

Revascularisation for Left Anterior Descending Artery Stenosis – A Review of the Evidence That Supports Practice

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Condensed abstract

Disease of the proximal left anterior descending artery (LAD) is a common pathological finding often combined with disease in other coronary arteries. In this article we review specifically the evidence (and the guidelines arising from the data) for lesions isolated to the proximal LAD only. Critical review of the data reveals limitations with few trials that reflect contemporary practice. Much of the data is observational rather than from randomised trials and therefore subject to bias. We identified two randomised trials of drug-eluting stents versus LIMA for isolated lesions of the proximal LAD. One reported no difference in MACE but at an early time-point (6-months), which is likely to be too early to reveal treatment differences. In the second trial TLR excess was noted in the drug-eluting stent arm. Therefore at the current time little data is available to inform interventional cardiologists as to the best revascularisation strategy for isolated lesions of the proximal LAD. Further randomised control trials are urgently needed.

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Methods

The primary aim was to perform a systematic review of the published data comparing coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI) for isolated stenoses of the proximal LAD. Using Medline and Google Scholar the search was limited to studies published in English between 1998 and 2014. Search keywords included ("Minimally invasive direct coronary artery bypass" OR "MIDCAB" OR 'Coronary Artery Bypass') AND ('Percutaneous Coronary Intervention' OR PCI OR primary stenting OR stenting) AND (Left Anterior Descending). To broaden the search we also crosschecked the references of the articles identified in the initial Medline results as well the references of the several published meta-analyses. Finally the references of the major guidelines discussed were also searched. Eleven studies were identified that compared bare-metal stent PCI or balloon angioplasty (PCI-BMS) versus CABG and 9 studies that compared drug-eluting stent PCI (PCI-DES) versus CABG. Several observational studies were identified that compared mixed BMS and DES use against CABG and these were excluded.

Bare Metal Stents vs. CABG

Underpinning both the European guidelines and the US guidelines for revascularisation of the isolated proximal LAD stenoses are two large meta-analyses examining the outcomes of a series of historical trials comparing CABG vs. PCI (almost exclusively with BMS) for isolated proximal LAD disease: 1) Aziz et al who performed a meta-analysis of minimally invasive internal thoracic artery

bypass versus percutaneous revascularisation for isolated lesions of the LAD in >1900 patients; 2) Kapoor et al who examined outcomes of isolated disease of the proximal LAD comparing the effectiveness of percutaneous coronary interventions and CABG surgery in >1200 patients.¹⁻⁵ Although there were no differences in either meta-analysis for mortality, myocardial infarction (MI) or stroke between the two revascularisation strategies there was a three to five fold increase in repeat target vessel revascularisation (TVR) in patients treated with PCI compared to CABG.

Although at first glance this evidence appears impressive (21 studies reporting outcomes of 3,162 patients) it is important to note is that the two meta-analyses largely reproduce the same studies and duplicate the patient numbers. After exclusion of duplicated studies the 2 meta-analyses report the findings of 11 studies of 2380 patients. The 11 studies reported in total are summarised in Table 1.⁶⁻¹⁶ Additionally the two largest studies were non-randomised observational studies that may duplicate the same group of patients.^{11,13} Given the limitations of such observational data in these 2 studies the meta-analyses authors actually excluded them from their main analysis. Also it is important to note however that the largest of randomised study of PCI-BMS vs. CABG included only 220 patients.¹²

Therefore the meta-analyses finally report 9 studies report the outcomes of 1239 patients randomised to PCI or CABG providing the best quality data with selection and treatment biases are minimised as far a possible. In analysing the randomised subgroup Kapoor et al found that although there were no differences in survival, strokes or myocardial infarctions at 30 days, 1 year, or 5 years, repeat revascularization was significantly less after CABG than after PCI (at 1 year: 7.3% vs. 19.5%; at 5 years: 7.3% vs. 33.5%). Additionally angina relief was significantly greater after CABG than after PCI (at 1 year: 95.5% vs. 84.6%;

at 5 years: 84.2% vs. 75.6%). Similarly in an analysis confined to the randomised trials only Aziz et al found no differences in death, MI or stroke but showed a higher rate of recurrence of angina (odds ratio 2.62, 95% confidence interval 1.32 to 5.21) and need for repeat revascularisation (4.63, confidence interval 2.52 to 8.51) with percutaneous stenting. Therefore within their acknowledged limitations these 2 meta-analyses appear to demonstrate the superiority of CABG over PCI for the revascularisation of proximal LAD stenosis with respect to symptom relief and repeat revascularization, but not for death, stroke or MI. However it is important to note that several of these studies had short follow up (<12-months) and more prolonged follow-up may have further emphasized the superiority of CABG over PCI. Although hard clinical end-points such as repeat revascularisation occur less frequently with CABG than PCI-BMS it is interesting to note that in the two studies that reported on quality of life (as measured by Seattle Angina Questionnaire (SAQ) and the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36)) there was little difference between the two treatments.^{8,14} However there was a significant improvement in quality of life with both treatments at follow-up compared to baseline and such outcome data is very relevant when informing patient choice prior to treatment.

