Long term outcomes of drug-eluting stent versus coronary artery bypass grafting for left main coronary artery disease: a meta-analysis

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Abstract

Background It is still controversial whether percutaneous coronary intervention with drug-eluting stent (DES) is safe and effective compared to coronary artery bypass graft surgery (CABG) for unprotected left main coronary artery (ULMCA) disease at long-term follow up (≥ 3 years).

Methods Eligible studies were selected by searching PubMed, EMBASE, and Cochrane Library up to December 6, 2016. The primary endpoint was a composite of death, myocardial infarction (MI) or stroke during the longest follow-up. Death, cardiac death, MI, stroke and repeat revascularization were the secondary outcomes.

Results Four randomized controlled trials and twelve adjusted observational studies involving 14,130 patients were included. DES was comparable to CABG regarding the occurrence of the primary endpoint (HR = 0.94, 95% CI: 0.86–1.03). Besides, DES was significantly associated with higher incidence of MI (HR = 1.56, 95% CI: 1.09–2.22) and repeat revascularization (HR = 3.09, 95% CI: 2.33–4.10) compared with CABG, while no difference was found between the two strategies regard as the rate of death, cardiac death, MI, stroke and repeat revascularization were the secondary outcomes. Results Four randomized controlled trials and twelve adjusted observational studies involving 14,130 patients were included. DES was comparable to CABG regarding the occurrence of the primary endpoint (HR = 0.94, 95% CI: 0.86–1.03). Besides, DES was significantly associated with higher incidence of MI (HR = 1.56, 95% CI: 1.09–2.22) and repeat revascularization (HR = 3.09, 95% CI: 2.33–4.10) compared with CABG, while no difference was found between the two strategies regard as the rate of death, cardiac death, MI, stroke and repeat revascularization were the secondary outcomes. Results Four randomized controlled trials and twelve adjusted observational studies involving 14,130 patients were included. DES was comparable to CABG regarding the occurrence of the primary endpoint (HR = 0.94, 95% CI: 0.86–1.03). Besides, DES was significantly associated with higher incidence of MI (HR = 1.56, 95% CI: 1.09–2.22) and repeat revascularization (HR = 3.09, 95% CI: 2.33–4.10) compared with CABG, while no difference was found between the two strategies regard as the rate of death, cardiac death, MI, stroke and repeat revascularization were the secondary outcomes.

Conclusions Although with higher risk of repeat revascularization, PCI with DES appears to be as safe as CABG for ULMCA disease at long-term follow up. In addition, treatment with DES could be an alternative interventional strategy to CABG for ULMCA lesions with low to intermediate anatomic complexity.


Keywords: Coronary artery bypass graft; Drug-eluting stent; Long term; Unprotected left main coronary disease

1 Introduction

Significant unprotected left main coronary artery (ULMCA) disease occurs in 5%–7% of patients undergoing coronary angiography.1,2 For several decades, coronary artery bypass graft surgery (CABG) has been recommended as the standard treatment for ULMCA disease owing to its survival benefit over medical therapy.1,2 At the same time, the adaptation of drug-eluting stent (DES) in percutaneous coronary intervention (PCI) has led to a significant reduction in the risk of restenosis and repeat revascularization in comparison with bare-metal stent (BMS).3,4 With the improvement of stent design, procedural technique and adjunctive medical therapy, PCI with DES is increasingly considered as a safe and feasible approach for patients with ULMCA disease.

Previous studies suggested the incidence of long-term death and overall safety endpoint of death, myocardial infarction (MI) or stroke were comparable between PCI and CABG for ULMCA disease.5–7 In the current guidelines, PCI receives a class I or IIa recommendation for patients with low SYNTAX score, while a class IIa or IIb recommendation for patients with intermediate anatomic complexity.6,7 Obviously, PCI with DES can be a viable alternative to CABG for ULMCA disease, especially in patients with low to intermediate anatomic complexity.

