

Contemporary considerations in left main stem treatment



Anthony H. Gershlick*, BSc, MBBS, FRCP; Amerjeet Banning, BSc, MBBS

Department of Cardiovascular Sciences, University of Leicester, Leicester Biomedical Research Centre, University of Leicester NHS Trust, Leicester, United Kingdom

Percutaneous interventional treatment for disease affecting the left main stem has historically been considered problematic for a number of reasons. Firstly its site, at the origin of the coronary tree, means that any percutaneous therapy has to be absolutely robust. A post-procedural occlusion of a mid or distal circumflex or right coronary artery, while less than ideal, carries far less risk than occlusive stent thrombosis affecting the left main stem. Only recently has stenting become predictably safe through advances in techniques, devices and adjunctive pharmacology. Secondly, left main stem disease is heterogeneous. Treating ostial/shaft disease is very different from treating complex distal bifurcation/trifurcation. Finally, and as a follow on, we have failed to develop standard strategies for bifurcation disease in general. Provisional crossover stenting appears to be the best there is currently, but for significant disease in the side branch (which may be the large circumflex) this procedure can be far from satisfactory. Despite some data on their value, bifurcation techniques such as double-kiss-crush appear to have failed to have been taken up. Unfortunately, up to 70% of LMS disease affects the distal bifurcation.

Recent trial data have confirmed, however, that the role of PCI in LMS disease can be expanded. It remains essential that, if LMS intervention is being considered, the following basics are understood: one should know the published data, understand the

angiogram in detail, consider the whole patient and their comorbidities, consider the risks; have a management strategy and specifically a PCI strategy (and especially be experienced in the various bifurcation techniques if appropriate), and be able to interpret intravascular imaging.

The old and new data

Based on historic data, caution around treating LMS disease with PCI was justified. While many of these data were limited through being registry-based, the conclusions were sobering. The ULTIMA registry was published in 2001. In 250 patients, the 12-month MACE rate was 24% and the 12-month cardiac mortality rate was 9.1%¹. In-hospital mortality for higher-risk patients (elderly, bifurcation disease and surgical rejects) was 15%. Subsequent smaller registries reported similar findings. In those days, the use of bare metal stents meant that the restenosis rate was high, varying from 17.4%² to 33.6%¹. In 2005, Park et al reported a dramatic fall in MACE due to a reduction in restenosis (from 17.4% to 2%)³ with the use of drug-eluting stents. However, as a prelude to contemporary results, Takagi et al⁴ showed that MACE was doubled if distal bifurcation disease was treated with two stents. This was supported by a later report by Takagi et al which showed higher event rates especially driven by restenosis, even with the use of “generation 2”

*Corresponding author: Department of Cardiovascular Sciences, University of Leicester, Leicester Biomedical Research Centre, University of Leicester NHS Trust, Groby Road, Leicester, LE3 9QP, United Kingdom. E-mail: agershlick@aol.com

drug-eluting stents⁵. In 2008, Kim et al⁶ reported an event-free survival of 95% for overall LMS stenting, but a death, MI and TVR event-free survival of only 71% (with an HR for MACE of 12.9) when bifurcation disease was being treated. All these published data were in the absence of randomised trials of PCI versus coronary artery bypass surgery (CABG). Patient presentation also had an impact, with worse outcomes in those with emergent presentation⁷.

Therefore, at this time the indications for percutaneous intervention in LMS disease were: patients refusing CABG, those at very high risk for CABG, those with limited life expectancy, patients presenting with acute MI and/or cardiogenic shock, or those with protected LM disease. A number of studies, beyond registry data, then emerged. While these were still substudies, they added to our knowledge base with a picture emerging of likely outcomes with patients treated with either PCI or CABG. Firstly, there was the LMS substudy of the SYNTAX trial. The results of the substudy were dictated by the extent of non-LMS disease (as adjudicated by the SYNTAX score [SS]). Thus, for patients with an SS <32 (n=221), the MACE rate at five years was 31.3%, and with CABG (n=196) 32.1%. For those with an SS >32, the respective outcomes were 46.5% for PCI (n=135) but 29.7% for CABG (n=149), HR 1.78, p=0.003⁸. Such results, together with those from a meta-analysis, such as that from Cavalcante et al (n=1,305)⁹, which combined SYNTAX LMS and the PRECOMBAT trial, confirmed the impact of SS. A larger meta-analysis of four randomised trials from Capodanno et al¹⁰ showed no difference in death or MI, but an excess of strokes with CABG (HR favouring PCI 0.15 [0.03-0.67], p=0.01) and excess need for revascularisation with PCI (HR favouring CABG 2.25 [1.54-3.28], p<0.001). A picture emerged – in lower SS patients mortality may be no different, but revascularisation was higher in PCI patients.