The SIMA trial recently reported the 10 year follow up of the original cohort reported in 1998 (and included in the meta-analyses).^{7,36} In this report a decade on, not one patient with a LIMA to the LAD had undergone repeat revascularisation to the LAD compared to 16 (25.8%) patients who received a bare metal stent. Interestingly the non-LAD revascularisation rates were identical and very low (4.8% vs. 4.8%) in the two study arms. This long follow up and lack of need for revascularisation in the CABG arm reinforce the excellent outcomes of a LIMA to the LAD. It is an impressive benchmark against which PCI (DES or not) must perform.

Relevance to contemporary clinical practice

One consideration in assessing the strength of these data is the comparison of practice between the included studies and contemporary PCI practice. Kapoor et al published their paper in 2008 and included trials that recruited patients between 1989 and 2003. Similarly Azziz et al published their analysis in 2007 and included trials that recruited patients between 1998 and 2003. As a result only one trial in these meta-analyses used drug-eluting stents (PCI-DES) with CABG. Additionally three of the randomised studies did not involve routine bare metal stent (PCI-BMS) use and either were solely balloon angioplasty without stenting or a mixture of balloon angioplasty only and/or stents.^{6,9,14} In current PCI practice stents are standard of care and it would be extremely unusual to perform balloon angioplasty only (without stenting) of the proximal LAD artery. Additionally in contemporary practice drug-eluting stents rather than a bare-metal stent would commonly be used in the proximal LAD. However only one study included in either meta-analysis utilised drug-eluting stents (Hong et al) randomising 119 patients to a first generation Cypher stent or 70 patients to CABG (see below).

Whilst the data supporting the conclusion that PCI-BMS increase the risk of TVR three to five-fold compared to CABG appears robust, it is important to note that these remaining studies do not show any evidence of a mortality benefit with CABG vs. PCI-BMS with the benefit of CABG being exclusively driven by TLR. Two other meta-analyses of the same trials have largely reproduced the findings of the two meta-analyses reported in the 2010 guidelines.^{17,18} What does appear clear however from later large scale randomised control trials and subsequent meta-analyses is that drug-eluting stents offer a significant reduction in TLR when compared to bare metal stents. Indeed several meta-analyses of RCTs comparing first generation DES with BMS report similar rates of death, cardiac death, and non-fatal myocardial infarction, but a 50-70% relative risk reduction in repeat target vessel revascularization with DES.¹⁹

Drug-eluting stents vs. CABG

In an attempt to derive further insights into comparisons between PCI-DES and CABG (and thus to draw conclusions regarding contemporary practice) we identified 9 studies of 2752 patients comparing PCI-DES with CABG for isolated LAD stenosis and these are listed in Table 2.²⁰⁻²⁹ However as with the PCI-BMS vs. CABG data the majority of the studies are observational and retrospective in design. Only 2 studies were randomised with a total of 184 patients treated by PCI-DES and 135 by CABG.^{20,24} Therefore there are very limited data from which conclusions can be drawn as to the optimal revascularisation strategy for isolated proximal LAD disease in contemporary practice. Additionally the findings from the two studies rather than being consistent are divergent. Hong et al found no difference in TLR between the PCI-DES and CABG cohorts but the very short follow-up (6-months) is a limitation and reduces the robustness of the conclusion that the two strategies offered comparable TLR rates.²⁰ In contrast at 12-months Thiele et al reported a 6.2% TLR rate in the PCI-DES group vs. 0% in the CABG group, a finding which indicated a failure of a non-inferiority comparison between PCI-DES and CABG.²⁴ At 7-year follow-up the authors reported similar death and MI rates between the two revascularisation strategies but a very significant excess of TLR in the PCI-DES cohort (20.0% vs. 1.5%) that was highly statistically significant.²⁵ Although only a single study has reported on the quality of life with PCI-DES vs. CABG, as with studies comparing PCI-BMS with CABG there appears to be little difference in quality of life between treatments as measured by SF-36 at either 12-months or 7-years follow-up.^{24,25}

In examining the results of the retrospective observational analyses of PCI-DES vs. CABG it is also unexpected to observe that the results favour CABG (Table 2). In the absence of definitive data many interventionalists in practice are likely to undertake PCI in "straightforward" lesions and refer complex unsuitable lesions

for CABG. Therefore one might expect that PCI would perform well in these circumstances vs. CABG but the data as it is do not support this hypothesis. The confounding effect of baseline factors such as age and comorbidity is uncertain and as yet unstudied. The optimal strategy in contemporary practice needs to be properly tested in an appropriately powered randomized trial to be definitive and powered to allow age and comorbidity to be sufficiently stratified.

Two meta-analyses including the randomised and observational studies for DES-PCI vs. CABG have been performed.^{30,31} In the first a subgroup analysis concluding that the PCI-DES cohort (4 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).³⁰ The second meta-analysis considered only the 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.³¹ Aside from the relative lack of data (randomised or not) and the divergent results it must be recognized that both randomized trials and the majority of the observational trial used first generation stents (Cypher or Taxus). Studies of newer generation DES (such as Xience or Resolute) however report a 35% reduction of mortality, 30% reduction in cardiac death and myocardial infarction and >50% reduction in stent thrombosis at >3 years follow up compared to first generation DES.^{32,33} However whether this observed TLR reduction in stent vs. stent trials translates into equivalency against CABG (or indeed superiority) for revascularisation of an isolated proximal LAD stenosis whilst seeming intuitively plausible remains unproven.

