DES was associated with a significant reduction in the risk of MACE, ST, TVR, and MI in the LMCA stenosis. This was in agreement with previous trials. The potential mechanism was that compared to first-generation DES with stainless-steel platforms, second-generation DES have cobalt-chrome or platinum-chrome platforms with thinner strut thickness and more biocompatible polymer coatings, which helped improve the safety endpoints of stent thrombosis and the efficacy outcome of MACE(21, 22).

In line with previous trials, rates of all-cause mortality and cardiac mortality in LMCA stenosis patients who treated with second-generation and first-generation DES did not differ significantly. In the SORT OUT IV trial, which was a randomized multicenter, single-blind, all-comer, noninferiority trial comparing clinical outcomes of EES versus SES in coronary artery disease, results indicated that rates of mortality and cardiac mortality did not differ significantly between the 2 stent groups at the 18-month follow-up(23). A pooled analysis of 2-year outcomes from the SPIRIT II and III trials showed that there were no significant differences in the risk of all-cause mortality and cardiac mortality between first-generation and second-generation DES(24). However, in the randomized SPIRIT III trial with a follow-up duration up to 5 years, results indicated that EES resulted in lower rates of all-cause mortality(25). In addition, Fuku, et al. found that treatment with second-generation DES was associated with a lower incidence of all-cause mortality and cardiac mortality in patients with unprotected LMCA lesions(26). However, it is worth noting that the median follow-up duration of first-generation DES in this study was as long as 1,685 days. Therefore, the length of follow-up time may be a potential confounding factor. RCTs with longer follow-up duration are needed to further confirm these findings.

As for TLR, the impact of second-generation DES on TLR remains controversial. In the EXCELLENT trial, which was a prospective, randomized, open-label, multicenter trial comparing EES

versus SES in patients undergoing PCI, Park, et al. found that rate of TLR was numerically lower in the SES group but was not statistically significant(27). Additionally, results from the ESSENCE-DIABETES trial showed that at 12 months, the incidence of ischemia-driven TLR was not statistically different between EES and SES(28). Nevertheless, in the SPIRIT IV trial, Stone, et al. found that EES was superior to PES with respect to the endpoint of TLR at 1 year follow up(19). In the current study, the TLR rate in LMCA lesions patients undergoing PCI treated with DES-2 did not differ from that receiving first-generation DES. The exact mechanism remains unclear. But, of note, 8 out of 11 studies included in the meta-analysis reported the use of intravascular ultrasound (IVUS) between two type stents, Previous studies have demonstrated that IVUS can reduce the risk of restenosis and TLR, which partially explained the lower TLR rate in our study(29, 30). Therefore, small sample size may decrease the statistical power to properly evaluate the associations between the two type stents and the incidence of TLR. Larger-scale trials are required to further confirm true effect of second-generation DES on the incidence of TLR in patients with LMCA.

Finally, the significant heterogeneity was identified between studies with regard to the endpoint of MACE. Therefore, we conducted subgroup analyses to explore the sources of the heterogeneity. The results of the subgroup analysis indicated that the heterogeneity decreased significantly in studies with a follow-up duration of less than 2 years and in Asian populations. Thus, ethnicity and the follow-up duration length may have been sources of the heterogeneity.

Limitations

There were several limitations of this meta-analysis. First, the meta-analysis included only 11 studies involving 4345 patients and the small sample size may have decreased the statistical power to properly evaluate the associations between first-generation and second-generation DES. Second, although this meta-analysis included four propensity score matching studies, we could not assess whether all baseline characteristics were balanced among groups. Third, of the studies included in this meta-analysis, only one was a randomized controlled trial, which greatly decreased the statistical power of the analysis. Four, the latest study included in the meta-analysis may limits the follow-up duration for second-generation DESs. Finally, the definition of MACE varied among the included studies. Despite the limitations, the present

study is the first meta-analysis to systematically compare the safety and efficacy of first-generation and second-generation DES on the outcomes in LMCA patient treated with PCI. Larger randomized controlled trials are needed to confirm the findings.

Conclusion

In LCMA lesion patients, compared with first-generation DES, second-generation DES was associated with lower risk of MACE, stent thrombosis, TVR, and MI. No differences were found with respect to all-cause death, cardiac death, and TLR.

Acknowledgments

On behalf of my co-authors, I would like to declare that this is an original study that has not been published before or considered for publication elsewhere, in whole or part. All the listed authors have approved the attached manuscript. On behalf of all the co-authors, I sign and assume the responsibility of publishing this manuscript.

