**Meta-analysis of Percutaneous Coronary Intervention with Drug Eluting Stent Versus Coronary Artery Bypass Grafting for Isolated Proximal Left Anterior Descending Coronary Disease**

Running title: PCI with DES vs CABG for proximal LAD disease

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**ABSTRACT**

We performed a meta-analysis of the studies comparing the efficacy and safety of coronary artery bypass surgery (CABG) against percutaneous coronary intervention with drug-eluting stents (PCI-DES) among patients with isolated LAD disease.Due to limited randomised trial datatheoptimal revascularisation strategy for patients with isolated LAD disease remains uncertain. Using MEDLINE and EMBASE to source data 11 articles (3 randomized trials and 8 cohort studies) including 5,044 participants were identified. No significant difference in mortality between PCI-DES to CABG (111/2,122 (5.2%) and 120/2,574 (4.7%); RR 1.23;95%CI 0.90-1.69) was detected. For MACE, PCI-DES was associated with significant increase in adverse events (RR 1.41;95%CI 1.03-1.93, 8 studies, 4,230 participants). There were no significant differences in the risk of myocardial infarction (RR 0.86;95%CI 0.58-1.26) or stroke (RR 2.36;95%CI 0.54-10.43) between the two groups. There were 239 TVR events among 2,237 participants in the PCI-DES group (10.7%), and 145 TVR events among 2,793 participants in the CABG group (5.2%) with a significant increase risk of TVR in the PCI group (RR 2.52;95%CI 1.69-3.77, 5,030 participants) compared to CABG. In conclusion, for patients with isolated disease of the LAD, meta-analysis of the available data suggests revascularization with a PCI-DES strategy offers similar mortality, MI and stroke rates to CABG at the expense of increased TVR. Much of the data is derived from registries using first generation DES and further randomized trials with more contemporary platforms are needed.

**Keywords**: percutaneous coronary intervention; drug-eluting stents; coronary artery bypass graft; proximal left anterior descending artery

**Introduction**

The optimal revascularization strategy for patients with isolated disease of the LAD remains uncertain, in part due to the relative lack of high quality published reports.1 At the current time there are only a small number of randomized control trials of percutaneous coronary intervention with drug eluting stents (PCI-DES) vs. coronary artery bypass surgery (CABG) with small sample sizes and divergent results reported. Consequently, most data in support of the guidelines and best practice are derived from a modest number of small registries, and are thus subject to the usual limitations of observational study. Only a single study has been large enough to allow propensity matching in an effort to correct for these confounders, and demonstrated a significant excess of repeat revascularization with PCI.2

Two small meta-analyses comparing PCI-DES vs. CABG have been published previously with inconsistent results reported.3,4 One meta-analysis pooled results from 2 RCTs4 whilst a second undertook a subgroup analysis of 5 studies in which outcomes for PCI-DES were compared to MIDCAB.3 Since the publication of these previous meta-analyses, several other registries and one small RCT have reported. Therefore the aim of the current study was to provide an updated review of the literature comparing the efficacy of coronary artery bypass graft surgery to that of percutaneous coronary intervention with drug-eluting stents amongst patients with isolated proximal left anterior descending artery disease.

**Methods**

We searched MEDLINE and EMBASE on October 2015 using the search terms: (drug eluting stent or DES or percutaneous coronary intervention or PCI) AND (bypass or coronary artery bypass graft or CABG or left internal mammary artery or LIMA) AND (left anterior descending or LAD). The search results were reviewed by two independent judicators (CSK, AN) for studies that met the inclusion criteria and relevant reviews. The studies identified were validated by MAM. The bibliographies of included studies and relevant reviews were screened for additional studies.

We included studies that met the following inclusion criteria:

1. Studies had to have two or more groups with one group having PCI with DES and the other having CABG in participants with isolated proximal LAD disease.
2. Studies had to evaluate one or more of the following outcomes: mortality, myocardial infarction, target vessel revascularization, stroke or a composite cardiovascular outcome including some or all of the above endpoints.

We excluded studies that had multi-vessel disease, studies where PCI was undertaken using bare metal stents, and reviews with no original data. Data was extracted from each study and the data collected included the study design, country, year of study, number of participants, age of participants, percentage of male participants, participant selection criteria, stent type, operation, outcomes, follow-up and results. Quality assessment of the included studies was performed by considering whether the study was prospective, whether the study had more than 100 participants in each treatment arm, whether there were reliable ascertainment of outcomes, whether there was low loss to follow up, whether the randomized studies had no baseline differences between arms, and cohort studies has adjusted for confounders.

