

Why coronary artery bypass surgery is still the optimal treatment strategy for left main stem disease: an evidence-based review with a Malaysian surgical perspective

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INTRODUCTION

Left main stem (LMS) coronary artery disease (CAD) remains an important risk factor for increased mortality and morbidity at all stages of diagnosis and treatment of coronary artery disease. Anatomically, the LMS is a crucial vessel, as it provides two-thirds of the myocardial blood supply. Significant flow limiting stenosis usually results in low-tolerance angina and has prognostic implications. Historically, coronary artery bypass grafting (CABG) has been the treatment of choice for LMS revascularisation, but advances in percutaneous coronary intervention (PCI) have challenged this surgery-only paradigm. This article is a surgical appraisal of the current evidence regarding the optimal revascularisation strategy for LMS disease in terms of safety, efficacy and durability.

CLASSIFICATION, AETIOLOGY AND PREVALENCE

LMS length is highly variable (2–40 mm) and does not appear to correlate with heart or patient size.¹ LMS stenosis can be subdivided into three distinct lesions, ostial, body and bifurcation lesions, which have important therapeutic implications. LMS disease is a relatively common pathology, present in approximately 5–10% of patients undergoing coronary angiography. Prevalence is generally higher among Asians with over 20–30% of Malaysian CABG patients having significant LMS disease at surgery.² Obstructive LMS disease is usually part of more widespread atherosclerotic CAD. Non-atherosclerotic causes of LMS lesions are rare and include tertiary syphilis-induced aortitis, Takayasu's arteritis and spontaneous dissection (most commonly in young women during the peripartum or early postpartum period). Iatrogenic causes include mediastinal radiation-induced fibrosis, and stenosis from traumatic surgical cannulation for delivery of antegrade cardioplegia, PCI intubation or malposition of an aortic-valve prosthesis.³

In Malaysia, in contrast to the West, premature CAD is a common finding; the reported mean age of patients undergoing PCI, is comparatively young at 56.7 years in contrast to major contemporary PCI registries.⁴ Given this earlier manifestation of CAD here, it is vital that any therapeutic intervention, be it PCI or surgery, be durable, otherwise the patient will be at risk of further future intervention. It is imperative that in addition to evaluating early surgical bypass graft or stent patency, the longer-term event-free survival and freedom from reintervention are also carefully considered.

Another feature of local CAD including LMS disease is the higher proportion of diabetics in Malaysia. In 2007, 45.6% of patients who had PCI were diabetic.⁴ Diabetes results in a micro-vasculopathy that manifests with small calibre and diffuse CAD, making any intervention technically challenging and potentially less durable. The Bypass Angioplasty Revascularisation Investigation (BARI) trial multi vessel disease (PCI vs CABG for symptomatic MVD) demonstrated a highly significant prognostic benefit with CABG in diabetics at 5 years' follow-up (5-year survival: 80.6% CABG vs 65.5% PCI; $p=0.003$).⁵ These findings were subsequently validated by similar results from the Coronary Angioplasty versus Bypass Revascularisation Investigation (CABRI) and Emory Angioplasty versus Surgery Trial (EAST) trials.^{6,7} All three trials, however, were from the era of conventional balloon-only angioplasty prior to the advent of stenting. Over 90% of contemporary PCI activity in Malaysia now involves stenting.⁴

EVIDENCE FOR SURGERY IN LMS DISEASE

CABG has a proven symptomatic and prognostic benefit for LMS disease. The pathological importance of LMS disease is illustrated by its adverse influence on surgical outcomes following isolated CABG as evidenced by data from both the UK Society for Cardiothoracic Surgery (SCTS; post-operative survival data: 96.5% LMS vs 98% non-LMS disease) and the North American Society of Thoracic Surgeons (STS; database—perioperative mortality RR of 1.3 for LMS vs non-LMS patients).⁸ Three widely cited historical randomised clinical trials (RCT), namely the Coronary Artery Surgery Study (CASS), the European Coronary Surgery Study (ECSS) and the Veterans Administration Coronary Artery Bypass Surgery Co-operative Study (VA), established unequivocally the superiority of CABG over the best available medical therapy at the time, for LMS disease.^{9–14} Other CAD patient subsets in whom CABG was beneficial included those with triple-vessel disease, proximal LAD stenosis, and patients with impaired ventricular function. These historical trial patients however bear little resemblance to contemporary patients who are older and with more comorbidities.

