

Key words: Percutaneous coronary intervention, PCI, left main stem

Unprotected stenosis of the left main coronary artery greater than 50% has traditionally been managed with coronary artery bypass surgery (CABG). There is now emerging evidence to support the use of percutaneous coronary intervention (PCI) with drug-eluting stents, especially in patients at high risk for surgery. However, the widespread use of PCI instead of CABG remains very controversial.

In this issue, an interventional cardiologist discusses this question and presents his own perspective on the appropriate selection of therapeutic strategy. The available evidence is reviewed and summarized and some of the unanswered questions are highlighted. Several large clinical trials comparing percutaneous to surgical intervention are currently in progress and the results of these will help clarify the situation.

In the next issue, the question will be viewed from the perspective of a cardiac surgeon.

Left main stem stenting

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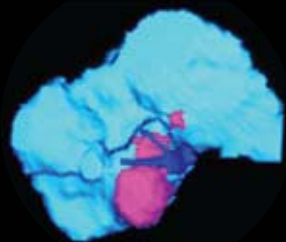
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Dr Gershlick trained in cardiology in London and moved to the University of Leicester in 1990 to take up a formal Senior Lecturer's post, transferring to the NHS in 1993. However, he has maintained a significant research interest, publishing extensively in the area of vessel wall/blood interactions especially those that occur following percutaneous coronary intervention. Research has included basic laboratory work involving drug-eluting stents, and he has also been principal investigator in a number of national and international studies. Dr Gershlick is currently involved in studies of myoblast injection and bone marrow cells for patients with failed lysis and impaired left ventricular function. He is a council member of the British Cardiac Society, Scientific Officer of the British Cardiovascular Intervention Society and Chairman of the local Cardiovascular Programme Board.

Abstract

Percutaneous treatment of obstructive coronary disease has, for a number of years, been undertaken more commonly than the coronary artery bypass graft (CABG). Technical developments, operator skill and the advent of drug-eluting stents has meant that most lesions can be treated effectively with little associated morbidity and with rapid patient discharge. When considering more complex disease two issues need to be considered:

- Can it be technically undertaken safely with percutaneous coronary intervention (PCI)?
- Are there data to suggest the benefit of one revascularisation technique over another?

There are no robust data that approach the rigours of unchallengeable evidence to support CABG over PCI. The only randomised study comparing the two will be published in 2008. In the meantime, each case should be viewed individually – patients with co-morbidity or with lesions in the ostium or the body should be seriously considered for PCI. Those with bifurcation disease might, because of the increased technical aspects of PCI in such cases, be considered for CABG.

Introduction

Percutaneous coronary angioplasty is now the dominant therapy for treating symptomatic obstructive coronary disease. It has progressed from being a therapy tailored towards straightforward simple lesions to encompassing complex disease previously considered suitable for coronary artery bypass graft (CABG) surgery only. This article will

explore the devolution of percutaneous coronary intervention (PCI) into previously surgical disease, address the data available and indicate best contemporary practice.

The evolution of PCI

Percutaneous coronary angioplasty has undergone considerable development and overcome many inherent problems since it was first introduced by Andreas Gruntzig in 1977. The 1980s saw a rapid expansion in PCI with crossover in numerical terms from CABG to angioplasty occurring as early as 1998 in the United States. However, there were problems that needed resolving.

The first of these was restenosis, which in the early 1990s was a catch-all term describing the pathological changes that developed in up to 35% of patients after balloon angioplasty, resulting in the need for a repeat procedure. Restenosis was thought to be the consequence of scar tissue formed through response-to-injury mechanisms within the vessel wall which then encroached on the lumen. A more immediate problem was acute vessel closure. PCI causes intimal layer disruption – indeed, this is partly how balloon angioplasty works. In the late 1980s/early 1990s, acute closure of ballooned vessels led to many patients needing emergency CABG surgery to prevent myocardial infarction/death.

The development of the stent to prevent the disrupted flap from obstructing the lumen was a critical breakthrough. As stent use accelerated to 90% throughout the 1990s, the need for emergency

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surgery plummeted and is now rare (<0.5%). Safer PCI was a major turning point in the shift from surgery. Furthermore, it was observed that with increased stent use the restenosis rate/need for a repeat procedure also fell from 35% with balloon alone to 15–20% with stenting. Our understanding of the causes of luminal re-narrowing now had to take account of other benefits of stenting. Recurrence was composed of 3 components: recoil of the vessel wall, late negative re-modelling and the response-to-injury scar. Stents clearly dealt with the recoil and the negative re-modelling, leaving only the problematic scar formation.