Data analysis was performed using Review Manager (Version 5.3.3, Nordic Cochrane Centre, Copenhagen, Demark 2014) to perform random effects meta-analysis using generic inverse variance method. Analysis was stratified by whether the analysis used adjustment for potential confounders or propensity score matching or the studies were unadjusted. Where there were asymmetric 95% confidence intervals for reported estimates we used the absolute larger interval to generate the overall estimate in the pooled results. The I2 statistic was used to assess statistical heterogeneity.

**Results**

Our search yielded 1,617 relevant articles and after screening and reviewing full manuscripts, 11 articles met the inclusion criteria that included 3 randomized trials.2,5-16 The process of study selection is shown in Figure 1.

The study designs and participant characteristics of the included trials are shown in Table 1. There were 3 randomized trials and 8 cohort studies. There were a total of 5,044 participants (range of participants in each study 129 to 1,430) with an average age of 63 years and 72% were male participants. Supplementary Table 1 shows the quality assessment of included studies. There were 3 randomized trials and 4 retrospective cohort studies but the designs of the remaining 4 studies were unclear. The majority of studies had more than 100 participants in each arm except for 4 studies (Blazek 2015, Hong 2005, Thiele 2009 and Ungureanu 2013). Five studies reported reliable methods for ascertaining outcomes (Benedetto 2014, Blazek 2015, Hong 2005, Thiele 2009 and Toutouzas 2007) while the remaining studies did not report how outcomes were ascertained. All 3 randomized trials had similar baseline characteristics among participants and 4 other studies reported some forms of adjustments or propensity score matching.

Study outcomes are listed in Table 2. The risk of mortality with PCI-DES compared to CABG for isolated proximal LAD disease is shown in Figure 2a. There were a total of 111 deaths among 2,122 participants (5.2%) who received PCI with PCI-DES and 120 deaths among 2,574 participants (4.7%) who received CABG from 9 studies. The pooled results suggest no significant difference in mortality comparing PCI-DES to CABG for both adjusted and unadjusted results.

For major adverse cardiovascular events (Figure 2b), PCI-DES was not associated with a significant increase in adverse events with adjustments (RR 1.68; 95%CI 0.97-2.90, 4 studies, 2,515 participants) but there was a statistically significant increase in adverse events overall (RR 1.41;95%CI 1.03-1.93, 8 studies, 4,230 participants). For myocardial infarction, treatment with PCI-DES was associated with 23 events among 1,047 participants (2.2%) while patients who received CABG had 29 events in 869 participants (3.3%). The pooled results suggest no significant difference in myocardial infarction rates between PCI-DES to CABG for both adjusted and unadjusted results.(Figure 3a).

There were a total of 239 TVR events among 2,237 participants in the PCI-DES group (10.7%), and a total of 145 TVR events among 2,793 participants in the CABG group (5.2%). The pooled results of PCI-DES were associated with significant increases in TVR for both adjusted (RR 2.73;95%CI 1.49-4.98, 2,386 participants), unadjusted (RR 2.44 95%CI 1.21-4.89, 2,644 participants) and overall results (RR 2.52;95%CI 1.69-3.77, 5,030 participants) compared to CABG (Figure 3b).

For stroke events there were 2 studies with 9 events in 225 participants in the PCI-DES group (4.0%) and 6 events in 329 participants in the CABG group (1.8%). The pooled results suggest no significant difference for adjusted, unadjusted and overall results (Figure 3c).

Sensitivity analysis considering the effect of study design and use of adjustments, year of publication (mean <2006 or >2006) and studies of only MIDCAB for mortality and MACE (Supplementary Table 2). Among the randomized controlled trials and adjusted or propensity matched results there was no difference between DES and CABG (Supplementary Figure 1a). For MACE, there was greater risk of adverse events with DES but not for randomized trials and unadjusted studies (Supplementary Figure 1b). Further analysis was performed considering older studies (before 2006) and newer studies (after 2006). None of the results were statistically significant (Supplementary Figure 2a and 2b). Additional analysis was undertaken considering studies which only used MIDCAB and results were significant for MACE but not for mortality (Supplementary Figure 3a and 3b).

**Discussion**

In the current study we performed a meta-analysis of 3 randomized trials and 8 cohort studies enrolling 5,044 participants. The results of the analysis suggest revascularization with a PCI-DES strategy offers similar mortality, MI and stroke rates at follow-up compared to CABG but at the expense of increased TVR.

