The role of CABG in the era of drug-eluting stents: a surgeon’s viewpoint

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ABSTRACT
Advances in transcatheter technologies, from balloon angioplasty to bare metal stents to drug-eluting stents, have resulted in improved outcomes following percutaneous coronary intervention (PCI). As a consequence, the differences in outcomes between coronary artery bypass graft surgery (CABG) and PCI have become less significant over short-term follow-up. In addition, the number of patients undergoing coronary revascularisation with PCI has increased and far exceeds that of CABG, which has declined, the ratio stabilising in recent years. With the advent of drug-eluting stents and the increasing off-label use of these stents—and in the setting of questionable public awareness of the relative risks and benefits of the therapeutic options of optimal medical treatment and revascularisation by PCI or CABG—the role of CABG requires clarification and reaffirmation. Recent clinical trials have helped to better define the relative benefits of each treatment modality. The mid- and long-term results of these studies remain to be seen, however, while the evidence for the role of PCI in left main stem disease remains inconclusive at the present time. In this context of continually emerging clinical evidence, this review seeks to provide a balanced opinion regarding the role of CABG in the era of drug-eluting stents.

INTRODUCTION
The management of coronary artery disease has evolved significantly over the past three decades. This time period has witnessed improvements in the management of angina and acute myocardial infarction (AMI), improvements in risk factor management and in primary and secondary prevention, continually improving outcomes following coronary artery bypass graft surgery (CABG), the development of percutaneous coronary intervention (PCI), and the continuing technological innovations for PCI—performed initially by balloon angioplasty (POBA), then using bare metal stents (BMS), and now drug-eluting stents (DES) and drug-eluting balloons (DEB). In combination, these medical, surgical and interventional advances have translated into fewer patients presenting with transmural myocardial infarction, better survival rates following AMI and reduced coronary heart disease mortality.

While some of the improvement in coronary heart disease survival can be attributed to increasing numbers of patients undergoing coronary revascularisation over the past two decades, by far the majority of the reduction in mortality is attributable to reductions in major risk factors (primarily smoking), and to improvements in medical management and in primary and secondary prevention.1 2 Revascularisation itself has had a small impact on coronary heart disease survival,3 and with this in mind we hope to retain some perspective. With regard to the observed increase in revascularisation rates, this is accounted for largely by a rise in PCI volume rather than in CABG volume.3 4 Although this trend has stabilised in recent years, the advent of DES and the emerging evidence from recent trials mean the time has come to re-evaluate the respective roles of CABG and PCI in the current era.

PCI OR CABG: THE EVIDENCE BEFORE DES
In recent years, controversy has arisen to fuel the debate between PCI and CABG for coronary revascularisation.4 5 It is clear from the evidence available that, when performed appropriately, PCI offers excellent mid-term survival outcomes for patients when compared with CABG, with similar mortalities over 5 years in clinical trials where PCI is performed either by POBA or using BMS,6 and in trials using BMS at PCI.7 These comparable survival outcomes are seen particularly in non-diabetic patients with uncomplicated two- vessel disease6 and in patients younger than 55 years of age.5 The controversy arises from the extrapolation of this evidence, derived from highly selected clinical trial patient populations,4 to justify PCI in patients with complex multivessel disease—despite good ‘real-world’ data reaffirming the superiority of CABG in patients with severe triple-vessel disease.5

Closer scrutiny of the previous trials comparing PCI and CABG has highlighted significant bias in trial design against CABG showing any survival benefit to patients.4 To quote Professor Taggart, in previous trials comparing PCI with CABG (excluding the recent Syntax Study): ‘the vast majority of these patients had single-vessel or double-vessel disease and normal left ventricular function, a population in whom it had already been clearly established that there was no prognostic benefit from surgery.7 This patient recruitment bias inherent in the trials (that are not quoted directly in this paper, but are discussed in Taggart,8 Bravata et al.6 Daemen et al7 and Hlatky et al8) is also reflected in the New York cardiac registry data for CABG and PCI,9 where it was shown that patients in the CABG group had more comorbidity (and hence would have been excluded from the earlier trials), and that risk-adjusted survival outcomes actually favoured CABG for both two- and three-vessel disease.