Meanwhile, it became clear that stenting carried with it a risk of thrombus formation. Pivotal studies comparing anti-thrombotics (e.g. coumadins) with anti-platelet medication highlighted the value of pre- and post-procedural dual anti-platelet therapy (aspirin for life and thienopyridines such as clopidogrel for one month).

A critical development in PCI was that of drug-eluting stents (DES) that inhibit tissue growth. Throughout the 1990s, studies were published on the loading/elution from stents of tiny but locally high concentrations of drugs.¹ Rapid expansion of the concept of DES and research developments by many groups led to pivotal clinical trials.²⁻⁴ Use of DES reduced clinical recurrence by 80% (from 15+% to ~5–7%) especially in those patients at greatest risk of recurrence (small vessel diameters, long lesions and diabetics). Such indications were approved by the National Institute for Clinical Excellence (NICE) in 2003. Concerns regarding the small chance of excess stent thrombosis beyond the time frame for a bare metal stent are currently under review, with prolonged anti-platelet therapy recommended.

Results with contemporary PCI reflect the evolution described. The British Cardiovascular Society 2005 audit figure returns indicate procedural success rates of 92%; Q wave MI rates of 0.3% and mortality of 0.59%. In the UK in 2005, 28% of cases were multivessel PCI and on average, 1.28 lesions were treated per case. Longer-term clinical repeat revascularisation rates for complex real world off-label lesions with drug-eluting stents have recently been published at 4–8%.⁵

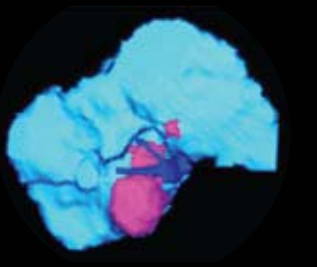
The question that is pertinent of course is how PCI and surgery compare in studies of more complex patients and in particular multivessel/left main stem (LMS) disease?

PCI vs. surgery in multi-vessel disease

Any reported so-called benefit for surgery in such patients appears to be based on rather questionable registry data. The first registry reported was that by Hannan⁶ who compared 3-year survival outcomes of CABG and PCI patients from two New York State databases, and showed an apparent advantage favouring surgery. Why only a small proportion of patients treated in New York State during this period (37,212 reported of 75,217 CABGs performed and 22,102 reported of 137,798 PCIs performed) were included in this analysis is unclear. The demographic data for the two cohorts were very different with p values of <0.01 for most comparators, and while these appear to disadvantage the surgical cohort, many of the differences are small (EF 53% vs. 50%) or would appear not to have a major impact on mortality (peripheral vascular disease). Previous myocardial infarction was "significantly" higher in the stent group. In any event, whether any statistical correction can take account of such differences is questionable. The unadjusted hazard ratios show no difference in outcome, irrespective of 2- or 3-vessel disease or involvement of the left anterior descending artery (LAD); the significant differences only appeared once the ratios were "adjusted" to attempt to equalise groups. Such differences in patient cohorts make comparisons non-robust and highly questionable.

Similar criticism can be directed towards Brener⁷ who apparently showed a similar benefit for surgery, this time using propensity analyses. Even the authors acknowledge that although "propensity analyses are powerful, they are inherently limited by the number and accuracy of the variable evaluated. There have been substantial changes in the management of PCI since this cohort was analysed." Since differences between the registry populations were again so large, one should be sceptical that any statistical test could take account of these and the two groups – of 800 PCIs and 5000 CABGs – could be considered different non-comparable populations.

Finally, a meta-analysis by Hoffman⁸ suggests a survival benefit favouring surgery in patients with multivessel disease at 5 and 8 years (but no difference at 1 and 3 years) and must be questioned. Patency of grafts falls over time making the contention of increased benefit of surgery over time counter-intuitive. Worse still, 10 of the 13 trials included in the meta-analysis were in the pre-stent (balloon angioplasty) era.