However, previous meta-analyses had a limited follow-up duration of ≤3 years, while the most recent meta-analysis concentrating on long-term outcomes comparing DES and CABG was restricted to a small sample size and studies using mixtures of BMS and DES were enrolled.7,8 Recently, the EXCEL trial indicates that PCI with everolimus-eluting stents is noninferior to CABG with respect to the overall
combined incidence of death, myocardial infarction (MI) or stroke at three years,\textsuperscript{[9]} while the NOBLE study suggests CABG may be better than biolimus-eluting stent regarding lower rate of 5-year major adverse cardiac or cerebrovascular events (MACCE).\textsuperscript{[10]} Unfortunately, it is still controversial whether DES is safe and effective compared to CABG for ULMCA disease at long-term follow up. We performed a meta-analysis including only trials with a follow-up duration of at least three years to examine the long-term relative safety and efficacy of DES and CABG for ULMCA lesions.

2 Methods

2.1 Search strategy

A comprehensive search of electronic database in PubMed, EMBASE, and Cochrane Library up to December 6, 2016 was performed to identify the pertinent articles regarding DES versus CABG for ULMCA disease. The following medical subject headings and search terms were used: “percutaneous coronary intervention”, “PCI”, “stent”, “drug-eluting stent”, “DES”, “coronary artery bypass”, and “left main”. The references of the identified articles and relevant reviews were screened to include other potentially suitable trials.

2.2 Study selection

Studies satisfying the following criteria were eligible: (1) randomized controlled trials (RCTs) or adjusted observational studies (propensity-score matching > propensity-score adjusted > multivariable adjusted) regarding ULMCA disease; (2) compared DES to CABG; (3) followed for ≥ 3 years. Studies were excluded if they met any one of the following criteria: (1) not published in English; (2) published as an abstract or conference proceedings; (3) with the same patient sample; (4) using BMS exclusively or mixtures of BMS and DES without outcomes comparing DES with CABG separately. When several reports overlapped with each other, we selected the largest and the latest study. Two independent investigators (MDZ and WW) reviewed the studies to determine whether they met the inclusion criteria and any disagreement was resolved by consensus.

2.3 Data extraction

The following data was independently extracted by two authors (FX and MZ) through a standardized form: study characteristics, patient characteristics, and clinical outcomes. Hazard ratios (HR) of the time-to-event outcomes or odds ratios (OR) calculated from dichotomous outcomes were extracted. The primary endpoint was a composite of death, MI or stroke during the longest follow-up. Death, cardiac death, MI, stroke and repeat revascularization were the secondary outcomes, and they were defined variable in each study (Table 1S).

2.4 Quality assessment

The RCTs were evaluated by following the methodological criteria recommended by the Cochrane Collaboration: sequence generation, concealment of allocation, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias,\textsuperscript{[11]} whereas the observational studies were evaluated by the Newcastle-Ottawa Scale criteria.\textsuperscript{[12]}

2.5 Statistical analysis

Quantitative analysis with the generic inverse variance random-effect model was performed to estimate the pooled HRs or ORs with their 95% confidence intervals (CIs). Potential heterogeneity among studies was quantified with $I^2$ and a value of > 50% was defined as statistical heterogeneity. Furthermore, we used funnel plots to assess the potential publication bias.

Subgroup analysis was carried out to explore the sources of heterogeneity according to the study design (RCTs or adjusted observational studies). Additionally, sensitivity analysis was conducted by performing a separate analysis according to the following variables: (1) duration of follow up ≥ 5 years; (2) SYNTAX score ≤ 32 or > 32. To demonstrate the robustness of the results, we investigated the influence of a single study on the overall effect by omitting one study in each turn. All $P$ values were two-sided, and results were considered statistically significant at $P < 0.05$.

This study was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,\textsuperscript{[13]} and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist.\textsuperscript{[14]} All statistical analysis was performed with Review Manager 5.1 (Cochrane Center, Denmark).

3 Results

3.1 Eligible studies

After a comprehensive search, 2103 potentially relevant articles were identified in the initial analysis. One hundred and nineteen articles were chosen for complete review, and finally, 16 studies were included in the present meta-analysis.\textsuperscript{[9,10,15-28]} The process of selecting studies for the meta-analysis is briefly depicted in Figure 1 and the methodology as well as the population characteristics are presented in Table 1.
Among the 16 trials (four RCTs, six propensity-score matching studies, and six propensity-score adjusted studies), 6333 and 7797 patients were treated with DES and CABG, respectively. Odds ratios were reported or calculated in two studies from dichotomous outcomes provided at five year follow-up.[17,26] Eligible studies were published between 2009 and 2016, while the clinical follow-up period ranged from 3 to 8 years. Quality assessment results are described in Table 2S and Table 3S. The funnel plot of the primary endpoint indicates that no publication bias was found (Figure 1S). Overall, intravascular ultrasound (IVUS) guided PCI was performed in 56.1% of the patients. Additionally, 47.6% of the patients underwent CABG with off-pump technique, while a left anterior internal mammary artery graft was used in 92.5% of the patients who received CABG (Table 1).