The major shortcoming of PCI in the studies comparing PCI using POBA or BMS with CABG has been the greater need for repeat revascularisation following PCI.5 10 In this respect, although PCI can be said to be comparable with CABG in terms of patient safety outcomes in these studies, it
falls short with respect to clinical effectiveness in treating coronary artery disease. In addition to this shortfall in clinical effectiveness when compared with CABG, revascularisation by PCI does not always achieve better outcomes than medical management alone. Recent trials comparing PCI with optimal medical therapy in stable angina have not shown any significant benefit from PCI: although PCI was shown to provide better angina relief in the MASS-II study\textsuperscript{10} and short-lived benefits in quality of life in the Courage study\textsuperscript{11} compared with medical therapy, it did not achieve any survival benefit or prolong life\textsuperscript{10–14}.

The lack of a significant difference between PCI and optimal medical therapy is confirmed by the recent BARI 2D study in patients with diabetes.\textsuperscript{14} It is important to use caution in interpreting the findings of this study, however: it fell short of the target 2800 patients, with only 2194 patients completing the study as designed,\textsuperscript{14} and this small sample size may have resulted in a Type II error (ie, false-negative reporting due to inadequate sample size). Nevertheless, the key findings reported in this study—that are relevant to this discussion—are that, at 5-year follow-up, there was no difference in primary outcome (all-cause mortality) between revascularisation (by CABG or PCI) and optimal medical therapy, but that CABG provided better secondary outcomes (ie, freedom from death, myocardial infarction or stroke), whereas PCI did not.\textsuperscript{14} Although the CABG and PCI populations in this study are not directly comparable, this study supports the evidence that PCI offers no benefit over optimal medical therapy in stable coronary disease, and that CABG is a safe and effective approach where revascularisation is indicated.

Given the need for repeat revascularisation following PCI and the lack of benefit compared with optimal medical therapy in stable angina, the cost-effectiveness of PCI comes into question both for patients with stable angina that can be managed medically and for patients with multivessel disease requiring revascularisation who can be treated effectively by CABG. Despite this shortfall in clinical effectiveness and possibly also cost-effectiveness, however, PCI remains prevalent. The symptomatic and quality of life benefits—however short-lived—are real gains for patients with severe symptoms, and it is valid to note that the introduction and implementation of DES have improved outcomes following PCI. The controversy\textsuperscript{4} remains, and it is therefore important to consider the evidence for PCI using DES.

**CURRENT EVIDENCE FOR DES**

Although early studies showed reduced in-stent restenosis rates in DES compared with BMS,\textsuperscript{15,16} concerns have been raised over the safety of DES following reports of early stent thrombosis.\textsuperscript{17} These concerns have largely been laid to rest, with no evidence of increased rates of death or myocardial infarction following PCI with DES,\textsuperscript{18–20} despite a slightly higher incidence of stent thrombosis,\textsuperscript{18} compared with BMS. In addition to being at least as safe as BMS, PCI using DES appears to be superior with regard to lower revascularisation rates,\textsuperscript{18–20} most likely attributable to the lower in-stent restenosis rates previously reported.\textsuperscript{15,16} Given the established safety of DES with appropriate long-term antiplatelet therapy, however, there is to date only one truly randomised study comparing PCI using DES with CABG in multivessel coronary disease that has reported its early outcomes. Consequently, current assessments of DES can be made in the light of two prospective reports: the ARTS-II\textsuperscript{21} and Syntax\textsuperscript{22,23} studies.