There are data to support mortality equivalence for PCI and CABG in multi-vessel disease. There have been three randomised trials comparing stenting with surgery⁹⁻¹¹ which showed no mortality or acute myocardial infarction (AMI) difference in the groups at 1 year. The ARTS I study, which randomised patients to bare metal stents (BMS) or CABG, has now reported 92% survival for BMS and 92.4% for CABG at 5.5 years.¹⁰ These outcome data are supported by 5-year data from the recently published MASS II randomised trial¹¹ (which showed no significant difference in the hard endpoints of death or AMI in the CABG and PCI groups). A meta-analysis of all three DES trials at one year by Mercado¹² indicated mortality of 3% for PCI and 2.8% for CABG. Those who say that these trials favour PCI, because higher risk patients were excluded, should consider the similarity in demographic and extent of disease in both groups in these analyses. The ERACI III¹² and ARTS II^{13,14} DES trials show comparable mortality and AMI rates to BMS at 12 months. All of these data support there being no difference in mortality between the techniques (with or without DES) in randomised trials with up to 5-year follow-up.

Contemporary treatment of left main stem disease

The prevalence of stenosis of the left main coronary artery at coronary angiography is approximately 5%. There is no difference in presentation, electrocardiographic or stress test features compared with other severe coronary artery disease.

Current treatment considerations for left main stem disease are also evolving and the surgery-only paradigm has now been questioned, as PCI has become an increasingly reliable procedure with robust outcomes. The concept that surgery is the only acceptable treatment for left main stem disease is based on historical comparisons with medical therapy. It was the CASS registry (note this was a registry) of 1484 patients which established surgery as the preferred treatment option (compared to medical therapy); the 15-year survival showed a highly significant advantage for surgery (37% vs. 27%) with the mean surgical survival of 13.3 years vs. medical 6.6 years. Issues such as crossover and actual treatment received are difficult to pick out from these data. However, this set the bench mark and the standard of care at that time and since then. It should be noted that the results held only for those with impaired left ventricular function; 15-year cumulative survival for patients with normal LV systolic function in the surgical and medical groups was 42% and 51%, respectively.

Median survival was 14.7 years in the surgical group and >15 years in the medical group (p=NS). Those with severely impaired LV function did badly irrespective of surgical or medical treatment. There have been no published randomised comparisons of surgery with PCI.

What of PCI for left main stem disease? Initial reports, some 20 years after the first surgical reports, were in high-risk patients with the Oxford group reporting good outcomes in 5 elderly patients with unstable angina and significant co-morbidities. In the late 1990s, further reports appeared of good outcomes with bail-out stenting in patients suffering catheter-induced trauma to the left main stem. A retrospective registry from Marco in 2000 reported on 92 LMS patients treated with PCI, the first 39 of which were surgical rejects, and indicated an in-hospital mortality of 4% and an actuarial survival of 89% at 12 months and 85% at 36 months.¹⁵ The ULTIMA registry of 279 patients treated with PCI for LMS disease helped determine which patients did best with non-surgical treatment. The overall 12-month mortality was 9%, but when patients were divided according to risk (low risk = <75 years of age, EF >40%, large vessels >3 mm; high risk = older, surgical rejects, cardiogenic shock, LMS bifurcation disease, high Euroscore) then the outcomes were considerably different, with one-year mortality of 3.4% for the low-risk group and 28% for the high-risk group. The spectrum of patients treated with PCI, including the inclusion of surgical rejects, has led to variance in mortality after follow-up of 6–31 months ranging from 3.1% to 20.2% (Figure 1).

One issue has been recurrence due to restenosis. Three series have shown improved outcome in this context with the use of DES.¹⁶⁻¹⁸ While mortality did not increase with DES, the target lesion revascularisation rates fell from between 17–20% to 2–6% when bare metal stents were replaced with drug-eluting stents. However, this was not the case for all series with one from the Italian group¹⁶ reporting lesser reduction in need for repeat revascularisation.

The difference between the patients in this series and those from Rotterdam or South Korea was the frequency of LMS bifurcation disease, being present in 14% of the Colombo cohort but only in 6% and 2% of the other two.

