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Long-term mortality following PCI with DES compared with CABG for multivessel and left main disease: a meta-analysis

Short title: Meta-analysis of long-term mortality after PCI vs CABG

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**Introduction**

Several randomized controlled trials (RCTs) compared percutaneous coronary intervention (PCI) with coronary artery bypass grafting (CABG) for the treatment of coronary artery disease (CAD). CABG was associated with long-term survival benefit as compared to PCI with bare metal stent. Successive advancements in the interventional cardiology made such conclusions no longer valid. PCI with drug eluting stents (PCI-DES) showed lower rates of major adverse cardiovascular events. Tested against CABG resulted in similar safety results but mainly in short-/mid-term follow-up. Whether this persist in the long-term ($\geq 5$ years) remains inconclusive. Also, the available evidence is conflicting in different clinical scenarios of left main disease (LMD) vs multivessel disease (MVD). Current report assesses the mortality risk following PCI-DES as compared to CABG separately in LMD and MVD based on the RCT with long-term ($\geq 5$ years) follow-up.

**Methods**

A meta-analysis was performed in accordance to PRISMA statement. Online databases (PubMed, MEDLINE, EMBASE, CENTRAL, Web of Science) were screened until March 31st, 2020. RCT or follow-up study of RCT comparing PCI-DES vs CABG in the LMD and/or MVD settings and reporting crude mortality data over $\geq 5$ years of follow-up were considered eligible. The study was approved by the local ethics committee. Informed consent to participate in the study was not required.

**Statistical analysis.** Pooled odds ratios (ORs) and 95% confidence intervals (95% CIs) of mortality at reported $\geq 5$ years follow-up were calculated using a random effects model with the Mantel-Haenszel method. Heterogeneity was assessed with Cochran’s Q test and publication bias by using a funnel plot with logOR plotted against standard error.
Results and Discussion

Six studies enrolling 7,312 patients [1-6] and meeting inclusion criteria were included. Two studies excluded [2,5] by design patients with previous PCI. Detailed study characteristics are available as Table S1. Three studies focused [1,4,6] on LMD. Two studies focused [3,4] on MVD exclusively and used as a definition of MVD significant stenosis in 2 or more major epicardial vessels involving at least 2 separate coronary artery territories excluding LMD. The SYNTAXES study [5] reported separately on both LMD and three-vessel disease (significant stenosis in vessels supplying all three major epicardial territories excluding LMD) which contributed to the pooled analysis in MVD. Studies which contributed to the analysis of LMD included patients with simultaneous LMD and history of two- or three-vessel disease (Table S1). No signs of publication bias were noted (Figure S1). In total, 3,659 (50.0%) subjects underwent PCI-DES, 3,653 (50.0%) underwent CABG surgery. Patients were stratified to: LMD (4,394 [60.0%]) and MVD (2,918 [40.0%]) subgroups. In the subgroup of LMD, overall mortality was 585/4,394 (13.3%) over 6.83 years of mean weighted follow-up. There was no difference between PCI-DES and CABG with respect to all-cause mortality: OR 1.12; 95%CIs (0.91-1.38); P = 0.30, I² = 25% with corresponding event rates of 14.0% (308/2,197) and 12.6% (277/2,197) for PCI-DES and CABG, respectively (Figure 1). In the subgroup of MVD, overall mortality was 486/2,918 (16.7%) over 8.01 years of mean weighted follow-up. PCI-DES was associated with 44% increase of the mortality odds as compared to CABG: OR 1.44; 95%CIs (1.18-1.76); P < 0.001, I² = 0% with respective event rates of 19.1% (279/1,462) and 14.2% (207/1,456) for PCI-DES and CABG. A difference between subgroup statistical interaction (P_int = 0.09) did not reach statistical significance.

The current meta-analysis is the first to assess long-term (≥ 5 years) mortality between PCI-DES as compared to CABG; with its subgroup design being able to show 44%
relative increase in mortality odds with PCI-DES in the setting of MVD, while equal safety in LMD. Together with nearly significant subgroups interaction, meta-analysis reflects different risk profile between LMD and MVD patients resulting from less or more diffuse CAD. Indeed, the mortality in the PCI-DES arm was 14.0% vs 19.1% depending on the extent of CAD (LMD vs MVD). The mortality rates following CABG remained merely similar (12.6% vs 14.2%). Completeness of revascularization which is less frequently achieved with PCI-DES in MVD disease must had also played a role. Another potentially important feature not yet addressed in neither RCT, is history of PCI; one recent study demonstrated inferior outcomes in patients who underwent PCI prior to CABG [7]. Lastly, coronary complexity is not to be missed; in fact, current ESC/EACTS guidelines [8] indicate that PCI is an appropriate alternative to CABG in LM disease and low-to-intermediate anatomical complexity; on the other hand, among patients with LM disease and high anatomical complexity, the number of patients studied in RCTs is low due to exclusion criteria and recommendation cannot be made for PCI for the moment. Reflecting findings from previous studies [1,4] it becomes apparent that that PCI-DES may be equally safe in the setting of LMD as compared to CABG even in long-term. The above findings are also in line with one recent meta-analysis [9] which found no significant differences between PCI and CABG for the risk of all-cause mortality (relative risk (RR) 1.03, 95% confidence interval (CI) 0.81–1.32; \( P = 0.779 \)) or cardiac death (RR 1.03, 95% CI 0.79–1.34; \( P = 0.817 \)) at mean weighted follow-up of 5.5 years. Yet, in MVD, CABG confers long-term survival benefit over PCI-DES due to higher rates of achieved complete revascularization and this has to be considered when tailoring the therapy for the patient.
References:


Figure 1. Comparison between PCI with DES and CABG with respect to all-cause mortality