### 3.2 Primary endpoint

In summary, the composite of death, MI or stroke was reported in 13 studies. Treatment with DES was comparable to that of CABG regarding the incidence of a composite of death, MI or stroke without heterogeneity for ULMCA disease (HR = 0.94, 95% CI: 0.86–1.03, P = 0.20, I² = 0) (Figure 2).

### 3.3 Secondary endpoints

There was no significant difference in the incidence of all-cause death (HR = 1.11; 95% CI: 0.92–1.32, P = 0.28) (Figure 3) as well as the risk of cardiac death (HR = 1.13, 95% CI: 0.75–1.72, P = 0.55) (Figure 4) between the two strategies. Nevertheless, signs of statistical heterogeneity regarding cardiac death were found across trials (I² = 73%). Subgroup analysis by excluding observational studies showed the rate of cardiac death was comparable between the two groups without statistical heterogeneity (HR = 1.00, 95% CI: 0.72–1.39, P = 0.99, I² = 21%).

Overall, the risk of MI was significantly higher in the DES group in comparison with the CABG group (HR = 1.56, 95% CI: 1.09–2.22, P = 0.01, I² = 69%) (Figure 5). Subgroup analysis showed treatment with DES was associated with increased risk of MI in observational studies (HR = 1.67, 95% CI: 1.05–2.63, P = 0.03, I² = 56%), whereas no significant difference was found between the two groups in RCTs (HR = 1.48; 95% CI: 0.85–2.58, P = 0.17, I² = 67%).
<table>
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<th>Study</th>
<th>No. patients</th>
<th>Study design</th>
<th>Adjusted method</th>
<th>Study period</th>
<th>Follow up, yrs</th>
<th>Type of DES</th>
<th>Off-pump procedure, %</th>
<th>LIMA-LAD graft, %</th>
<th>Complete artery grafting, %</th>
<th>Guidance with IVUS, %</th>
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<td>ASAN-MAIN 2010[15]</td>
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<td>Retrospective, multicenter</td>
<td>Propensity-score matching</td>
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<td>Not needed</td>
<td>2008.12–2015.1</td>
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<td>First-generation DES 11%, BES 89%</td>
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*The numerals indicate the numbers of patients in the DES group and the CABG group, respectively. ASAN-MAIN: ASAN medical center-left main revascularization; BES: biolimus-eluting stent; CABG: coronary artery bypass grafting; DELTA: drug-eluting stent for left main coronary artery disease; DES: drug-eluting stent; EES: everolimus-eluting stent; EXCEL: evaluation of Xience versus coronary artery bypass surgery for effectiveness of left main revascularization; IVUS: intravascular ultrasound; LAD: left anterior descending coronary artery; LIMA: left internal mammary artery; MAIN-COMPARE: revascularization for unprotected left main coronary artery stenosis: comparison of percutaneous coronary angioplasty versus surgical revascularization study; NA: not applicable; NOBAL: Nordic-Baltic-British left main revascularization; PES: paclitaxel-eluting stent; PRECOMBAT: premier of randomized comparison of bypass surgery versus angioplasty using sirolimus-eluting stent in patients with left main coronary artery disease; RCT: randomized controlled trial; SES: sirolimus-eluting stent; SYNTAX: synergy between percutaneous coronary intervention with TAXUS and cardiac surgery; ZES: zotarolimus-eluting stent.
Figure 2. Forest plot of the composite of death, myocardial infarction or stroke. CABG: coronary artery bypass graft surgery; DES: drug-eluting stent.