Medical therapy has evolved considerably since then with widespread use of statins and angiotensin-converting enzyme inhibitors in addition to β blockers and antiplatelet therapy. Equally, surgical practice has improved with superior myocardial

protection techniques including off-pump beating heart CABG, prophylactic intra-aortic balloon pump use and more arterial grafting including an almost universal use of the pedicled left internal mammary artery (LIMA) graft on the LAD vessel. The LIMA graft has excellent unparalleled long-term patency and a proven prognostic benefit.¹⁵ Despite inherent limitations, all three trials showed improved 5-year survival for patients with LMS disease who were randomised to CABG rather than medical therapy.^{9–14} Since the publication of these trials, non-surgical therapy has expanded to include the entire gamut of PCI procedures, and any meaningful comparison of treatment outcomes must incorporate the results of PCI.

Historically, PCI was performed for LMS disease in three scenarios; elective PCI for 'protected' LMS disease with an existing patent bypass graft, or as an emergency treatment for acute vessel closure at diagnostic catheterisation or in the setting of an acute myocardial infarction. Success in these limited scenarios led to more widespread application of PCI for LMS disease.

CONTEMPORARY DATA

Several RCTs comparing the efficacy of PCI with drug-eluting stents (DES) versus CABG specifically for LMS disease have been conducted. In the Premier of Randomised Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease (PRECOMBAT) trial of unprotected LMS disease (300 randomised to CABG and 300 to PCI with DES-Sirolimus), Park *et al* showed non-inferiority for PCI in relation to CABG at 1- and 2-year intervals for the composite primary endpoint of death, myocardial infarction, stroke and target vessel revascularisation (TVR).¹⁶ At 2 years, the cumulative event rate for the primary end point was 12.2% PCI vs 8.1% CABG ($p=0.12$). However, ischaemia-driven TVR occurred twice as often in the PCI group (9.0% PCI vs 4.2% CABG ($p=0.02$)).¹⁷

Boudriot *et al* (RCT—201 patients) similarly reported non-inferiority of PCI to CABG in terms of freedom from major adverse cardiac and cerebrovascular events (MACCE), but PCI was inferior to surgery for repeat TVR.¹⁸ In a propensity-matched cohort analysis (2240 LMS patients—1102 PCI vs 1138 CABG), Ki Bae Seung *et al* (MAIN—COMPARE registry) observed no significant difference at 5 years, in the composite outcome of mortality, stroke or Q-wave myocardial infarction (MI) but a significantly higher TVR rate with PCI even with DES (HR 4.76, 95% CI 2.80 to 8.11). In fact, there was a trend towards a higher mortality and the composite end point with use of DES over BMS.¹⁹

The landmark multicentre Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial (1800 patients—85 centres) failed to reach the primary endpoint of non-inferiority for PCI versus CABG but still yielded important information. The SYNTAX score is an angiographic tool utilising solely coronary anatomy and hence is technically salient. Analysis of the subgroup of LMS patients showed for patients with a low SYNTAX score (<33) mortality at 2 years was lower with PCI (2.7% PCI vs 7.9% CABG, $p=0.02$) but there was no difference in overall MACCE.²⁰ However, in LMS patients with a higher SYNTAX score (>32), surgical mortality was markedly lower (4.1% CABG vs 10.4% PCI, $p=0.01$) at 2 years, and TVR was a significantly less frequent occurrence (9% CABG vs 22% PCI, $p=0.003$). Overall, TVR for all LMS patients was higher with PCI (11.8% PCI vs 6.5% CABG, $p=0.02$).²⁰

A major Asian study recently reported long-term outcomes of CABG versus stenting (BMS and DES) for unprotected LMS disease. At 10 years' follow-up, Park *et al* concluded there was no difference in the composite of death, Q-wave MI or stroke (HR 0.81 $p=0.50$) between BMS or CABG treatment of LMS lesions despite a significantly higher rate of TVR in the BMS group (HR 10.34 $p<0.001$). A 5-year analysis of more contemporary practice using DES similarly showed no difference in the risk-adjusted primary composite outcome but improved reintervention rates, although TVR was still significantly more frequent in the PCI-DES group (HR 6.22 $p<0.001$).²¹

A recent meta-analysis comparing safety and efficacy of CABG with PCI (DES) for unprotected LMS disease (eight studies: 2905 patients) showed no significant difference at 1 year between the two groups in terms of mortality, myocardial infarction or stroke. TVR was significantly lower with CABG (OR 0.44; 95% CI 0.32 to 0.59).²²

FUTURE TRIALS

The results of a further RCT comparing the efficacy of PCI with CABG for unprotected LMS disease, the Evaluation of Xience Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularisation (EXCEL) and the prospective observational single-arm PRECOMBAT-2 trial, to evaluate outcomes of DES (everolimus) implantation for unprotected LMS disease, are awaited.^{23 24}

