

# The optimal treatment of multivessel coronary artery disease

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*“The time of ad hoc angioplasty for the patient with multivessel coronary artery disease has passed.”* James Wilson, Texas Heart Institute.

## Abstract

The practice of percutaneous coronary intervention has overtaken coronary bypass surgery in the treatment of ischaemic heart disease. Several randomized controlled as well as registry and observational trials have addressed the issue of patient selection and outcomes in order to provide the cardiologist with data enabling optimal treatment selection. This article reviews the major trials performed over the past 25 years, underscoring their strengths and limitations and draws on lessons and guidelines that are relevant to our local practice.

## Introduction

Coronary artery bypass grafting (CABG) was popularised in the 1970's. Within a decade this operation became the commonest and most comprehensively studied major surgical procedure in the Western world. Randomised trials proved that, in certain subsets of patients, it was superior to medical treatment. A third treatment modality, that of percutaneous coronary intervention (PCI), initially with balloon angioplasty and later with stent implantation, has captured an increasing share of the market over the past 25 years, such that the current volume of PCI has far outstripped surgery. This situation has fuelled intense debate as to which treatment best serves the patient with severe coronary artery disease. Numerous trials have been conducted, comparing PCI with CABG, and these have resulted in guidelines, reached by consensus amongst the European Societies of interventional cardiologists and cardiac surgeons, defining the optimal treatment for these patients.

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This paper describes these developments, analyses the local situation, and asks whether guidelines are being adhered to in the interest of best practice.

## Key Words

Ischaemic heart disease, multivessel disease, coronary surgery, percutaneous intervention

## CABG versus medical therapy

In 1994 the Lancet published a meta-analysis of seven randomised trials of CABG versus medical treatment, analysing 2650 patients with a follow-up of ten years.<sup>1</sup> The authors showed there was a survival advantage and marked symptom improvement with CABG as compared with medical therapy in left main stem (LMS) disease, triple vessel disease (3VD) and proximal left anterior descending (LAD) disease. These benefits were enhanced with severe symptoms, a positive stress test and impaired ejection fraction (EF). The results were analysed on an intention-to-treat basis although 40% of patients assigned to medical treatment crossed over to surgery. Only 10% of patients received a left internal thoracic artery (LITA) graft, known to be an important component of surgery. There was no survival value in CABG for single or double vessel disease and normal LV function. The authors concluded that future trials comparing CABG with another treatment should include a high proportion of patients in whom surgery is known to be beneficial. However this never happened.

## CABG versus PCI

### Randomised controlled trials

From 1994 to 2002 five major randomised controlled trials of CABG versus PCI were conducted, namely the Randomised Intervention Treatment of Angina (RITA),<sup>2</sup> the Coronary Angioplasty versus Bypass Revascularisation Investigation (CABRI),<sup>3</sup> the German Angioplasty Bypass Surgery Investigation (GABI),<sup>4</sup> the Bypass Angioplasty Revascularisation Investigation (BARI),<sup>5</sup> and the Stent or Surgery trial (SoS).<sup>6</sup> None of the patients selected in these trials had LMS disease and EF was either normal or not specified. From an initial combined population exceeding 100,000, patient selection resulted in only 5% entering these trials (range 3-12% for individual trials). The resultant

samples were unrepresentative of the real world CABG population where LMS disease is present in over 20% and low EF in over 35%. The incidence of 3VD in the studies was a mean of 31%, that of proximal LAD disease was either low or unspecified and LITA usage was 75% (all parameters over 90% in the real CABG world).<sup>7</sup> In summary the vast majority of these patients had single or double vessel disease and normal LV function, a population in whom there was no expected prognostic benefit from surgery. Conversely these trials largely excluded those patients who are known to benefit prognostically from surgery, namely those with LMS disease and 3VD, those with proximal LAD disease and impaired EF.

A meta-analysis of 5 trials comparing CABG and PCI also excluded patients with LMS disease and impaired EF. Patients selected in these trials represented 2 to 5% (depending on the particular trial) of the initial population. The overall incidence of 3VD was 42%.<sup>8</sup> The Arterial Revascularisation Therapy Study, ARTS, one of these five trials, included 68% of patients with single or double vessel disease, and all patients had normal LV function. The authors reported similar one and five-year survival rates for surgery and PCI. However, reintervention rates were 30% for PCI versus 9% for CABG and mortality in a subset of 208 diabetics was 13% for PCI and 8% for CABG.<sup>9</sup> The SoS trial, also included in this meta-analysis, reported a significantly higher one-year mortality in the PCI group (2.5 versus 0.8%).<sup>6</sup> The 6-year median follow-up confirmed a sustained significantly higher mortality of 10.9% for PCI versus 6.8% with CABG.