Figure 3. Forest plot of all-cause death. CABG: coronary artery bypass graft surgery; DES: drug-eluting stent.
In the pooled estimate, the risk of stroke was not significantly different between the two treatment strategies with statistical heterogeneity (HR = 0.61, 95% CI: 0.29–1.29, \( P = 0.20, I^2 = 84\% \)) (Figure 6). However, CAGB was inferior to DES in terms of higher rate of stroke in observational studies (HR = 0.39, 95% CI: 0.17–0.91, \( P = 0.03, I^2 = 73\% \)).

The data in Figure 7 indicated that the pooled HR of DES for repeat revascularization was significantly higher in the overall analysis (HR = 3.09, 95% CI: 2.33–4.10, \( P < 0.0001, I^2 = 79\% \)), RCTs (HR = 1.70, 95% CI: 1.42–2.05, \( P < 0.0001, I^2 = 0 \)) and observational studies (HR = 3.92, 95% CI: 3.05–5.04, \( P < 0.0001, I^2 = 48\% \)).

### 3.4 Sensitivity analysis

Sensitivity analyses conducted through the removal of any single trial showed that it did not essentially affect the overall pooled estimate. Furthermore, when the study by Zheng, et al.\(^{[28]}\) was removed, no statistical heterogeneity

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**Figure 4. Forest plot of cardiac death.** CAGB: coronary artery bypass graft surgery; DES: drug-eluting stent.

**Figure 5. Forest plot of myocardial infarction.** CAGB: coronary artery bypass graft surgery; DES: drug-eluting stent.
was found regarding cardiac death (HR = 0.99, 95% CI: 0.74–1.32, \( P = 0.92, I^2 = 24\% \)) (Data not shown), while statistical heterogeneity was not existed any more by excluding the EXCEL study\(^9\) in terms of MI (HR = 1.78, 95% CI: 1.33–2.37, \( P < 0.0001, I^2 = 33\% \)) (Data not shown).

Besides, sensitivity analyses according to the follow-up study...
duration (≥ 5 years) obtained mostly similar results compared to the overall analysis. Analysis after excluding the trials with follow-up duration < 5 years showed DES was associated with higher rate of MI compared with CABG without heterogeneity (HR = 1.92, 95% CI: 1.37–2.69, \( P = 0.0002, I^2 = 0 \)) (Figure S2).

In patients with SYNTAX score ≤ 32, DES was superior to CABG in terms of the composite of death, MI or stroke (HR = 0.80, 95% CI: 0.67–0.95, \( P = 0.01, I^2 = 0 \)). Nevertheless, treatment with DES was inferior to CABG regarding the primary endpoint (HR = 1.45, 95% CI: 1.06–1.97, \( P = 0.02, I^2 = 42\% \)) in patients with SYNTAX score > 32 (Figure S3).

4 Discussion

The present meta-analysis with approximately 15,000 patients comparing the long-term safety and efficacy between DES and CABG for ULMCA disease demonstrated that: (1) PCI with DES was comparable to CABG regarding the rate of the primary endpoint composing death, MI or stroke; (2) The incidence of MI and repeat revascularization were higher in the DES group compared with the CABG group, while no significant difference was found between the two treatment strategies regarding the risk of death, cardiac death and stroke; and (3) DES might be a safe and effective alternative to CABG for ULMCA disease with low to intermediate anatomic complexity.

Studies with small sample size demonstrated that no difference for the safety endpoint composing death, MI or stroke between the two strategies for patients with ULMCA lesions.[7,8] Nevertheless, one study mixed BMS in the PCI group,[7] while the other enrolled study with outcomes at only 1 year follow-up,[8] therefore severe heterogeneity could not be avoided under the circumstances. In our study, the occurrence of the primary endpoint composite of death, MI or stroke in the DES group was comparable to the CABG group without heterogeneity.

All-cause mortality remained similar between the two strategies, which was in accordance with the studies with short-term data[5,6] and meta-analyses with long-term follow-up.[7,8] Furthermore, we found that there was no difference between the two strategies regarding long-term cardiac mortality which was not reported in prior studies.

