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Is off-pump coronary artery bypass grafting superior to drug-eluting stents for the treatment of coronary artery disease? A meta-analysis of randomized and nonrandomized studies ☆

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ABSTRACT

Background: As drug-eluting stent (DES) has almost overcome the disadvantage of frequent restenosis, off-pump coronary artery bypass grafting (OPCAB) has been introduced to avoid complications of cardiopulmonary bypass. However, which approach may promise better outcomes for patients with coronary artery disease remains controversial.

Methods: Three databases were searched. The outcomes of interest were major adverse cardiac and cerebrovascular events (MACCE), all-cause death, target vessel revascularization (TVR), repeat revascularization (RRV), myocardial infarction (MI), and cerebrovascular events (CVE). The relative risk (RR) was calculated as the summary statistic.

Results: 11,452 patients from 22 studies were included, of which 4949 patients underwent OPCAB and 6503 patients received DES. The cumulative rates of MACCE (RR [95% CI] = 0.43 [0.34, 0.54], $P < 0.00001$), all-cause death (RR [95% CI] = 0.56 [0.33, 0.96], $P = 0.03$), TVR (RR [95% CI] = 0.33 [0.21, 0.53], $P < 0.00001$), RRV (RR [95% CI] = 0.22 [0.11, 0.42], $P < 0.00001$) and MI (RR [95% CI] = 0.13 [0.05, 0.29], $P < 0.00001$) at 3 years were all lower in OPCAB group. The incidences of in-hospital death (RR [95% CI] = 1.31 [0.81, 2.13], $P = 0.27$) and MI (RR [95% CI] = 1.03 [0.60, 1.78], $P = 0.92$) were not different between groups, but the rate of in-hospital CVE was lower (RR [95% CI] = 2.6355 [1.0033, 6.9228], $P = 0.05$) in DES group.

Conclusions: OPCAB presents better long-term outcomes of MACCE, all-cause mortality, TVR, RRV and MI but uncertain outcome of postoperative CVE without influencing the incidences of in-hospital death and MI.

1. Introduction

According to the World Health Organization (WHO), there're more than 7 million deaths each year attributed to coronary artery disease (CAD) worldwide [1]. Each year in America, 635,000 people will have a new coronary attack, 280,000 will have a recurrent attack, and an additional 150,000 silent first myocardial infarctions will occur, which means approximately every 34 s, an American will have a coronary event, and approximately every minute, someone will die of one [2]. On the other hand, it's estimated that 20,000–40,000 individuals of the population per million suffer from angina in most European countries [3].

Coronary artery bypass grafting (CABG) still remains superior to percutaneous coronary intervention (PCI) in treating stable ischemic heart disease according to guidelines written by the American Heart Association (AHA) [4] and the European Society of Cardiology (ESC) [3] because of their different levels of evidence. However, PCI has become the key treatment for ST-elevation myocardial infarction (STEMI) according to the guidelines [5,6], and urgent CABG rather than PCI is only recommended when patients with STEMI and coronary anatomy not amenable to PCI have ongoing or recurrent ischemia, cardiogenic shock, severe heart failure (HF), other high-risk features, or mechanical defects, mainly due to its need for more preoperative preparation [5,6].

Ever since the technology of percutaneous transluminal coronary angioplasty (PTCA) was introduced in 1977 [7], the high rate of restenosis has always been its biggest problem that kept itself from replacing CABG in treating CAD, which in turn encouraged the development of bare metal

