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Coronary artery bypass graft surgery versus percutaneous coronary intervention with drug-eluting stents for left main coronary artery disease: A meta-analysis of randomized trials

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ABSTRACT

Background: Despite several clinical studies, efficacy of coronary artery bypass grafting (CABG) surgery versus percutaneous coronary intervention (PCI) in patients with left main (LM) disease remains controversial. The objective of this meta-analysis of randomized trials was to evaluate the clinical outcome of CABG versus PCI with drug-eluting stents in LM coronary disease.
Methods: We systematically searched online databases up to March 2017 for randomized trials comparing CABG to PCI with drug-eluting stents. We calculated odds ratios (ORs) and 95% confidence intervals (CIs).
Results: We included data from 5 randomized trials and 4595 patients. At 30 days, CABG was associated with higher stroke (OR 2.54 [95% CI, 1.02–6.31]) and periprocedural myocardial infarction (OR 1.45 [95% CI, 1.00–2.10]), with no other significant differences compared to PCI. At 1 year, CABG reduced repeat revascularization (OR 0.56 [95% CI, 0.40–0.77]), but increased stroke (OR 5.11 [95% CI, 1.62–16.12]). At 3–5 years, CABG reduced repeat revascularization (OR 0.55 [95% CI, 0.45–0.67]) and non-periprocedural myocardial infarction (OR 0.45 [95% CI, 0.29–0.70]), without significant differences on other outcomes.
Conclusions: From the present updated meta-analysis of available studies on LM coronary disease treatment, there were no differences in mortality, myocardial infarction, and stroke rate at 3–5 years follow-up after CABG or PCI, but CABG decreased the rate of repeat revascularization and non-periprocedural infarction. However, at short-term follow-up, CABG showed higher rate of stroke and periprocedural myocardial infarction, but these effects attenuated over time. These findings merit further investigation at longer follow-up.

1. Introduction

Left main (LM) coronary artery disease is an anatomical narrowing of the lumen >50%. Left main disease is found in 4–6% of all patients who undergo coronary angiography and is associated with high-risk life-threatening events as myocardial infarction, sudden death, and left ventricular dysfunction [1,2]. Current guidelines recommend surgical revascularization with coronary-artery bypass grafting (CABG) as primary treatment [3,4]. However, since the introduction of percutaneous coronary intervention (PCI) with drug-eluting stents (DES), the most appropriate treatment for LM disease turned into considerable discussion. Some studies and randomized trials (RTs) have shown that PCI with DES and CABG have similar incidence of death, myocardial infarction (MI), and stroke [5–8]. On the other hand, different large registries and RTs suggested that CABG might provide a better clinical outcome for the treatment of the LM coronary disease compared to the PCI [9–11], but other series also showed opposite results in favor for PCI [12]. Because of these contrasting results and equivocal evidences available in the current literature, we performed a systematic review and meta-analysis of RTs in order to compare the effects of CABG and PCI with DES on mortality, MI, stroke, and repeat revascularization in patients with LM coronary disease.

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2. Methods

We conducted a systematic review and meta-analysis of randomized trials in compliance to the Cochrane methodology [13] and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [14], and according to a pre-published protocol on PROSPERO database (CRD42016050823). A complete PRISMA 2009 checklist is provided in the supplement (Supplementary material 1). This study had no funding and authors did not have any conflicts of interest.

2.1. Search strategy

Two trained investigators (AP, EAM) independently searched PubMed, the Cochrane Central Register of clinical trials, and EMBASE (last updated on March 1st, 2017) for appropriate articles. The full PubMed search strategy is presented in the supplementary material (Supplementary material 2). The search strategy aimed to include any RT ever performed comparing CABG surgery and PCI with DES in adult humans suffering from significant LM coronary disease. No language restriction was enforced. In addition, references of eligible studies and identified reviews were searched by hand.

2.2. Study selection

Records obtained from searches were first independently examined at an abstract level by two trained investigators (AP and EAM). Following the initial abstract assessment, all identified studies were acquired as full-text. Eligible studies met the following PICOS criteria: 1) Population: adult cardiac surgery patients; 2) Intervention: CABG surgery; 3) Comparison intervention: PCI with drug-eluting stents; 4) Outcome: any primary or secondary outcome of the present systematic review (see below); 5) Study design: randomized clinical trial. The exclusion criteria were: overlapping populations and pediatric studies. Two investigators (AP and EAM) independently assessed selected studies for the final analysis, with eventual divergences resolved by consensus.

2.3. Data abstraction and study characteristics and quality

Two authors (AP and EAM) independently extracted data from studies and entered them into a predefined database. Discrepancies were identified and resolved through consensus. We collected potential sources of significant clinical heterogeneity such as publication year, inclusion and exclusion criteria, primary endpoints of each study, age, sex, prevalence of diabetes, proportion of patients with acute coronary syndrome, mean EuroSCORE, mean SYNTAX score, prevalence of distal LM lesions, data on the predefined outcomes, and information necessary to assess risk of bias.

The predefined primary outcomes of the study were: all-cause mortality, myocardial infarction, stroke, and repeat revascularization. The predefined secondary outcomes were: cardiovascular mortality, periprocedural myocardial infarction, and non-periprocedural myocardial infarction. The predefined follow-ups were: longest follow-up reported (minimum ≥2 years), 1-year, and 30-days. The data extraction followed the intention-to-treat basis whenever possible.