References

1. Park SJ, Kim YH, Park DW, Yun SC, Ahn JM, Song HG, et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease. The New England journal of medicine. 2011;364(18):1718-27.
2. Capodanno D, Stone GW, Morice MC, Bass TA, Tamburino C. Percutaneous coronary intervention versus coronary artery bypass graft surgery in left main coronary artery disease: a meta-analysis of randomized clinical data. J Am Coll Cardiol. 2011;58(14):1426-32.
3. Tada T, Byrne RA, Simunovic I, King LA, Cassese S, Joner M, et al. Risk of stent thrombosis among bare-metal stents, first-generation drug-eluting stents, and second-generation drug-eluting stents: results from a registry of 18,334 patients. JACC Cardiovasc Interv. 2013;6(12):1267-74.
4. Stettler C, Wandel S, Allemann S, Kastrati A, Morice MC, Schomig A, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet. 2007;370(9591):937-48.
5. De Luca G, Dirksen MT, Spaulding C, Kelbaek H, Schalij M, Thuesen L, et al. Drug-eluting vs bare-metal stents in primary angioplasty: a pooled patient-level meta-analysis of randomized trials. Archives of internal medicine. 2012;172(8):611-21; discussion 21-2.
6. Salvatella N, Morice MC, Darremont O, Tafflet M, Garot P, Leymarie JL, et al. Unprotected left main stenting with a second-generation drug-eluting stent: one-year outcomes of the LEMAX Pilot study. EuroIntervention. 2011;7(6):689-96.
7. Simard T, Hibbert B, Chong AY, Ruchin P, Le May M, Labinaz M, et al. Unprotected left main coronary artery stenting with zotarolimus (Endeavor) drug-eluting stents: a single center retrospective experience. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2012;80(2):E15-22.

8. Buchanan GL, Chieffo A, Bernelli C, Montorfano M, Carlino M, Latib A, et al. Two-year outcomes following unprotected left main stenting with first vs. new-generation drug-eluting stents: the FINE registry. EuroIntervention. 2013;9(7):809-16.
9. Cassese S, Kufner S. Three-year efficacy and safety of new- versus early-generation drug-eluting stents for unprotected left main coronary artery disease insights from the ISAR-LEFT MAIN and ISAR-LEFT MAIN 2 trials. 2016;105(7):575-84.
10. De La Torre Hernandez JM, Alfonso F, Sanchez Recalde A, Jimenez Navarro MF, Perez De Prado A, Hernandez F, et al. Comparison of paclitaxel-eluting stents (Taxus) and everolimus-eluting stents (Xience) in left main coronary artery disease with 3 years follow-up (from the ESTROFA-LM registry). American Journal of Cardiology. 2013;111(5):676-83.
11. Haiek C, Fernandez-Pereira C, Santaera O, Mieres J, Rifourcat I, Lloberas J, et al. Second vs. First generation drug eluting stents in multiple vessel disease and left main stenosis: Two-year follow-up of the observational, prospective, controlled, and multicenter ERACI IV registry. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2017;89(1):37-46.
12. Kim YH, Park DW, Ahn JM, Yun SC, Song HG, Lee JY, et al. Everolimus-eluting stent implantation for unprotected left main coronary artery stenosis. The PRECOMBAT-2 (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) study. JACC Cardiovasc Interv. 2012;5(7):708-17.
13. Lee MS, Mahmud E, Ang L, Lluri G, Cheng RK, Aragon J, et al. Comparison of sirolimus-, paclitaxel-, and everolimus-eluting stent in unprotected left main coronary artery percutaneous coronary intervention. Journal of the Saudi Heart Association. 2013;25(2):75-8.
14. Montefusco A, D'Ascenzo F, Gili S, Smolka G, Chieffo A, Baumbach A, et al. Self-expandable sirolimus-eluting stents compared to second-generation drug-eluting stents for the treatment of the left main: A propensity score analysis from the SPARTA and the FAILS-2 registries. Catheterization and Cardiovascular Interventions. 2019;93(2):208-15.
15. Moynagh A, Salvatella N, Harb T, Darremont O, Boudou N, Dumonteil N, et al. Two-year outcomes of everolimus vs. paclitaxel-eluting stent for the treatment of unprotected left main lesions: a propensity score matching comparison of patients included in the French Left Main Taxus (FLM Taxus) and the LEft MAin Xience (LEMAX) registries. EuroIntervention. 2013;9(4):452-62.
16. Naganuma T, Chieffo A, Takagi K, Panoulas VF, Mitomo S, Sticchi A, et al. First generation versus new generation drug-eluting stents for the treatment of ostial/midshaft lesions in unprotected left main coronary artery: The Milan and New-Tokyo (MITO) registry. Catheterization and Cardiovascular Interventions. 2015;85(3):E63-E9.
17. Park KW, Lim WH, Ahn HS, Kang SH, Han JK, Lee SE, et al. Everolimus-versus sirolimus-eluting stents for the treatment of unprotected left main coronary artery stenosis (results from the EXCELLENT registry). International journal of cardiology. 2013;168(3):2738-44.
18. Valenti R, Migliorini A, Parodi G, Carrabba N, Vergara R, Dovellini EV, et al. Clinical and angiographic outcomes of patients treated with everolimus-eluting stents or first-generation Paclitaxel-eluting stents for unprotected left main disease. J Am Coll Cardiol. 2012;60(14):1217-22.
19. Stone GW, Rizvi A, Sudhir K, Newman W, Applegate RJ, Cannon LA, et al. Randomized comparison