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stent (BMS) [8] and drug eluting stent (DES) [9] thereafter. According to the latest outcome of the SYNTAX trial, PCI with the first-generation paclitaxel-eluting stent (PES) seems to be an acceptable alternative for patients with less complex disease (low SYNTAX scores) or left main coronary disease (low or intermediate SYNTAX scores) [10]. As it's minimally invasive and more easily to be accepted by patients at almost the same curative effect level when compared with the conventional CABG, the latter one seems to be challenged. On the other hand, especially for the most benefits of the high-risk people, in order to avoid the complications of cardiopulmonary bypass (CPB) which includes the metabolic acidosis, electrolyte disturbances, coagulation dysfunction, brain damage, cognitive abnormalities, kidney injury and so on, off-pump coronary artery bypass grafting (OPCAB) was first introduced in 1960s [11]. With the development of the minimally invasive technology for surgery, minimally invasive CABG without CPB using an anterolateral minithoracotomy [12–14] and total endoscopic computer enhanced CABG [15,16] were developed one after another. Then reasonably, comparison of the novel OPCAB and the conventional on-pump CABG has become one of the most attractive research topics in the area of therapeutic strategy for CAD. It was demonstrated that OPCAB might reduce the incidence of post-operative stroke compared with the conventional CABG [17], especially in high-risk patients [18], while not significantly reduce the incidence of short-term [17,18] and long-term [18] all-cause mortality and post-operative myocardial infarction [17]. By this taken, there seems to be a trend that OPCAB may take the place of the conventional CABG or at least be another effective alternative. However, there have been few registered clinical trials comparing OPCAB and PCI with DES for treating patients with CAD. To date, several observational studies have been done, which aimed specifically to compare these two different means, but no consensuses on the outcomes of OPCAB and DES have been established to our knowledge. Furthermore, according to the results of the SYNTAX trial mentioned above, the rates of death and myocardial infarction were similar between CABG and PES at 12 months, while stroke was significantly more likely to occur with CABG (85% on-pump) [19]. Considering the comparison results of on-pump and off-pump CABG mentioned above, whether the incidence of post-operative stroke in OPCAB treated patients is similar to that in DES treated patients remains unclear.

2. Methods

2.1. Strategy for literature search

To achieve eligible evidence, MEDLINE (PubMed interface), Embase and the Cochrane Library were searched without any restrictions on publication status, type, date or language. The following terms were used in our search: "off(−)pump", "OPCAB", "off-pump bilateral internal thoracic arterial grafting", "BITA", "minimally invasive direct coronary artery bypass", "MIDCAB", "beating heart surgery", "octopus", "off-pump internal thoracic artery", "without extra-corporeal circulation", "drug(−)eluting stent(s)", "DES(s)", "sirolimus-eluting stent", "SES", "paclitaxel-eluting stent", "Cypher", "Taxus", "everolimus-eluting stent", "EES", "limus-eluting stent", "LES", "Resolute zotarolimus-eluting stent", "R-ZES", "Endeavor zotarolimus-eluting stent", "E-ZES", "biolimus A9-eluting stent", "novolimus-eluting stent", "pimecrolimus-eluting stent", "cobalt-chromium everolimus eluting stent", "CoCr-EES", "Xience V". The last search was conducted on August 24th, 2013. Details for search strategy were presented in Appendix A.

2.2. Study selection

The major inclusion criteria were as follows: (i) adult patients diagnosed with single- or multi-vessel CAD suitable for revascularization with either OPCAB or DES; (ii) assessing OPCAB versus DES specifically, or CABG versus PCI with outcome details of both OPCAB and DES; (iii) reporting at least one pertinent clinical outcome of short-term, mid-term or long-term follow-up; and (iv) containing original data sufficient for calculating the hazard ratio (HR) or *P* value. The included studies should be published in English, while with no restrictions on publication types.

Studies were excluded according to the following criteria: (i) not reporting the outcomes of both OPCAB and DES simultaneously; (ii) irretrievable or insufficient data for statistical analysis; (iii) duplication; and (iv) unavailable full text of original articles.