We used the Cochrane method [13,15] to evaluate the methodological quality of each included trials. Each trial was judged to be of low, unclear, or high risk of bias. Due to the nature of the interventions, all studies are not blinded; we considered the blinding not crucial for the outcome. The quality of the evidence (QoE) for each outcome was summarized with GRADE (Grading of Recommendations Assessment, Development, and Evaluation) method [13,15,16].

2.4. Statistical analysis

We calculated the odds ratio (OR) with 95% confidence interval (CI) for each outcome and the p value for the comparison between the groups. A p value of <0.05 was considered statistically significant. Heterogeneity was explored by the Cochran Q statistic and characterized with I^2. We used a fixed-effect model for meta-analysis in the absence of significant heterogeneity, defined as p value >0.10 and $I^2 <50\%$. In case of significant heterogeneity, we employed the random-effects model except if few trials dominate the available evidence or if publication bias was present [13].

We performed predefined sensitivity analyses for each outcome to explore the robustness of the results. Finally, due to the lack of individual patient data and subgroup reports, we performed post-hoc subgroup analysis to assess the effect of CABG versus PCI on major adverse cardiac or cerebrovascular events (MACCE, major adverse cerebrovascular or cardiovascular events, a combined endpoint of all cause mortality, myocardial infarction, and stroke) in patients with and without diabetes or presenting a SYNTAX score ≥33 or <33 points [17]. Due to the small number of the trials included, we did not perform the predefined meta-regression analyses and we did not assess publication bias using funnel plot [13]. The meta-analysis was performed using Review Manager (RevMan [Computer program], Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

3. Results

3.1. Study characteristics

In total, 2425 references were examined. The PRISMA study flow chart and major exclusions are presented in the supplement (Supplementary material 3). Finally, 5 randomized clinical trials [1,5,9,18,19] (4595 randomized patients) and 9 publications [1,5,8,9,18–22] were included in the analysis.

Eligible trials included from 201 to 1905 patients and were all multicenter.

Two trials employed sirolimus-eluting stents [18,19], 1 trial paclitaxel-Eluting Stents [1], 1 trial mainly biolimus-eluting stent [9], and 1 trial everolimus-eluting stents [5].

All the trials but one [18] were industry-sponsored. All randomized trials were rated at unclear risk of bias (Supplementary material 4).

Characteristics of the trials are listed in Table 1 and in the supplement (Supplementary material 5).

3.2. Thirty-days follow-up

CABG surgery compared to PCI was associated with higher stroke (OR 2.54 [95% CI, 1.02 to 6.31], p 0.05; QoE: moderate) and no significant differences in mortality (OR 1.54 [95% CI, 0.72, 3.30], p 0.27; QoE: high), MI (OR 1.33 [95% CI, 0.94, 1.88], p 0.11; QoE: moderate), and repeat vascularization (OR 1.67 [95% CI, 0.88, 3.18], p 0.12; QoE: high) (Fig. 1). Periprocedural MI was higher with CABG (OR 1.45 [95% CI, 1.00, 2.10], p 0.05; QoE: low) and no significant difference in non-periprocedural MI was present (OR 0.53 [95% CI, 0.15, 1.96], p 0.35; QoE: low) (Supplementary material 6).

3.3. One-year follow-up

CABG reduced need of repeat revascularization (OR 0.56 [95% CI, 0.40, 0.77], p 0.0004; QoE: high), but increased stroke (OR 5.11 [95% CI, 1.62, 16.12], p 0.005; QoE: high), with no significant difference on mortality (OR 1.44 [95% CI, 0.91, 2.27], p 0.12; QoE: moderate) and myocardial infarction (OR 0.90 [95% CI, 0.59, 1.36], p 0.62; QoE: high) compared to PCI (Fig. 2).

3.4. Three- and five-years follow-up

CABG reduced the need of repeat revascularization (OR 0.55 [95% CI, 0.45, 0.67], $p < 0.00001$; QoE: high) with no significant differences in mortality (OR 0.93 [95% CI, 0.74, 1.16], p 0.51; QoE: high), cardiovascular mortality (OR 0.96 [95% CI, 0.72, 1.29]; QoE: moderate), MI (OR 0.81 [95% CI, 0.63, 1.03], p 0.09; QoE: moderate), and stroke (OR 1.14 [95% CI, 0.76, 1.73], p 0.53; QoE: high) were present when compared to PCI (Fig. 3). Non-periprocedural MI was lower with CABG (OR 0.45 [95% CI, 0.29, 0.70], p 0.0003; QoE: moderate) and periprocedural MI was non-significantly higher with CABG (OR 1.41 [95% CI, 0.98, 2.03], p 0.06; QoE: low), with 2 trials and 3089 patients included (Supplementary material 6).

3.5. Clinical characteristics and outcomes at long-term follow-up

The rate of MACCE (combined outcome of mortality, myocardial infarction, and stroke) at 3–5 years did not significantly changed in diabetic (OR 1.04 [95% CI, 0.72, 1.51], p 0.82, 655 patients) and non-diabetic patients (OR 1.01 [95% CI, 0.78, 1.30], p 0.94, 1917 patients) with 2 trials included [1,5] (p for interaction 0.89).

The rate of MACE did not change significantly in patients presenting a SYNTAX score ≥33 (OR 0.79 [95% CI, 0.55, 1.14], p 0.21, 764 patients) or <33 (OR 1.17 [95% CI, 0.90, 1.52], p 0.23, 1811 patients) with 2 trials included [1,5] (p for interaction 0.09).

4. Discussion

The main findings of the present study is that in a population of relatively young patients, with average intermediate complexity lesions, eligible both for PCI and CABG according to the heart-team evaluation, there were no differences in mortality, MI, and stroke between CABG

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