Original Articles

Debate- PCI or CABG for diabetics with left main stem disease

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Position

Coronary artery bypass grafting remains the treatment of choice for diabetics with left main stem disease.

The optimum revascularisation strategy for left main stem (LMS) disease between percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) remains controversial. No single trial has compared outcomes following percutaneous coronary intervention (PCI) or surgical coronary artery bypass grafting (CABG) in diabetics with unprotected LMS disease as the primary analysis. However, several randomised controlled trials (RCTs) comparing the two treatments include this comparison in subgroup analyses. 5-year follow up data is available for the NOBLE[1] and EXCEL trial[2] with 10 year data available for the SYNTAX[3] and PRE-COMBAT trials[4]. Of these studies, only SYNTAX was sufficiently powered for mortality as a primary endpoint with the others favouring the composite outcome of Major Adverse Cardiac and Cerebrovascular Events (MACCE), including cardiac death, stroke, and myocardial infarction.

The Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial was an non-inferiority RCT comparing PCI with 1st generation paclitaxel-eluting stents with surgery for patients with three vessel disease or LMS disease . Ten year follow up data of the extended study SYNTAX trial (SYTNAXES) showed no significant difference in the combined primary outcome of rates of all-cause death for patients with LMS disease HR 0·92 [95% CI 0·69–1·22 or patients with diabetes.[3] However, there was no subgroup analysis performed to analyse the interaction of diabetes purely in the presence of left main stem disease. No other secondary endpoints such as rate of repeat revascularisation or periprocedural myocardial infarction (MI) are reported by the SYNTAXES study.

Similar results were reported from the 10 year data of the PRE-COMBAT (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) Trial. The primary outcome of MACCE occurred in 28.9% of PCI patients and 24.7% of CABG patients [HR with PCI vs CABG, 1.25 [95% CI, 0.93–1.69]. None of the secondary endpoints of all-cause mortality, cardiovascular mortality, stroke or MI were statistically different between the groups. However, the incidence of ischaemia driven target vessel revascularisation was significantly higher in the PCI group at 21.3% versus 10.6% with surgery. It should be noted that the PRE-COMBAT trial had a relatively high crossover rate from CABG to PCI which could bias the study findings towards a neutral effect on outcomes. In the as-treated analysis PCI was found to be inferior to CABG in terms of the primary outcome [HR 1.51 (95% CI, 1.11–2.060]. Similar results were demonstrated in the per protocol analysis. Again, this was primarily driven by higher rates of repeat revascularisation rates in the PCI cohort [23% in 327 PCI patients Versus 7.6% in 272 CABG patients]. These analyses are important as they can be said to mimic real-world practice. In subgroup analyses, there was no significant interaction with diabetic status and any of the specified outcomes. However, triple vessel disease in the presence of LMS disease conferred a survival advantage in favour of surgery. The PRE-COMBAT trial is limited by relatively low number of patients per cohort and a low event rate, resulting in it being underpowered to detect clinically significant endpoints.

These two studies reflect practice from 15 years ago including the use of 1st generation paclitaxel and sicrolimus-eluting stents and different practices between the cohorts in terms of long-term secondary prevention medication. Two more recent studies comparing PCI with 2nd generation drug eluting stents (DES) and surgery have reported 5-year outcome data. The Nordic–Baltic–British Left Main Revascularisation (NOBLE) trial recruited 1200 patients with LMS disease randomised to PCI or CABG (5). At 5 years the authors report inferior clinical outcomes in the PCI cohort due to higher rates of non-procedural myocardial infarction at 8% following PCI versus 3% after CABG (HR 2·99 [95% CI 1·66–5·39]; p=0·0002) and higher rates of repeat revascularisation at 17% after PCI versus 10% after CABG (HR 1·73 [95% CI 1·25–2·40]; p=0·0009).[1] In

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subgroup analysis, no interaction was found with the presence of diabetes.

In a second trial by the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) Investigators, 1905 patients with LMS disease were randomised to revascularisation with PCI or surgery. No difference was found for the primary composite outcome of death, stroke or myocardial infarction. However, rates of all cause death were significantly higher in the PCI group [13% versus 9.9% (OR 1.39 (CI 1.03-1.85))] and there has been some controversy surrounding the definition of myocardial infarction (MI). This controversy centres on the definition used for MI. Using the pre-specified protocol definition, procedural MI reached 3.6% of the PCI group and 6.1% of CABG recipients (*P*=0.015). However, using the 3rd Universal Definition of MI, procedural MI's rose to 4% for PCI and dropped to 2.2% for CABG (p=0.025).[6] This definition, which requires less in terms of biomarker elevation but more in terms of accompanying evidence of ischaemia, was also prespecified as a secondary endpoint in the trial protocol but omitted from the 3 and 5 year results. Critics have argued that the use of the pre-specified protocol unfairly biases the results against surgery where some degree of myocardial injury, and hence biomarker release, is inherent to the procedure. Definitions of MI that rely purely on biomarker elevation have also been found to be less predictive of mortality following CABG than those that require other evidence of ischaemia.[7] Finally, the rate of repeat revascularisation in this cohort was significantly higher with PCI (17.2% versus 10.5% (OR 1.79 (CI 1.36-2.36))]. In a pre-specified subgroup analysis of the EXCEL trial the effect of diabetes in patients with LMS disease treated with PCI versus CABG was investigated.[8] The authors found no significant effect of diabetes on outcomes with either treatment strategy.

