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Prolonged effectiveness of coronary artery bypass surgery versus drug-eluting stents in diabetics with multi-vessel disease: An updated systematic review and meta-analysis ☆,☆☆

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ABSTRACT

Background: Currently, the appropriateness of percutaneous coronary intervention (PCI) using drug-eluting stents (DES) versus coronary artery bypass grafting (CABG) for patients with diabetes (DM) and multi-vessel disease (MVD) is uncertain due to limited evidence from few randomised controlled trials (RCTs). We aimed to compare the clinical effectiveness of CABG versus PCI-DES in DM-MVD patients using an evidence-based approach.

Methods: A systematic review and meta-analyses were conducted to compare the risk of all-cause mortality, myocardial infarction (MI), repeat revascularisation, cerebrovascular events (CVE), and major adverse cardiac or cerebrovascular events (MACCE).

Results: A total of 1,837 and 3,052 DM-MVD patients were pooled from four RCTs (FREEDOM, SYNTAX, VA CARDS, and CARDia) and five non-randomised studies. At mean follow-up of 3 years, CABG compared with PCI-DES was associated with a lower risk of all-cause mortality and MI in RCTs. By contrast, no significant differences were observed in the mean 3.5-year risk of all-cause mortality and MI in non-randomised trials. However, the risk of repeat revascularisations following PCI-DES compared with CABG was 2.3 (95% CI = 1.8–2.8) and 3.0 (2.3–4.2)-folds higher in RCTs and non-randomised trials, respectively. Accordingly, the risk of MACCE at 3 years following CABG compared with PCI-DES was lower in both RCTs and non-randomised trials [0.65 (: 0.55–0.77); and 0.77 (0.60–0.98), respectively].

Conclusions: Based on our pooled results, we recommend CABG compared with PCI-DES for patients with DM-MVD. Although non-randomised trials suggest no additional survival-, MI-, and CVE- benefit from CABG over PCI-DES, these results should be interpreted with care.

1. Introduction

Type II diabetes mellitus (DM) is a leading predictor of development of atherosclerosis and a key contributor to the rising burden from cardiovascular disease [1]. Approximately 285 million of world's population are estimated to be living with this condition [Europe: 6.9%; North America: 10.2%; South Asia: 7.6%; Eastern Mediterranean and Middle-East: 9.3%], and this figure is expected to double by 2030 [2]. In particular, patients with co-existing DM and multi-vessel coronary artery disease (MVD) are at higher risk of mortality and morbidity following invasive treatment for coronary artery disease. Globally, the DM-subset alone makes up around 25 per cent of the all patients admitted for coronary revascularisation procedures [3].

Currently, coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) using drug-eluting stents (DES) offer two mechanisms of revascularisation for patients with coronary artery disease. Historically, CABG was known to offer better outcomes compared with PCI in patients with DM and MVD [3–5]. In fact, the BARI trial [6] has been the first study to report a significant survival benefit from

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CABG compared with PCI in diabetic patients in the bare-metal stent (BMS) era. However, a similar effect was not confirmed through large non-randomised registry studies [7]. Accordingly, some guidelines identify DM as an indication for surgery in patients with advanced MVD [8], while others acknowledges the gap in evidence concerning the effectiveness of surgery versus PCI in the drug-eluting stent (DES) era [9,10].

Although the early-generation stents such as BMS carried a high-risk of restenosis, this shortcoming was later ameliorated by the advent of DES, and the introduction of dual-antiplatelet therapy. However, until recently, the evidence base for the effectiveness of CABG versus PCI-DES was limited among DM-MVD patients. Between 2010 and 2013, four randomised controlled trials (RCTs) emerged with evidence on effectiveness of CABG versus PCI using DES in the DM-MVD subset [11–14]. However, two out of the four recent trials were too underpowered to demonstrate effectiveness [12,13]. This study therefore aims to synthesise evidence to compare the clinical effectiveness of CABG versus PCI-DES in the DM-MVD patient subset and the contrast results observed in randomised versus non-randomised trials.

2. Materials and methods

A meta-analysis was undertaken to compare the prolonged effectiveness of CABG versus PCI-DES in DM-MVD patients. Studies that complied with following pre-specified criteria were included: (i) comparative effectiveness studies of CABG versus PCI using DES; (ii) published data adult patients with pre-existing DM and MVD; (iii) all RCTs meeting the above criteria, or prospective observational studies with more than 12-months follow-up; (iv) reported outcomes in one or more of the following clinical end-points: all-cause mortality, myocardial infarction (MI), cerebrovascular events (CVE), repeat revascularisation, or major adverse cardiac or CVE (MACCE); and (v) were published in the English language. We adhered to methods outlined by the Cochrane Collaboration [15] and the guidelines set out by the 'Meta-analysis of Observational Studies in Epidemiology' group [16].

A search strategy was developed to identify all relevant literature meeting the pre-specified criteria. An electronic search for articles published to date (10th March 2013) was conducted in MEDLINE, Embase, PubMed, CINAHL, and the Cochrane databases. Keywords and medical subject headings (MeSH) were used for specific searches. In each database, the MeSH terms "stents" or "angioplasty, transluminal, percutaneous coronary," or "drug-eluting stents" were combined with the MeSH term "myocardial ischaemia". These terms were then combined with MeSH terms "coronary artery bypass" and "diabetes mellitus." The keyword terms corresponding to each of these MeSH terms were also mapped in a similar manner. The search was further refined by searching for the following terms on the title or abstract fields of the retrieved citations: "drug-eluting stents" or "sirolimus-eluting stents" or "paclitaxel-eluting stents"; "bypass" or "surgery" or "revascularisation" or "CABG" or "off-pump.