This factor becomes the linchpin of the discussion. The outcomes with contemporary PCI for LMS disease in lower-risk patients appear to show low mortality

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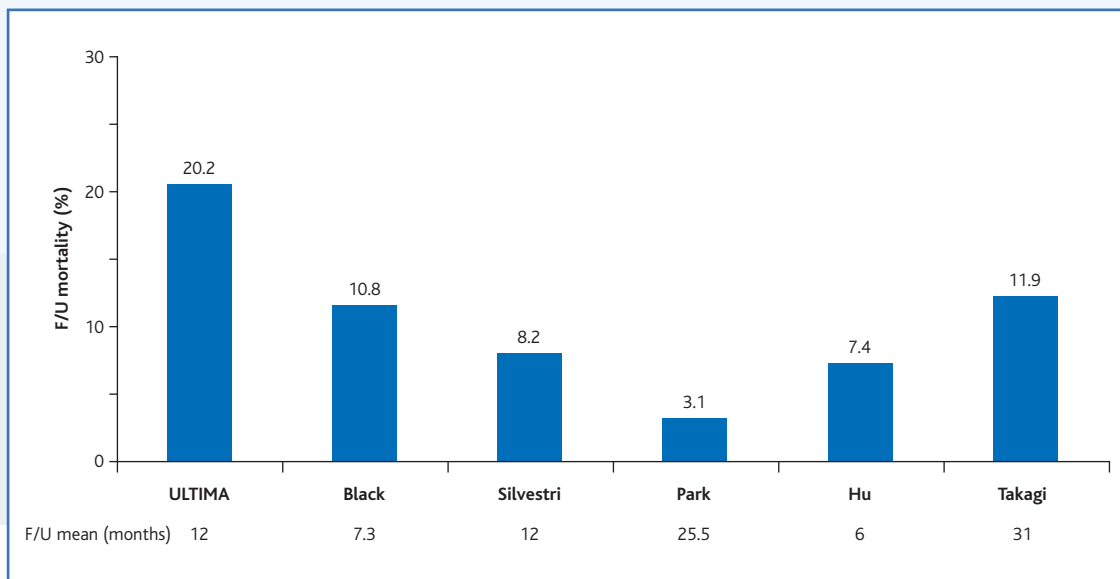


Figure 1. Mortality at follow-up in PCI series in unprotected left main stem stenosis.

and low incidence of need for repeat procedure. The issues are how good the interventionists are at dealing with bifurcation disease (especially important if this disease is at the end of the LMS) and what level of risk helps determine outcome and therefore which treatment strategy should be adopted. There is a relationship between bifurcation and major adverse cardiac events (MACE), which relates to the technical aspects of treating a bifurcation. Many of the original techniques involved the use of two stents with various methods utilised (crush, culotte) to cover the origin of both vessels. Increasingly, single so-called provisional (simplified) stenting has become the standard method of dealing with bifurcation disease particularly following publication of the Nordic data.¹⁹ Such considerations are important since the mean incidence of bifurcation disease in all LMS series is 53%, with ostial or body disease making up the rest. In the European retrospective multicentre study of 12-month outcomes for LMS PCI (n= 300), 12-month mortality was 4.8% irrespective of the presence of bifurcating disease or not but the need for a repeat procedure was 8.7% in the bifurcating cases compared to 2.4% in the non-bifurcated cases (Figure 2).

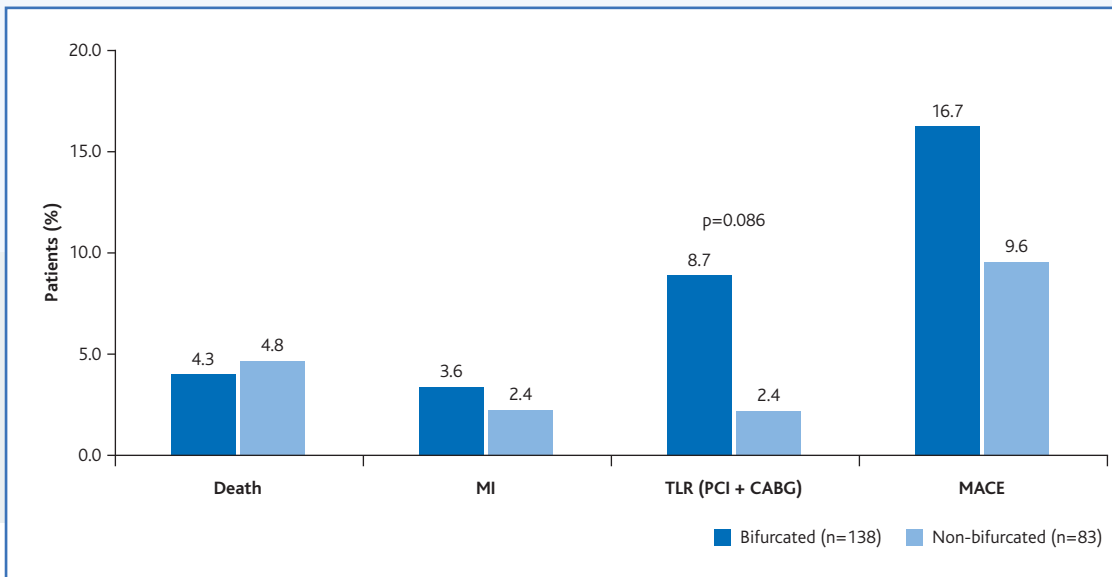
Hence, with simple and especially with ostial and body lesions of the LMS, PCI outcomes appear good, especially in lower-risk patients. In the absence of direct surgical comparisons, what evidence do we have concerning the outcomes with surgery and which patients should receive which therapy? When reported, the surgical data tend not to include the