Based on the evidence from these RCTs, the optimum revascularisation strategy for isolated left main stem disease remains surgical revascularisation irrespective of diabetic status. This is based on the consistent findings that PCI is associated with higher rates of surgical revascularisation and isolated findings of higher all cause mortality in the EXCEL trial and higher non-procedural MI in the NOBLE trial. In contrast none of the RCT's have to date demonstrated any significant benefits of PCI over CABG for any of the endpoints measured. A common argument for advocating PCI over surgery for LMS disease is that the increased rates of revascularisation with PCI are an acceptable trade off when balanced against the less invasive nature of the index procedure. However, this argument ignores the evidence that need for repeat revascularisation is by far a benign entity. In a follow up study by the EXCEL investigators, repeat revascularisation at 3 years was found to be associated with a 2-fold all-cause mortality risk (adjusted hazard ratio: 2.05; 95% confidence interval: 1.13 to 3.70; p = 0.02) and a 4-fold cardiovascular mortality risk (adjusted hazard ratio: 4.22; 95% confidence interval: 2.10 to 8.48; p < 0.0001).[9]

From subgroup analysis of the same studies, diabetes status was consistently found not to effect outcomes for either PCI or surgery. However, it should be noted that these subgroup analyses contained reduced numbers of patients and might therefore not have been sufficiently powered to detect a true difference between PCI and CABG.

The FREEDOM trial is a large RCT comparing outcomes in diabetics with multivessel disease treated with either PCI or CABG. In the follow-on study, PCI was been found to be associated with worse all-cause mortality at up to 8 years.[10] One patient group that consistently demonstrated a survival benefit across the studies outlined above was patients with LMS and co-existing multi-vessel disease.[4, 11] In the SYTNTAXES trial, 2/3rds of patients with LMS disease had co-existing multivessel disease (228/348 = 66%).[3] Extrapolating the results of the FREEDOM trial would suggest that diabetics with multivessel disease and LMS would also fair worse with PCI compared to surgery.

It is worth noting that the current studies comparing PCI and CABG represent the standards of care that existed at their inception. For the SYNTAX and PRE-COMBAT trial that meant using 1st generation drug eluting stents. Proponents of PCI point to the use of these early generation DES to explain the worse clinical outcomes seen with PCI compared to surgery for LMS disease and multivessel disease, particularly the higher rates of repeat revascularisation seen. However, this is a dangerous assumption to make in the absence of well-run RCTs utilising these newer stents. Whilst studies comparing 3rd generation stents to 2nd or 1st generation showed improved clinical outcomes with the latest models this cannot be extrapolated to direct comparisons with surgery.[12]

In the same way that advancements have been made in percutaneous treatment so have improvements been made in cardiac surgery as a whole. Advancements in the field of cardiac surgery including improvements in pre-operative optimisation, intra-operative techniques, cardiopulmonary bypass circuits, and post-operative critical care have resulted in steady reductions in mortality.[13] This has resulted in the need to modify risk stratification tools such as the EuroSCORE to account for the improved outcomes seen with surgery.[14] It is also the case that the majority of CABG operations performed currently still utilise the long saphenous vein as the second conduit after the left internal mammary artery. The body of evidence to date suggests improved graft patency rates and clinical outcomes when arterial grafts are preferred to saphenous vein.[15, 16] As such any modern trial comparing outcomes between PCI and CABG should compare the best versions of each procedure; i.e 3rd generation stents versus surgery with total arterial revascularisation. In the absence of such trials, the results of the existing studies should be taken at face value.

In summary, the current evidence suggests that for diabetic patients with LMS disease and co-existing multivessel disease, surgery is the treatment of choice based on all-cause mortality. For the remaining patients with isolated LMS disease surgery remains the preferred treatment option irrespective of diabetic status due to consistent findings of improve rates of repeat revascularisation and isolated findings of reduced non-procedural MI[1] and all-cause mortality.[2]

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Declaration of competing interests

Nothing to declare.

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