of everolimus- and paclitaxel-eluting stents. 2-year follow-up from the SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) IV trial. J Am Coll Cardiol. 2011;58(1):19-25.
20. Smits PC, Kedhi E, Royaards KJ, Joesoef KS, Wassing J, Rademaker-Havinga TA, et al. 2-year follow-up of a randomized controlled trial of everolimus- and paclitaxel-eluting stents for coronary revascularization in daily practice. COMPARE (Comparison of the everolimus eluting XIENCE-V stent with the paclitaxel eluting TAXUS LIBERTE stent in all-comers: a randomized open label trial). J Am Coll Cardiol. 2011;58(1):11-8.
21. Stefanini GG, Holmes DR, Jr. Drug-eluting coronary-artery stents. The New England journal of medicine. 2013;368(3):254-65.
22. Sabate M, Cequier A, Iniguez A, Serra A, Hernandez-Antolin R, Mainar V, et al. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. Lancet. 2012;380(9852):1482-90.
23. Jensen LO, Thayssen P, Hansen HS, Christiansen EH, Tilsted HH, Krusell LR, et al. Randomized comparison of everolimus-eluting and sirolimus-eluting stents in patients treated with percutaneous coronary intervention: the Scandinavian Organization for Randomized Trials with Clinical Outcome IV (SORT OUT IV). Circulation. 2012;125(10):1246-55.
24. Onuma Y, Serruys PW, Kukreja N, Veldhof S, Doostzadeh J, Cao S, et al. Randomized comparison of everolimus- and paclitaxel-eluting stents: pooled analysis of the 2-year clinical follow-up from the SPIRIT II and III trials. Eur Heart J. 2010;31(9):1071-8.
25. Gada H, Kirtane AJ, Newman W, Sanz M, Hermiller JB, Mahaffey KW, et al. 5-year results of a randomized comparison of XIENCE V everolimus-eluting and TAXUS paclitaxel-eluting stents: final results from the SPIRIT III trial (clinical evaluation of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions). JACC Cardiovasc Interv. 2013;6(12):1263-6.
26. Fuku Y, Kadota K, Habara S, Tanaka H, Yamamoto H, Fujii S, et al. Clinical impact of second-generation DES compared with first-generation DES in patients with unprotected left main coronary artery lesions. EuroIntervention. 2013;9:112.
27. Park KW, Chae IH, Lim DS, Han KR, Yang HM, Lee HY, et al. Everolimus-eluting versus sirolimus-eluting stents in patients undergoing percutaneous coronary intervention: the EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) randomized trial. J Am Coll Cardiol. 2011;58(18):1844-54.
28. Kim WJ, Lee SW, Park SW, Kim YH, Yun SC, Lee JY, et al. Randomized comparison of everolimus-eluting stent versus sirolimus-eluting stent implantation for de novo coronary artery disease in patients with diabetes mellitus (ESSENCE-DIABETES): results from the ESSENCE-DIABETES trial. Circulation. 2011;124(8):886-92.
29. Tan Q, Wang Q, Liu D, Zhang S, Zhang Y, Li Y. Intravascular ultrasound-guided unprotected left main coronary artery stenting in the elderly. Saudi Med J. 2015;36(5):549-53.
30. Ye Y, Yang M, Zhang S, Zeng Y. Percutaneous coronary intervention in left main coronary artery disease with or without intravascular ultrasound: A meta-analysis. PloS one. 2017;12(6):e0179756.

Figure and Table Legends

Figure 1 Flow diagram of study selection.

Figure 2a Forest plots for major adverse cardiovascular events in left main stenosis patients with first-generation versus second-generation drug-eluting stents.

Figure 2b Forest plots for stent thrombosis in left main stenosis patients with first-generation versus second-generation drug-eluting stents.

Figure 2c Forest plots for secondary outcomes in left main stenosis patients with first-generation versus second-generation drug-eluting stents.

Figure 3 Funnel plot assessing publication bias in the included studies.

Table I-III Baseline clinical characteristics of patients included in studies.