The SYNTAX trial LMS substudy drove the US and 2014 ESC/EAPCI/EACTS Guidelines – SS 0-22, USA: PCI=IIa B/CABG=I B; ESC: I B for both. With SS 23-32, USA: PCI=IIb B/CABG=I B; ESC: PCI=IIa B/CABG=I B. For SS >32 for both USA Guidelines and ESC Guidelines, PCI=III B and CABG=I B^{11,12}.

All of the data up until this time had been either registry data, or substudies of primarily non-LMS trials, and none reflected contemporary revascularisation practice. First-generation stents were used (which had in the interim been shown to be significantly inferior to contemporary stents), intravascular ultrasound and fractional flow reserve were uncommon adjuncts, discretionary angiographic follow-up had tended to overinflate the number of events in the PCI arms, and best standards of coronary surgery were also underused. All patients had been included in the SYNTAX trial but this study had shown survival advantage for CABG in those patients with an SS >32. A randomised trial comparing contemporary revascularisation for LMS disease in appropriate, lower SS patients was clearly needed. Then, just when one trial was needed, two came along. The relative merits of these studies (EXCEL¹³ and NOBLE¹⁴) have been hotly debated. They were certainly different studies in some ways but similar in others. Both used contemporary drug-eluting stents (although 10% first-generation stents were used in

NOBLE), both supposedly enrolled patients with an SS <32 (specified in EXCEL), IVUS and FFR were recommended in both studies and routine angiography mandated against. Follow-up was for three years. The difference between the trials, which dictated somewhat the outcomes, was in the primary endpoint which consisted of MACCE comprising death, MI and cerebrovascular accident (CVA) in EXCEL, but these plus target vessel revascularisation in NOBLE. The former thus rather favoured PCI, the latter CABG. NOBLE excluded MI in the first 30 days.

EXCEL recruited 1,905 patients at 126 sites in 17 countries in the USA and the EU, between 2010 and 2014. NOBLE recruited 1,201 patients at 36 sites in nine EU countries between 2008 and 2015. Diabetics made up 30% of EXCEL and 15% of NOBLE patients, distal location was 80% in both, IVUS use approximately 75% in both, but off-pump and arterial conduit-only use were different (29% EXCEL versus 16% NOBLE, and 25% EXCEL versus 14% NOBLE, respectively). The value of the SS in LMS assessment has come to be questioned since, contrary to trial protocol in EXCEL, 17% of PCI patients and 14% of CABG patients were classified by the core lab as having an SS >32 – suggesting that there is great variance in physicians' ability to calculate the SS accurately. Similarly with NOBLE, an SS >32 occurred in 33% of the PCI group and 24% of the CABG group when this too was meant to be a “low SS” trial.

Both trials were presented back-to-back at TCT 2016. The major findings in EXCEL were that there was no difference in MACE at median follow-up of three years (15.4% versus 14.7%, HR 1.0) but an excess of morbidity in CABG patients at 30 days (the rate of death, stroke, or MI was significantly higher among the CABG-treated patients [4.9% vs. 7.9%; HR 0.61, 95% CI: 0.42-0.88]). This difference was driven by a significantly increased risk of MI (3.9% vs. 6.2%; HR 0.63, 95% CI: 0.42-0.95) at this time point. The EXCEL trial investigators concluded that “In patients with left main coronary artery disease and low or intermediate SYNTAX scores by site assessment, PCI with everolimus-eluting stents was non-inferior to CABG with respect to the rate of the composite end point of death, stroke, or myocardial infarction at 3 years”. There was, however, still a significant excess of the need for revascularisation (secondary endpoint) in the PCI arm despite third-generation DES.

There were some interesting observations in the NOBLE study. The MACE primary endpoint was significantly higher in the PCI arm, 28.7% versus 19.1% (difference exceeded limit for non-inferiority [p=0.007 for superiority]). Mortality (11.6% PCI versus 9.5% CABG) was no different. Oddly, there was an accumulation of MIs over time, with an incidence of 6.9% in the PCI arm versus 1.9% in the CABG arm up to five years (albeit only 120 in each arm at this time). This is something interventionists do not recognise (or do not look for), as was the rather unexpected reported excess of strokes in the PCI arm (4.9% versus 1.7%). Even more counterintuitive was the finding in NOBLE that the MACCE rate was higher in the PCI arm in the SS <22 subgroup as well as in the (to be expected) SS >32 subgroup.