The ARTS-II study, using historical ARTS-I PCI (with BMS) and CABG groups for comparison with the ARTS-II PCI (with DES) study population, confirmed the impression that DES technology has closed the gap with CABG with regard to the need for repeat revascularisation.\textsuperscript{21} In terms of the primary endpoint of freedom from all-cause death, stroke, myocardial infarction or repeat revascularisation, in contrast with the ARTS-I PCI (with BMS) group, there was no significant difference in outcome in the ARTS-II PCI (with DES) group compared with the ARTS-I CABG group.\textsuperscript{21} The secondary endpoint of freedom from repeat revascularisation for ARTS-II PCI (with DES) was much better than in the ARTS-I PCI (with BMS) group but still inferior to CABG in ARTS-I.\textsuperscript{21} As with previous clinical trials comparing PCI with CABG, however, the original CABG population in ARTS-I was highly selected with an inherent bias against CABG showing any benefit.\textsuperscript{4}

In contrast, the Syntax study\textsuperscript{22} has been a groundbreaking investigation. It is unique in accepting all comers with complex multivessel coronary artery disease into the study, as opposed to the highly selected patient groups\textsuperscript{5} seen in previous studies that compared PCI with CABG. On the basis of its primary outcome, of non-inferiority for major adverse cardiac or cerebrovascular events (MACCE: ie, all-cause death, stroke, myocardial infarction and repeat revascularisation) within 12 months of randomisation, the Syntax study showed that ‘CABG remains the standard of care for patients with three-vessel or left main coronary artery disease’\textsuperscript{22}: despite equivalent all-cause mortality (4.4% for PCI vs 3.5% for CABG, p=0.57) and myocardial infarction rates (4.8% for PCI vs 3.5% for CABG, p=0.11), and a higher stroke rate in the CABG population (0.6% for PCI vs 2.2% for CABG, p=0.003), the increased need for repeat revascularisation (15.5% for PCI vs 5.9% for CABG, p<0.001) continues to be a shortcoming for PCI even using DES.

More recently, the 2-year outcomes from the Syntax study have been reported,\textsuperscript{25} and some interesting observations have been made.\textsuperscript{24–26} Over 2 years, there have been cumulatively more myocardial infarctions and repeat revascularisations in the PCI group (myocardial infarction 5.9% for PCI vs 3.5% for CABG, p=0.01; repeat revascularisation 17.4% for PCI vs 8.6% for CABG, p<0.0001), and more strokes in the CABG group (1.4% for PCI vs 2.8% for CABG, p=0.03).\textsuperscript{25} Having seen no significant difference between groups during the first year of follow-up, the myocardial infarction rate was much higher in the PCI group during the second year of follow-up (1.2% for PCI vs 0.1% for CABG, p=0.008).\textsuperscript{25} The stroke incidence was noted to be similar in both groups during the second year of follow-up (0.7% for PCI vs 0.6% for CABG, p=0.82),\textsuperscript{25} and much of the difference in overall stroke incidence can be accounted for by preoperative and perioperative strokes in the CABG population.\textsuperscript{25} While stroke remains a potentially devastating complication for patients undergoing CABG, this remains an important consideration in the decision-making for revascularisation.

In addition to the 2-year outcome report for the two trial populations, subgroup analysis at 2 years yielded further observations.\textsuperscript{25} 24 26 The Syntax Score for grading complexity of coronary artery disease\textsuperscript{27} was shown to be relevant in both three-vessel and left main stem disease.\textsuperscript{23,24} Study patients with low Syntax scores (ie, Syntax score<23) had similar composite outcomes following PCI (MACCE 19.4% for PCI vs 17.4% for CABG, p=0.63), although repeat revascularisation remained significantly higher in the PCI group, even in these patients (15.7% for PCI vs 8.6% for CABG, p=0.01).\textsuperscript{23} Study patients with high Syntax scores (ie, Syntax score≥23) had better outcomes following CABG (MACCE 28.2% for PCI vs 15.4% for CABG, p=0.0001), with significantly better survival in the CABG group (mortality 9.4% for PCI vs 3.3% for CABG, p=0.002).\textsuperscript{23} In contrast, the Syntax score made no difference in
patients with diabetes, with better outcomes following CABG regardless of Syntax score.24
There was also a discrepancy between outcomes in patients with three-vessel disease and in those with left main stem disease randomised to CABG or PCI.23 24 In three-vessel disease the composite MACCE outcomes favoured CABG (25.8% for PCI vs 14.4% for CABG, p=0.0001), whereas in left main stem disease, the MACCE outcomes were comparable (22.9% for PCI vs 19.3% for CABG, p=0.27) between treatment groups.23 As with the low Syntax score subgroup, however, repeat revascularisation remained significantly higher in the left main stem subgroup.24
Furthermore, a review of the 1- and 2-year outcomes in the CABG registry arm26 demonstrated that the CABG registry group (who had more complex coronary disease and hence higher Syntax scores, and for whom PCI was deemed unsuitable) had better composite MACCE outcomes when compared with the CABG study group (for whom PCI and CABG were deemed able to achieve equivalent revascularisation).