2.3. Outcomes and data extraction

The outcomes of interest included target vessel revascularization (TVR), repeat revascularization (RRV), major adverse cardiac and cerebrovascular events (MACCE), all-cause death, cardiac death (also called as cardiovascular death), myocardial infarction (MI) and cerebrovascular events (CVE). TVR was defined as any repeat revascularization performed on initially treated vessels including target lesion revascularization (TLR) and new lesion revascularization within the target vessels, while RRV consisted of TVR and revascularization performed on new lesions of non-target vessels (non-TVR). MACCE included death of any cause, nonfatal MI, CVE, and repeat revascularization by percutaneous intervention or surgery. Time points for analysis were in-hospital, 30 days, 12 months, 2 years, 3 years and 5 years, as there were few studies reporting outcomes at 4 years. Subgroup analyses divided by the design of studies were performed.

Two investigators (L.D. and N.X.) reviewed all the references achieved through literature search independently for eligible studies at the level of title and/or abstract, and documented disagreements were solved through discussion with a third reviewer (W.W.). In addition, the related meta-analyses and reviews within the search results were further investigated at full-text level to achieve the possible hidden data.

The details of outcomes at established time points from these eligible studies were extracted by using a certain kind of spreadsheet that we developed to improve the efficiency of data extraction and avoid possible mistakes. Besides the outcomes, basic information was extracted as follows: first author, affiliation, published date, patient enrollment period, co-morbid conditions, CAD types, mean age, intervention details and follow-up duration.

2.4. Quality assessment

Methodological quality of the included studies was assessed independently by the two investigators mentioned above. For non-randomized cohort studies, the Newcastle–Ottawa scale (NOS) [20], a rating system consisted of three domains: selection, comparability and outcome, was used. Total score achieved from each section (selection 0–4, comparability 0–2, and outcome 0–3) ranged from 0 star to 9 stars, which was positively correlated with the study's quality. Studies awarded with more than 5 stars were considered to be of acceptable quality. See the detailed scores of the included studies in the table from Appendix B. Quality evaluation of the included randomized controlled trials (RCTs) was performed according to the Cochrane Collaboration's tool for assessing risk of bias (5.1.0) [21] with the following methodological items: random of sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other potential source of bias. Each item was classified as low risk, high risk, or unclear, which determined the general quality when taken together. The risk of bias graph and summary was presented in the figure from Appendix C. Disagreements were also resolved through discussion with the third reviewer.

2.5. Statistical analysis

Outcomes of interest in this study were all treated as dichotomous variables, and the relative risk (RR) and 95% confidence interval (95% CI) were used as the summary statistics to combine the incidence of these outcomes at each time point, respectively. Heterogeneity was measured by using the chi-squared test and calculating the I^2 statistic, which estimates the percentage of total variation across studies that is due to heterogeneity rather than chance. Significant heterogeneity was considered when $P_{het} \leq 0.1$ and $I^2 > 50\%$. In order to identify sources of heterogeneity, sensitivity analyses were performed by deselecting studies one by one to detect the influence of each study on I^2 and the pooled RR. The fixed effects model of Mantel–Haenszel method was preferred to calculate the pooled RR with acceptable heterogeneity ($I^2 \leq 50\%$), while the random effects model was used with substantial heterogeneity. Forrest plots were presented for overall impression of the contribution of each study and the pooled statistic. Funnel plots were generated to evaluate publication bias visually and Egger's test was used for statistical assessment. We were unable to conduct specific analyses considering confounding factors because original data were unavailable. All *P* values were 2-sided, of which except P_{het} the significance level was set at 0.05. Outcome combining analyses and related plots were managed by Review Manager version 5.2.6 (Cochrane Collaboration) and Egger's test was performed with Stata/SE version 12.0 (Stata Corp LP).

This meta-analysis was conducted in compliance with recommendations from PRISMA (preferred reporting items for systematic reviews and meta-analyses) [22].

3. Results

3.1. Eligible studies

As shown in Fig. 1, a total of 582 records were yielded by our search strategy. After eliminating 128 duplicate records, 454 records were screened at the level of title and abstract. Then 46 publications including