These were similar but different trials that reported similar, but also different, outcomes.

Are there any absolute messages about LMS revascularisation that can be derived from these two studies? The following can probably be considered true:

- There is no difference between PCI and CABG in overall or cardiovascular mortality (3%-3.5% for both groups, both trials at median three years).
- Incidence of MI appears to depend on how it is defined and how it is measured (early excess in EXCEL in CABG group to 30 days; cumulative excess in the PCI arm to five years in NOBLE).
- CABG is associated with a significant excess morbidity – for both trials. Any periprocedural event in EXCEL was seen in 8.1% of the PCI arm but in 23.0% of the CABG arm ($p < 0.001$). In NOBLE, re-operation and blood transfusion occurred highly more significantly in CABG and length of stay was significantly longer (nine days versus two days).
- Despite the use (even in EXCEL) of third-generation contemporary stents, revascularisation is required more often in PCI. This difference is about 4-5 absolute % points between PCI and CABG. However, we should note that this is for all cases – a *post hoc* analysis of EXCEL has been completed and this may not be true for ostial/shaft lesions.
- Excess of strokes in the CABG patient appears not to be confirmed by these two trials.
- The SYNTAX score appears to be of limited value in LMS disease. It was underestimated by 75% by the sites in EXCEL compared to the core lab.
- Five-year follow-up (and beyond) is essential.

What can we conclude so far? In the treatment of LMS coronary disease, PCI compared to CABG results in equivalent mortality benefits, lower rates of procedural morbidity, lower rates of periprocedural MI but higher rates of non-procedural MI, greater need for repeat revascularisation, and SYNTAX scoring is of limited use. Will these trials change the guidelines? Maybe not, since that would have been likely only if PCI had been shown to be superior, but they should help guide physicians and the Heart Team in deciding on strategies in individual patients (taking account of the skills of the operators and patient preference when there is revascularisation equipoise). It is unlikely that there will be further large randomised trials, but this will depend on hypothesis-generating information from the substudies.

There are indeed many *a priori post hoc* substudies from these studies still to come. For TCT 2017, 29 EXCEL abstracts have been accepted for presentation. These two trials and their substudies will help in smart decision making around LMS revascularisation – but we have to move on from the past and definitively not get stuck with “LMS disease automatically means CABG”. That is old thinking and definitely not in the patient’s best interest.

Conflict of interest statement

A. Gershlick receives travel sponsorship and speaker’s fees from Abbott Vascular and Medtronic. A. Banning has no conflicts of interest to declare.