Most recently Hannan et al propensity matched 715 pairs of patients who were treated with either DES or CABG for isolated LAD stenoses between 2008 and

2010 using a United States registry.³⁴ Mortality, MI and stroke were similar at 3-year follow-up between DES and CABG but despite the apparent contemporary practice repeat revascularisation rates were almost twice as high with DES (12.98 vs. 7.09%). Therefore even the most contemporary data (albeit registry-derived) appears to support CABG as the optimal revascularisation strategy for isolated proximal LAD disease.

The premise that proximal LAD lesions place patients at particular risk and thus deserves particular focus derives from the large territory of myocardium subtended, and hence at risk from vessel restenosis/occlusion. The left main stem subtends an even greater territory, so the recently published 5-year data from the SYNTAX trial on this sub-group is of some reassurance to interventionalists in the current proximal LAD data void.³⁵ Although it is tempting to extrapolate the SYNTAX left main data to support a PCI revascularisation strategy for proximal coronary lesions it is important to remember that the left main stem is significantly larger in diameter and shorter in length than the LAD, both factors which could impact on long term outcomes with stents. From a scientific perspective this “leap of faith” remains speculative at best because as noted above there are no published trials (first or second generation DES) that shows equivalency of PCI to CABG beyond 12-months of follow-up. Additionally given the lack of contemporary trial data the impact of improved surgical techniques during CABG and increased utilisation of off-pump surgery on the outcomes vs. PCI is also uncertain.

Revascularisation guidelines

In 2010 the European Society of Cardiology published revascularisation guidelines recommending CABG as being preferable to PCI in patients with proximal left anterior descending artery disease with CABG receiving 1A support.¹ For PCI the

level of recommendation in 2010 was IIa (conflicting evidence and/or divergence of opinion although the weight of evidence is in favour of its usefulness). The level of evidence supporting this recommendation was B (the data is derived from a single clinical trial or large non-randomised studies). In a similar fashion the 2011 AHA/ACC CABG and 2012 AHA/ACC stable angina guidelines both state that CABG with a LIMA graft to improve survival is reasonable in patients with significant (>70% diameter) stenosis in the proximal LAD artery and evidence of extensive ischemia (recommendation IIa, level of evidence B).² In contrast PCI is recommended at a level of IIb (uncertain benefit) but also with a B level of evidence.

However the latest ESC/EACTS guidelines on myocardial revascularisation published this year recommended treatment of an isolated proximal left anterior descending artery (LAD) stenosis with either coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) in patients presenting with stable angina or non-ST elevation myocardial infarction.³ This revascularisation strategy was recommended irrespective of co-existing coronary disease, thus it applied to isolated proximal LAD disease only as well as to multi-vessel disease. Both revascularisation strategies received equal support with a Class 1 indication (that the evidence and/or general agreement is that the treatment is beneficial, useful and effective). Additionally the level of evidence supporting this recommendation was deemed to be A (the data were derived from multiple clinical trials).

In a critical appraisal of the updated 2014 ESC/EACTS guidelines readers might expect that a major change to the proximal LAD revascularisation guidance would be supported by extensive new data since 2010. In fact the upgrade to for PCI from IIa/(B) - that there is conflicting evidence and/or divergence of opinion with the data is derived from a single clinical trial or large non-randomised studies - to

IA - that there is general agreement is that the treatment is beneficial, useful and effective with the data the data was derived from multiple clinical trials – is not supported by any referenced data in the guidelines. In fact none of the studies listed in Table 2 are included in the guideline references. Additionally there is no mention of the 2 recently published meta-analyses.^{30,31} Although 3 studies have reported between 2010 and 2014 ESC guidelines, in fact all three showed excess TLR with PCI vs. CABG (Etienne²¹ OR 5.88, Dohi²⁸ OR 12.5 and Benedetto²⁹ OR 2.0) However as discussed above there is a paucity of data which does not appear firm enough to allow definitive conclusions to be drawn and might be interpreted as supporting the continuation of CABG as the preferred treatment. Thus the data that drive the upgrade of PCI for proximal LAD revascularisation in the guidelines are not clear from the available evidence base.

Summary

In summary although most interventional cardiologists would assert that a 2nd or 3rd generation DES-PCI is the definitive treatment for isolated proximal LAD stenosis based on the low TLR rates of contemporary DES implantation, and reassuring data on left main stem intervention, there are few data available. Thus it remains scientifically unproven as to the optimal revascularisation strategy for isolated stenosis of the proximal LAD. To fill this data void (and paradoxically support the guidelines) a multi-centre randomised controlled trial with as complete and consecutive enrolment as practically feasible should be performed. However in order for this trial to be 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 would suppress their inherent biases about the best treatment and recruit to such a trial however remains to be seen.

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