12.8% New York State 3-year mortality or the 1374 patient Duke database of 22.6% death at 5 years. Veldkamp reported a survival of <20% for surgically treated LMS at 20 years.²⁰

So are there any registry data comparing the two treatments in the absence, as yet, of a randomised trial? Certainly, the French registry comparing 192 PCI patients with 230 surgical patients shows no difference in mortality at one year (9.4% vs. 11.6% respectively; Figure 3), and a similar Italian registry (Figure 4) suggests similar results in a comparison of 107 patients treated with DES, and 139 with CABG (84 off-pump and 55 on-pump). The mortality rates at one year were 2.8% and 6.4% (5.9%, 7.2%) respectively. Finally, Lee²¹ published outcomes for LMS disease. In this series of 183 patients of whom 50 had PCI with DES, PCI patients were required to be:

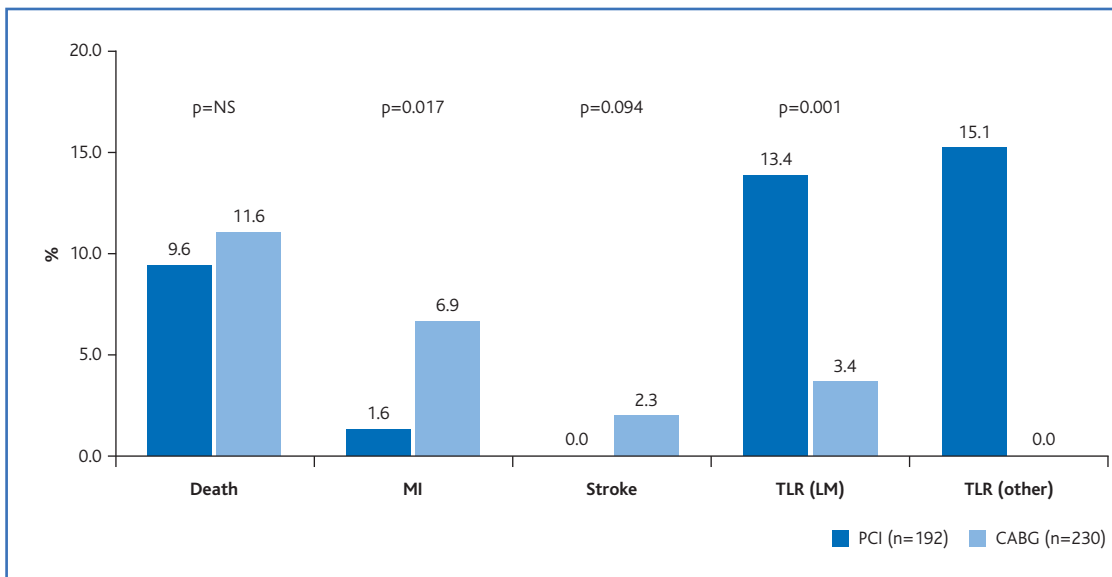
- high risk for CABG
- have limited life expectancy
- unwilling to undergo CABG
- deemed unsuitable for CABG by surgeon.