References

1. Tan WA, Tamai H, Park SJ, Plokker HW, Nobuyoshi M, Suzuki T, Colombo A, Macaya C, Holmes DR Jr, Cohen DJ, Whitlow PL, Ellis SG; ULTIMA Investigators. Long-term clinical outcomes after unprotected left main trunk percutaneous revascularization in 279 patients. *Circulation*. 2001;104:1609-14.
2. Silvestri M, Barragan P, Sainsous J, Bayet G, Simeoni JB, Roquebert PO, Macaluso G, Bouvier JL, Comet B. Unprotected left main coronary artery stenting: immediate and medium-term outcomes of 140 elective procedures. *J Am Coll Cardiol*. 2000;35:1543-50.
3. Park SJ, Kim YH, Lee BK, Lee SW, Lee CW, Hong MK, Kim JJ, Mintz GS, Park SW. Sirolimus-eluting stent implantation for unprotected left main coronary artery stenosis comparison with bare metal stent implantation. *J Am Coll Cardiol*. 2005;45:351-6.
4. Takagi K, Ielasi A, Shannon J, Latib A, Godino C, Davidavicius G, Mussardo M, Ferrarello S, Figini F, Carlino M, Montorfano M, Chieffo A, Nakamura S, Colombo A. Clinical and procedural predictors of suboptimal outcome after the treatment of drug-eluting stent restenosis in the unprotected distal left main stem: the Milan and New-Tokyo (MITO) registry. *Circ Cardiovasc Interv*. 2012;5:491-8.
5. Takagi K, Naganuma T, Chieffo A, Fujino Y, Latib A, Tahara S, Ishiguro H, Montorfano M, Carlino M, Kawamoto H, Kurita N, Hozawa K, Nakamura S, Nakamura S, Colombo A. Comparison Between 1- and 2-Stent Strategies in Unprotected Distal Left Main Disease: The Milan and New-Tokyo Registry. *Circ Cardiovasc Interv*. 2016 Nov;9(11).
6. Kim YH, Dangas GD, Solinas E, Aoki J, Parise H, Kimura M, Franklin-Bond T, Dasgupta NK, Kirtane AJ, Moussa I, Lansky AJ, Collins M, Stone GW, Leon MB, Moses JW, Mehran R. Effectiveness of drug-eluting stent implantation for patients with unprotected left main coronary artery stenosis. *Am J Cardiol*. 2008;101:801-6.
7. Almurdarra SS, Gale CP, Baxter PD, Fleming SJ, Brogan RA, Ludman PF, de Belder MA, Curzen NP; National Institute for Cardiovascular Outcomes Research (NICOR). Comparative outcomes after unprotected left main stem percutaneous coronary intervention: a national linked cohort study of 5,065 acute and elective cases from the BCIS Registry (British Cardiovascular Intervention Society). *JACC Cardiovasc Interv*. 2014;7:717-30.
8. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Stähle E, Colombo A, Mack MJ, Holmes DR, Choi JW, Ruzyllo W, Religa G, Huang J, Roy K, Dawkins KD, Mohr F. Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. *Circulation*. 2014;129:2388-94.
9. Cavalcante R, Sotomi Y, Lee CW, Ahn JM, Farooq V, Tateishi H, Tenekecioglu E, Zeng Y, Suwannasom P, Collet C, Albuquerque FN, Onuma Y, Park SJ, Serruys PW. Outcomes After Percutaneous Coronary Intervention or Bypass Surgery in Patients With Unprotected Left Main Disease. *J Am Coll Cardiol*. 2016;68:999-1009.

10. Capodanno D, Stone GW, Morice MC, Bass TA, Tamburino C. Percutaneous coronary intervention versus coronary artery bypass graft surgery in left main coronary artery disease: a meta-analysis of randomized clinical data. *J Am Coll Cardiol.* 2011;58:1426-32.
11. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J.* 2014;35:2541-619.
12. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, Douglas PS, Foody JM, Gerber TC, Hinderliter AL, King SB 3rd, Kligfield PD, Krumholz HM, Kwong RY, Lim MJ, Linderbaum JA, Mack MJ, Munger MA, Prager RL, Sabik JF, Shaw LJ, Sikkema JD, Smith CR Jr, Smith SC Jr, Spertus JA, Williams SV; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; American College of Physicians; American Association for Thoracic Surgery; Preventive Cardiovascular Nurses Association; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol.* 2012;60:e44-164.
13. Stone GW, Sabik JF, Serruys PW, Simonton CA, Généreux P, Puskas J, Kandzari DE, Morice MC, Lembo N, Brown WM 3rd, Taggart DP, Banning A, Merkely B, Horkay F, Boonstra PW, van Boven AJ, Ungi I, Bogáts G, Mansour S, Noiseux N, Sabaté M, Pomar J, Hickey M, Gershlick A, Buszman P, Bochenek A, Schampaert E, Pagé P, Dressler O, Kosmidou I, Mehran R, Pocock SJ, Kappetein AP; EXCEL Trial Investigators. Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease. *N Engl J Med.* 2016;375:2223-35.
14. Mäkikallio T, Holm NR, Lindsay M, Spence MS, Erglis A, Menown IB, Trovik T, Eskola M, Romppanen H, Kellerth T, Ravkilde J, Jensen LO, Kalinauskas G, Linder RB, Pentikainen M, Hervold A, Banning A, Zaman A, Cotton J, Eriksen E, Margus S, Sørensen HT, Nielsen PH, Niemelä M, Kervinen K, Lassen JF, Maeng M, Oldroyd K, Berg G, Walsh SJ, Hanratty CG, Kumsars I, Stradins P, Steigen TK, Fröbert O, Graham AN, Endresen PC, Corbascio M, Kajander O, Trivedi U, Hartikainen J, Anttila V, Hildick-Smith D, Thuesen L, Christiansen EH; NOBLE study investigators. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. *Lancet.* 2016;388:2743-52.