Two meta-analyses including the randomized and observational studies comparing PCI-DES vs. CABG have previously been performed.3,4 One study concluded that the PCI-DES cohort (5 studies; 456 patients) had a higher risk of recurrent angina (risk ratio 3.4, 95% CI: 1.9 to 6.2; *p*< 0.001) and target vessel re-interventions (risk ratio 4.16, 95% CI: 2.7 to 6.6; *p* < 0.001) at midterm follow-up (2-5 years) compared to minimally invasive direct coronary artery bypass graft surgery (MIDCABG).3 The second meta-analysis considered only 2 randomised trials of PCI-DES vs. CABG for proximal LAD disease as part of a larger meta-analysis of stents vs. CABG but reported that the data was insufficient for any firm conclusions to be made (2 studies; 319 patients).4 Since the publication of these earlier meta-analyses, several other registries and one small RCCT have reported and with these included, the present analysis largely confirms these previous studies although with more patients, more robust studies and longer follow-up included.

Of the 5,044 participants included in the current analysis, 448 patients were derived from randomised trials, hence the majority of data were derived from observational registries. In such observational registries (with selection bias present) it might be expected that PCI-DES would perform well against CABG i.e. that patients were selected for PCI on the expectation that outcome would be favourable with more complex lesion subsets more likely to undergo CABG. Despite such selection biases, our results show consistent findings in both registries as well as RCCTs where CABG was consistently superior in terms of TVR. In an attempt to correct for baseline differences in registry patients, a recent study propensity matched 715 pairs of patients who were treated with either PCI-DES or CABG for isolated LAD stenoses between 2008 and 2010.2 Data was derived from the New York CABG and PCI registries. Mortality, MI and stroke were similar at 3-year follow-up between PCI-DES and CABG but despite the apparent contemporary practice (although the type of DES was not specified), repeat target vessel revascularization rates were almost twice as high with PCI-DES (12.98 vs. 7.09%). Therefore, even the most contemporary data (albeit registry-derived) appears to support CABG as the optimal revascularization strategy for isolated proximal LAD disease.

The interpretation of the study findings will vary greatly depending on physicians’, surgeons’ and patients’ perspective. On one hand, equivalency of hard clinical end-points such as death or myocardial infarction at long-term follow-up is a testament to a PCI-DES strategy. On the other hand, a doubling of repeat revascularisation is an important consideration when planning treatment strategies. Although the design of most published randomised trials comparing PCI-DES vs. CABG for multi-vessel disease has traditionally included target vessel revascularisation, the importance of this end-point has recently been questioned. For example, the on-going EXCEL trial comparing PCI and CABG for left main disease does not include TVR in its composite primary end-point.17 Despite this, from a patient’s perspective these data (and this end-point in particular) are relevant when choosing between treatments. Therefore, each case should be treated on their individual merits and an acknowledgement of the significant excess of repeat TVR with a PCI-DES strategy is a factor should be made.

One relevant factor to consider when interpreting the findings of the study is whether the studies included reflect contemporary practice. The majority of data in the present analysis are derived from studies that used first generation stents (Cypher or Taxus). Studies of newer generation DES (such as Xience or Resolute) report a 35% reduction of mortality, 30% reduction in cardiac death and myocardial infarction, 20-40% reduction in TLR and >50% reduction in stent thrombosis at >3 years follow up compared to first generation DES.18,19 Whether this observed TLR reduction in stent vs. stent trials translates into equivalency against CABG (or indeed superiority) for revascularisation of isolated proximal LAD disease whilst seeming intuitively plausible remains scientifically unproven. Additionally, given the lack of contemporary trial data, the impact of improved surgical techniques during CABG (such as routine left internal mammary (LIMA) artery use and off-pump techniques) on the outcomes vs. PCI is also uncertain. What does appear clear from the available literature is the effectiveness of the LIMA for TVR outcomes. The SIMA trial (a randomized control trial comparing CAGB with LIMA to bare-metal stents for isolated proximal LAD disease) recently reported long-term follow up of the original cohort reported in 1998.20,21 After 10 years of follow-up, no patient with a LIMA to the LAD had undergone repeat revascularization to the LAD reinforcing the impressive benchmark against which PCI-DES strategy must perform.

To improve the evidence base a multi-centre randomised controlled trial with as complete and consecutive enrolment as feasible could be performed. However in order for this trial to be as informative as possible (and to minimise selection bias) it should be an all-comers trial with as complete randomisation of eligible patients as possible. Whether or not interventional cardiologists and indeed patients would be willing to be included however is uncertain. Further propensity-matched large-scale registries are needed particularly to include patients treated with newer technologies and techniques.

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