Perhaps not surprisingly, the PCI group contained fewer men (50% vs. 76%, p<0.01), more patients with chronic renal insufficiency (16% vs. 5%, p=0.02), more with unstable angina (46% vs. 25%, p=0.02) and had a higher mean Parsonnet score (18.3 vs. 13.7, p<0.01). Despite the adverse weighting, the freedom from MACE at one year was 82.9% for the PCI group and 75.2% for the CABG group (Figure 5).



CABG – Coronary artery bypass graft; MACE – Major adverse cardiac events; MI – Myocardial infarction; PCI – Percutaneous coronary intervention; TLR – Target lesion revascularisation

Figure 2. Clinical outcomes at 1 year after stenting in cases with and without bifurcation disease.



CABG – Coronary artery bypass graft; LM – Left main; MI – Myocardial infarction; PCI – Percutaneous coronary intervention; TLR – Target lesion revascularisation

Figure 3. Comparison of clinical outcomes at 1 year after CABG or PCI, in the bare metal stent era (French left main registry).¹⁵

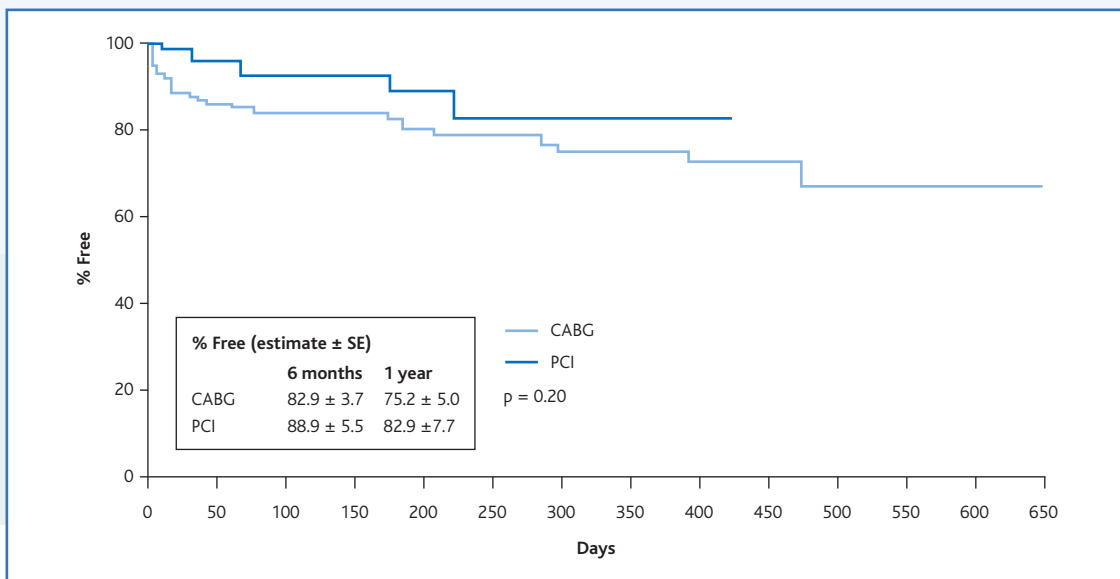
	One-year outcome			
	DES (n=107)	CABG (n=139)	On pump (n=84)	Off pump (n=55)
MI	1 (0.9%)	2 (1.4%)	1 (1.2%)	1 (1.7%)
TLR	17 (15.8%)	5 (3.6%)	2 (2.4%)	3 (5.4%)
TVR	21 (19.6%)	5 (3.6%)	2 (2.4%)	3 (5.4%)
CVE	1 (0.9%)	1 (0.7%)	1 (1.2%)	0
Death	3 (2.8%)	9 (6.4%)	5 (5.9%)	4 (7.2%)

CABG – Coronary artery bypass graft; CVE – Cardiovascular events; DES – Drug-eluting stents; MI – Myocardial infarction; PCI – Percutaneous coronary intervention; TLR – Target lesion revascularisation; TVR – Target vessel revascularisation

Figure 4. Clinical outcomes at 1 year after CABG (on or off pump) or PCI with DES (Italian registry).¹⁶

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CABG – Coronary artery bypass graft; DES – Drug-eluting stents; PCI – Percutaneous coronary intervention

Figure 5. Survival free of MACCE (major adverse cardiac and cerebrovascular events) in patients treated with CABG or PCI with DES.²⁷