The reasons that underlie the subgroup analysis findings outlined above are subject to speculation, but may fuel the debate between PCI and CABG. The less impressive CABG outcomes in the non-diabetic patients with low Syntax Scores, and in the study (ie, randomised) CABG group compared with the registry of non-randomisable CABG patients, could be attributable to the lower complexity of coronary disease.25 Less complex coronary stenoses could have been associated with high fractional flow reserve24 26 resulting in early graft occlusion or stent failure26—as demonstrated in the FAME study, which examined the impact of fractional flow reserve in PCI and found that restricting PCI to lesions with low fractional flow reserve (ie, FFR<0.80) resulted in significantly better outcomes with regard to death, myocardial infarction and repeat revascularisation compared with routine angiography-guided PCI.28

At the present time, what can be inferred from the 2-year Syntax results is that CABG remains the ‘standard of care’ for patients with complex multivessel coronary disease.25 Nevertheless, at least for 2 years of follow-up, PCI has not been shown to be inferior to CABG in the subgroup of patients with less complex multivessel disease and may therefore represent an acceptable alternative revascularisation strategy in such appropriately selected patients.25 As discussed with the BARI 2D study, however, the danger of a Type II error needs to be considered in the context of an appropriately powered subgroup analysis, and it is important to interpret the non-significant subgroup analyses from the Syntax study with caution. Only the final 5-year outcomes of this study and the results of further trials of DES in left main stem disease will be able to truly determine the ‘non-inferiority’ of PCI in the management of multivessel coronary disease.

CONCLUSIONS
There is no doubt the symptomatic benefits of PCI over medical treatment for coronary revascularisation in stable single- or double-vessel disease, and the survival benefits from primary PCI in acute myocardial infarction. The debate regarding revascularisation in triple-vessel and left main stem disease, however, remains.29 The recently reported 2-year Syntax trial outcomes suggest that PCI with DES may be an appropriate option in carefully selected patients with less complex multivessel disease.23 24 It is possible that younger non-diabetic patients might do better managed by PCI as the initial revascularisation strategy even with triple-vessel disease.29 Patients with diabetes, on the other hand, are clearly better off with CABG regardless of age.9 14 24 In the midst of this debate, the role of secondary prevention must be given its due, with appropriate risk factor management following both CABG and PCI to prevent or reduce coronary graft disease and native vessel disease progression.5 30

On the basis of the currently available evidence—comparing PCI with optimal medical therapy,10 12–14 comparing PCI with CABG6–10 and comparing DES with CABG21–26—for patients with multivessel coronary artery disease, the question should not be whether or not CABG is indicated, but whether or not PCI is appropriate. To quote Professor Serruys, for patients with multivessel disease, ‘CABG remains the standard of care’.22 29 When patient preferences and healthcare economics come into play, decision-making in the management of multivessel coronary artery disease is not always ‘black and white.’ Patients and their healthcare providers need to be well informed of the treatment options, of the risks associated with these options and of the evidence underpinning the benefits of these options in order to make the best decision for the individual patient. In the current era, the importance of a multidisciplinary discussion between surgeons, interventional and non-interventional cardiologists cannot be overstated,4 29 providing patients with balanced and fully informed advice.

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