IMPLICATIONS FOR MALAYSIAN PRACTICE

PCI commenced in Malaysia in 1983, and impressive rapid advances have since occurred in terms of both throughput volume and technical complexity, as reflected in the National Cardiovascular Disease Database 2007–2009 PCI report. Data analysis from seven participating centres showed that 39% (of 11 498) of PCI procedures featured high-risk characteristics such as ostial or bifurcation lesions and totally occluded vessels.⁴ PCI for isolated LMS disease accounted for only 1.9% (291 cases) of total activity, probably reflecting the inherent learning curve for the interventional cardiologists, and the relatively uncommon phenomenon of isolated LMS disease.⁴ PCI for LMS disease was enhanced with the use of intravascular ultrasound in 34% of cases and with prophylactic intra-aortic balloon pump use in 13.4% cases. Most cases were performed electively on unprotected LMS disease.⁴

RATIONALE FOR SURGERY

Significant LMS stenosis is usually concurrent with more distal MVD. Up to 90% of patients with LMS stenosis also have MVD. It has been validated that CABG revascularisation for LMS disease and/or MVD confers a survival benefit; hence most LMS patients with concomitant MVD are best treated with surgery. CABG is also the better revascularisation option for patients with impaired left-ventricular function.

In a majority of patients with LMS disease, the anatomical lesion is distal or at the bifurcation (53% of all LMS series), making PCI a less attractive option owing to the high restenosis rate. On the contrary, ostial and mid-shaft LMS lesions appear more amenable to PCI with a low in-hospital mortality. Analysis of the Unprotected Left Main Trunk Investigation Multicentre Assessment (ULTIMA) registry data (279 patients) helped to identify which LMS patients did best with non-surgical treatment (32). The overall mortality at 1 year was 9%, but when risk stratified, low-risk patients (<75 years, ejection fraction

>40% and large vessels > 3 mm) had a 3.4% mortality, while high-risk patients (including bifurcation disease) had a 28% mortality at 12 months.¹⁶

Given the rarity of isolated LMS disease and that anatomically most lesions are technically unattractive for PCI, surgery should remain the gold-standard treatment. In everyday real-life clinical practice however, the interventional cardiologist is often the gatekeeper who determines which patients merit discussion or referral to the cardiac surgeon.

LIMITATIONS WITH PCI

Advances in PCI have significantly reduced, but not eliminated, the associated technical deficiencies including acute thrombosis or vessel closure, vessel restenosis, in-stent restenosis (ISR) and incomplete revascularisation. The use of DES in general has reduced clinical recurrence of restenosis, especially in patients at greatest risk (small-calibre vessels, diabetics and long lesions). However, contemporary results of PCI—DES for unprotected LMS disease have shown a high incidence of ISR (17–42%) at routine surveillance or symptom-directed angiography.^{25 26} Data suggest the local ISR rate here for PCI of the LMS is approximately 8%, despite widespread use of DES and dual antiplatelet therapy (>12 months).⁴ The total case load of PCI for LMS lesions in Malaysia is still relatively small; hence, judicious interpretation of the data is required. ISR with either a DES or especially a BMS can make reintervention technically complex, such that CABG is often required.

Incomplete revascularisation with PCI for more complex coronary disease has also been shown to result in a lower MACCE-free survival at 5 years (HR 1.66, $p=0.001$) in comparison with CABG, reiterating the fact that in patients with complex pathology, a complete revascularisation is more likely to be achieved with surgery.²⁷

LIMITATIONS WITH SURGERY

The initial 30-day mortality, morbidity and treatment cost of CABG may be higher than in most reported PCI studies. The increased use of arterial grafts, especially the LIMA and widespread use of antiplatelet and statin therapy, and selective use of ACE inhibitors, however, have made attrition of patent vein grafts less of an issue. Reoperative CABG is increasingly uncommon, and stenosed vein bypass grafts account for only 0.9% of total annual PCI activity in Malaysia, which compares favourably with the reported local ISR rates (5%).¹² Malaysian PCI registry data revealed that when ISR was manifested clinically, patients presented with an MI in over 70% of cases including a ST segment elevation myocardial infarction (37.7%).⁴ The true incidence of ISR, however, may be higher with undetected silent restenosis.

Native vessel CAD progression beyond the graft site anastomosis is the Achilles heel of CABG and was historically reported in approximately 20% of grafts.²⁸ Contemporary secondary prevention measures with aggressive pharmacological control of cardiovascular risk factors and education on lifestyle modifications should hopefully slow or reverse native CAD progression.