PCI vs. CABG in LM (LE MANS randomised trial)			
Outcome 30 days	PCI (52)	CABG (53)	p
Death	0	2	
MI	1	2	
CVA	0	2	
MACE	2 (3.8%)	9 (20.7%)	<0.02
Outcome 1–12 months	PCI (52)	CABG (53)	p
Change LVF	+5%	0	<0.05
Death	1	2	
MI/CVA	0	0	
Revasc	8	7	
MACE	11 (21%)	11 (20%)	ns

CABG – Coronary artery bypass graft; CVA – Cerebrovascular accidents; LM – Left main; MACE – Major adverse cardiac events; MI – Myocardial infarction; PCI – Percutaneous coronary intervention

Figure 6. Clinical outcomes after PCI or CABG in the LE MANS randomized trial.

The most important study in this area, the SYNTAX trial (n=1800), has completed recruitment. Patients with 3-vessel disease or left main stem with or without 3-vessel disease were randomised following agreement between surgeons and interventionists to either PCI strategy (using DES) or surgery. Critically, there will be follow-up on the nested registry group of patients deemed by consensus to be best treated by either surgery or PCI and therefore not randomised. Even more importantly, following the presentation of the small LE MANS randomised trial which suggested equivalent outcome for PCI patients and surgery (Figure 6), the SYNTAX study was expanded to allow sufficient power to include analysis of LMS patients

alone and separately from the 3-vessel disease group. Angiographic follow-up at 15 months in both PCI *and* surgical patients will provide intriguing results. To date, the Data and Safety Monitoring Board (DSMB) have met twice for the SYNTAX study and the trial was allowed to randomise to completion.

Summary: how to decide on which therapy for which patient presenting with LMS disease

PCI has come a long way and for most patients is a day-case procedure with minimal morbidity and good longer-term outcomes. Those with LMS disease comprise a small heterogeneous but important group for whom choice of therapy is more difficult

not least being set against a background of the standard of care historically being CABG, albeit this has evolved from comparisons with medical therapy. Each patient with LMS disease should be discussed at a multidisciplinary team meeting and the following issues taken into account. Ostial and body disease in lower-risk patients should be considered primarily as suitable for PCI, with any concerns over the small and clinically insignificant excess late stent thrombosis leading to consideration of use of BMS in these essentially large vessels. Even so, patients should be told that in the absence as yet of any randomised data, the current standard of care even in this low risk for PCI group is CABG, with the multiple disadvantages of surgery also being highlighted. In higher-risk patients, especially those with recognised co-morbidity and in particular those constituting surgical rejects (which will vary according to surgeon),

the discussion requires even greater understanding of the issues. Those with bifurcation disease, in the absence of robust absolute understanding of how best to guarantee PCI results, may well still be considered to be surgical candidates. Those who will not survive an operation but who are at risk from their LMS disease or who have significant life-limiting symptoms should be considered for PCI with clear discussions with the patient and relative and clear indication of risk in any PCI audit database. SYNTAX may well tell us the answer as to how best treat LMS disease but it is clear that in this context, as for other comparisons of PCI vs. surgery, the shift is toward PCI. When the surgeons try to attract attention, one should consider if they are waving or drowning. From an interventional cardiologist's point of view, PCI will eventually replace CABG in all patients.

Study abbreviations

ARTS I – Arterial Revascularization Therapy Study I
ARTS II – Arterial Revascularization Therapy Study II
CASS Registry – Coronary Artery Surgery Study Registry
ERACI III Trial – Argentine Randomized Trial of Coronary Stents *versus* Bypass Surgery Trial
LE MANS – Study of Unprotected Left Main Stenting *versus* Bypass Surgery

MASS II – Medicine, Angioplasty, or Surgery Study
SYNTAX Trial – Synergy Between PCI and TAXUS and Cardiac Surgery Trial
ULTIMA Registry – Unprotected Left Main Trunk Intervention Multicenter Assessment Registry

Key Learning

- Don't depend on historical data
- Don't depend on the title of any study to convince you that its contents are robust
- Review all cases of LMS with colleagues – experienced interventionists as well as surgeons
- Discuss the real risks and outcomes with the patient and their relatives
- Await the results of randomised controlled trials before coming to any conclusions regarding the optimal treatment for LMS disease.

Left main stem stenting *continued*

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