Following the retrieval of results to a citation manager from each database, duplicates were identified and removed. The abstracts of the remaining records were then systematically screened for relevance by three investigators (TVA, ZA, and CHY). Two investigators (TVA and ZA) participated in the extraction of data including numbers of observed outcomes, sample sizes, and study characteristics from the selected articles. Where there were disagreements in data extraction the investigators met to discuss and resolve issues.

2.1. Statistical analysis

We used both fixed- and random-effects models to analyse aggregate data from selected studies. Where significant study heterogeneity was detected, pooled estimates were derived from the random-effects model (REM). Pooled relative risks (RR) and 95% confidence intervals (CIs) were used to measure the association between clinical end points of interest and type of treatment, CABG or DES. We evaluated heterogeneity by calculating the Cochrane's Q (x^2 test) and I^2 statistics. An I^2 of greater than 50% or significant x^2 test ($p < 0.05$) was desired. A regression-based test for publication bias was not carried out due to inclusion of less than 10 trials in our study [15,17,18]. Sensitivity analysis was conducted by eliminating one study at a time from the pooled analyses, in order to measure whether any particular study disproportionately influenced the size of effect. Our meta-analysis was carried out using Stata/IC version 11 (Windows).

3. Results

3.1. Study selection

The manner in which we conducted our systematic literature search and study selection is highlighted in Fig. 1 and Appendix 1 (supplementary material). Overall, 222 citations were retrieved from five medical databases to a citation library, where 92 were identified as duplicate records. The remaining 130 citations were then observed for appropriateness for inclusion. By observation of abstracts alone, 30 records were shortlisted for retrieval. Upon retrieval however, 18 studies were excluded for the following reasons: one article was published in Chinese language; one article included patients receiving bare-metal stents (BMS); five articles did not have adequate data on the DM subset; one article included DM-MVD patients with left-main coronary artery disease (LMCAD) exclusively; three articles did not have adequate data specific to the MVD subset; one article investigated patients with single vessel disease only; one article included data from pre-DES era; one article included patients with diabetic retinopathy only; and four studies (non-randomised) conducted 12-month follow-up only. Furthermore, prior studies from the Asan Medical Center (Seoul, Korea) [two] [19] and the Arterial Revascularisation Therapies Study–Part II (ARTS-II) [20] [one] were removed. In the end, we identified nine studies, which included four RCTs [11–14], and five prospective observational reports [19–23] that matched our pre-specified inclusion criteria.

We considered pooled outcomes from 2,393 patients who underwent CABG [880 from RCTs; and 1513 from non-randomised studies] and 2,496 patients who underwent PCI-DES [957 from RCTs; and 1539 from non-randomised studies]. The clinical and demographical characteristics of each study as well as matching criteria are reported in Table 1. Of note, the average length of follow-up in our meta-analysis of observational studies corresponded to 3.5 years [between 24 and 60 months of maximum follow-up], whereas the mean follow-up in our meta-analysis RCTs was 3.0 years [between 12 and 60 months of maximum follow-up].

3.2. Clinical outcomes

We focussed on four clinical end-points (all-cause mortality, MI, repeat revascularisation, and cerebrovascular accident) and two combined events (composite outcome of all-cause mortality, MI, or CVE; and MACCE). The forest plots of these pooled analyses are illustrated in Figs. 2, 3, and 4. The definitions of each end point as described in each individual study are listed in Appendix II (supplementary material). Heterogeneity was not statistically significant for the majority of the above end points analysed ($p > 0.05$), except the pooled risk for MI and repeat-revascularisation from RCTs ($p < 0.05$).

3.2.1. Mortality

All included studies reported data on all-cause mortality. A significant survival benefit following CABG compared with PCI was observed in our meta-analysis of RCTs at mean 3.0-year follow-up (RR = 0.62; 95% CI = 0.42 to 0.94). However, we found no significant difference in mortality at mean 3.5 years post-revascularisation in the meta-analysis of non-randomised studies (RR = 1.14; 95% CI = 0.86 to 1.50) (Fig. 2.).

3.2.2. MI

All included RCTs and four non-randomised studies reported data on non-fatal MI. Again, no significant difference was observed among the two revascularisation strategies in the pooled analysis of non-randomised studies at mean follow-up (RR = 1.06; 95% CI = 0.49 to 2.29) (Fig. 2). However, the meta-analysis of RCTs found significantly lower risk of MI in patients who underwent CABG compared with PCI-DES (RR = 0.61; 95% CI = 0.47 to 0.80).

3.2.3. Repeat revascularisation

All included studies reported data on repeat revascularisation. Both non-randomised studies and RCTs demonstrated that CABG was associated with significantly lower risk of repeat revascularisation compared with PCI-DES (RR = 0.33; 95% CI = 0.24 to 0.44, and RR = 0.44; 95% CI = 0.35 and 0.56, respectively) (Fig. 3).