Previous meta-analyses concluded that the risk of MI was comparable between the two revascularization approaches,[5,7,8] whereas Athappan, et al.[9] reported that there was a trend in favor of CABG regard as the lower risk of MI at 1 year, 2 years and 3 years. Although with statistical heterogeneity, the occurrence of long-term MI also showed a trend towards a lower risk in patients received CAGB in the present study. Nonetheless, the result should be interpreted with caution as no difference was found in RCTs. The predominantly used first-generation DES and the insufficiency antiplatelet therapies may have contributed to this finding. Recently, Palmerini, et al.[29] has demonstrated that newer-generation DES, especially cobalt-chromium everolimus-eluting stents, can reduce stent thrombosis as well as MI in comparison with first-generation DES. Therefore, the introduction of newer-generation DES and more potent antiplatelet therapies will likely reduce the occurrence of MI for patients received PCI.

In the current study, the long-term risk of stroke was reported to be comparable between the two groups which was consistent with other studies.[7,8] Nonetheless, the rate of stroke in the CABG group was reported to be significantly more frequent in adjusted observational studies. Notably, off-pump CABG could reduce the incidence of adverse neurological sequelae in contrast with cardiopulmonary bypass.[30] In addition, the lower incidence of dual antiplatelet therapy after revascularization with CABG might have resulted in this result. Overall, off-pump technique and dual antiplatelet therapy should be applied to reduce the risk of stroke for patients received CABG.

Over the past few years, CABG has improved the outcomes by the adaption of off-pump technique and arterial grafting. The internal mammary arteries have been widely used as the conduit to the left anterior descending coronary artery due to its long-term patency.[31] Interestingly, 92.5% of patients received a left internal mammary artery to left anterior descending coronary artery graft and complete artery grafting was performed in 53.6% of patients treated with CABG in our meta-analysis. Furthermore, the left internal mammary artery clearly exhibited less downstream coronary disease progression in the left anterior descending coronary artery compared with DES.[32]

First-generation DES was used in most of the studies, while it has been postulated that newer-generation DES with novel stent materials, platforms, as well as more bio-compatible polymers could reduce the incidence of revascularization.[33] With the development of the stent design, the gap will be narrowed between the two strategies. Furthermore, it should be noted that routine angiographic follow-up was performed to detect early left main in-stent restenosis rather than clinically driven in most of the studies, which may cause higher rate of revascularization in the DES group. For patients treated with CABG, clinical symptoms...
may not occur with graft occlusion if the blood to left ventricle myocardium was partly supplied through the native vessel, which may underestimate the repeat revascularization discrepancy.

IVUS plays an important role in assessing lesion severity, selecting treatment strategy, optimizing stent implantation and subsequently obtaining better clinical and angiographic results.[34] Furthermore, previous studies have demonstrated intravascular ultrasound-guided DES implantation is associated with a greater benefit in patients with complex lesions such as bifurcations and ULMCA disease[35] in that it supplies beneficial effect on stent expansion in complex settings. Although optical coherence tomography with high resolution has emerged as an alternative imaging modality in suitable patients, it is challenging to create a blood-free environment for clear image especially in the left main ostium.[36] Fractional flow reserve is a well-established adjunct for assessing the physiological significance of stenosis. In clinical scenarios, these new interventional techniques should be given a full consideration when performing PCI with DES in ULMCA lesions.

Our meta-analysis presents a number of limitations that cannot be ignored. First, this study included both, RCTs and adjusted observational studies which can introduce a potential bias. Second, the definition of clinical endpoints slightly differed across the individual trials, although no signs of heterogeneity were observed for the primary endpoint. In fact, stratified analysis limited to more homogeneous subgroups of patients was performed and random effects model was used to account for the heterogeneity. Third, the duration of follow-up across trials was variable, and subset analysis (≥ 5 years) was performed. Fourth, different types of DES in the various trials had become an important source of heterogeneity. Although first-generation DES was predominantly applied, newer-generation DES was used in some lesions. Among the CABG strategies, the rates of left internal mammary artery to left anterior descending coronary artery graft adaption, complete artery grafting and cardiopulmonary bypass adaption were different across the studies. Fifth, subset analyses to evaluate the effect of SYNTAX score on clinical endpoints were performed in our study. Nevertheless, available data was scarce and incomplete reporting may result in underpowered analyses for certain outcomes.

In conclusion, the current meta-analysis shows that treatment with DES appears to be as safe as CABG for ULMCA disease at long-term follow up, although with higher risk of repeat revascularization. In addition, PCI with DES could be an alternative interventional strategy to CABG for ULMCA lesions with low to intermediate anatomic complexity. More large-scale RCTs with long-term outcomes are needed.

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