CONCLUDING REMARKS

Patients with LMS disease comprise a small heterogenous but important group for which choice of treatment is difficult but vital. It is important to differentiate between non-inferiority and a superior therapy. Non-inferiority trials are questionable when mortality and serious complications are among the outcome measures. The term 'non-inferiority' in itself is misleading, as

such a study would not demonstrate that a new treatment (eg, PCI) is non-inferior to a control treatment (eg, CABG), but simply that the inferiority would not reach a prespecified level, deemed acceptable by the trial investigators. Nevertheless, it is reasonable to conclude that most registry and trial data report non-inferiority of PCI over CABG for low-risk patients with simple LMS lesions. Hence, PCI may be a reasonable alternative for such patients. PCI may be an excellent option for the surgically unfit patient or a patient who refuses an operation, or for technical reasons such as unavailable suitable conduit. Patients with a high SYNTAX score, distal or bifurcation LMS lesions, a short LMS, concurrent MVD or impaired LV function are probably better treated with CABG.

It is important to recognise that the survival and other clinical benefits of CABG revascularisation tend to accrue with time, often appearing 2–3 years following surgery and persisting for up to 10 years and beyond. These benefits unfortunately are not captured in most trials owing to a lack of robust long-term surveillance data. Additionally and reassuringly, surgical outcomes of CABG remain excellent and independent of coronary complexity (ie, the SYNTAX score).²⁹ This is probably due to the fact that with CABG, the stenosed or diseased segment is bypassed, whereas with PCI the intervention occurs at the site of disease.

Treatment durability is important given the preponderance of diabetes and relative youth of most CAD patients in Malaysia. Most investigators have demonstrated the procedural safety of PCI for LMS lesions. However the long-term safety and durability of PCI as an anatomical treatment remain largely undetermined; hence a sizeable area of myocardium is potentially at risk. The relatively high TVR rates in even contemporary LMS trials despite the use of DES and dual antiplatelet therapy is worrying, although for some reason this does not appear to manifest with a higher interim mortality or morbidity, at least with early and mid-term follow-up. Longer-term surveillance is required before PCI can be a routinely prescribed therapy for LMS disease, especially with smaller-calibre Asian vessels. Compliance with dual antiplatelet therapy may be an additional issue with less-educated or rural patients.

Evolution of PCI for LMS disease is best reflected in the changing gold-standard American Heart Association (AHA)/American College of Cardiology (ACC) clinical practice guidelines. In 1999, the ACC/AHA stated 'the benefit of surgery over medical treatment for patients with significant LMS stenosis is little argued,' and the updated 2004 AHA/ACC guidelines still recommended CABG over PCI for any patient with significant LMS disease regardless of symptom status. In the 2005 update, PCI for LMS disease was a Class III indication (evidence level C) if the patient was eligible for CABG and a Class IIa indication (evidence level B) if CABG was not an option. The latest 2009 AHA/ACC guidelines, however, have upgraded PCI to a Class IIa (evidence level B) indication for LMS disease in the CABG-eligible candidate.³⁰ However, the AHA/ACC guidelines acknowledge that PCI-amenable lesions represent only a small subset of a wider group of LMS patients and recommend that PCI be performed only by experienced interventionalists with readily available surgical backup.

Good ethical medical practice mandates that all cases of LMS disease requiring intervention be discussed jointly by cardiologists and cardiac surgeons to ascertain the optimal revascularisation strategy for a given individual patient. Technical expertise and availability, local treatment outcomes, cost and patient preference must be evaluated in addition to clinical factors. Informed consent requires that the patient, in the

absence of a life-threatening event, be made aware of the availability, safety, efficacy and limitations of the various therapeutic options. PCI for unprotected LMS disease, if performed outside the context of a trial, should be preceded by a case discussion with the local cardiac surgeon.

Despite a wealth of substantial evidence from meta-analyses, RCTs and registry data favouring CABG, PCI is often the most frequent initial treatment delivered by interventional cardiologists in everyday clinical practice to treat MVD. A similar practice should not evolve regarding LMS disease, as the margin for error is smaller, and the stakes for the patient higher.

Current evidence suggests that CABG confers a significant event-free survival benefit over PCI and thus should remain the standard of care for a majority of patients with significant LMS disease. Continued advances in PCI, however, will undoubtedly, and rightly, challenge this. In the foreseeable future, it is likely that PCI and CABG will become complementary, rather than competing, therapies in the management of significant LMS disease. A collaborative multidisciplinary team approach comprising the cardiac surgeon, interventional cardiologist and non-invasive cardiologist is the way forward in providing objective optimal patient care.

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