David Taggart, a cardiac surgeon from Oxford, UK, highlighted the inherent prejudice of these papers against surgery in that they included highly selected patient populations unrepresentative of multi-vessel disease in the real CABG world. Moreover editorials disregarded this basic flaw.<sup>10</sup>

### Registry and observational trials

A study by Hannan reported on long-term outcomes in almost 60,000 patients undergoing surgery or stenting.<sup>11</sup> Data was derived from the New York Registry during a 3-year period 1997 to 2000 and reflected a real world situation. One-year mortality for all groups was 6% after CABG versus 9% after PCI. The mortality at 3 years in patients with 3VD was 10.7% after CABG and 15.6% after PCI. The hazard ratio for death at 3 years with CABG versus PCI was 0.76 for 2-vessel disease and 0.65 for 3VD. The incidence of repeat revascularisation was 5% for CABG versus 35% for PCI.

The Syntax trial is another landmark study comparing bypass and stenting in the real world.<sup>12</sup> 1800 patients, in whom the cardiologist and surgeon

determined to offer equivalent revascularisation, were randomised to receive CABG or PCI. From the original 4337 patients 1262 were deemed ineligible, and a further 1275, deemed only suitable for one treatment modality, were entered into the registry (1077 in the CABG arm and 198 in the PCI arm). At one year the two groups had similar rates of death from any cause. The rate of repeat revascularisation was significantly increased in the PCI group (13.5 versus 5.9%), as was the overall rate of major adverse cardiac and cerebrovascular events (MACCE) (17.8 versus 12.4%). The Syntax trial provided insight into the subgroups benefiting most from surgery by way of the Syntax score, an indicator of coronary disease severity and complexity. Thus the greatest difference in the MACCE rates was seen in the high Syntax score patients ( $\geq 32$ ). At five years the overall rates of cardiac death (5.3 versus 9.0%), myocardial infarction (3.8 versus 9.7%), and reintervention (13.7 versus 25.9%), were significantly lower with CABG. The cumulative MACCE rate (25.8 versus 36.0%) was also significantly lower after CABG in intermediate score (23-32) patients. At 5 years the registry patients showed an even larger divergence in the incidence of major events with 23% after CABG versus 49% after PCI. The authors suggest that 71% of all patients, including 25% of patients of the original total in the CABG arm of the registry together with 46% of patients with Syntax scores above 22, are still best treated with CABG. For the remaining 29% of patients PCI is an alternative to surgery.

The ASCERT trial, published in 2012, analyses the comparative-effectiveness of CABG and PCI and is not a randomised trial like the Syntax trial.<sup>13</sup> Patients selected were over 65, without LMS disease, and requiring their first revascularisation. ASCERT represents over ten times as many patients as the total enrolment of all randomized trials comparing CABG and PCI (86,244 CABG and 103,549 PCI patients enrolled). This became possible because the Society of Thoracic Surgeons, the American College of Cardiology, and the Centres for Medicare and Medicaid Services pooled their data, sourced from the National Cardiovascular Data Registry and from the Society of Thoracic Surgeons Registry. This peri-procedural data, which was adjusted for risk, was combined with administrative data from the Medicare and Medicaid registries, providing records on long-term survival. The median follow-up was 2.7 years. Triple vessel disease was present in 80% of patients who underwent CABG and in 32% of patients undergoing PCI, confirming that treatment strategies were based on clinical grounds. The results at one year were similar, but over time the progressive survival advantage of CABG became significant. Survival at four years was 83.6% with CABG and 79.2% with PCI, the hazard ratio for death

was 0.79 and for combined stroke, death or MI was 0.81 for CABG compared with PCI. The benefit from CABG was seen in all subgroups studied. The sheer numbers of patients in this study lend weight to the findings that survival was significantly better with CABG at four years, the results were consistent across all subgroups, and were consistent with the Syntax results, another large real world trial.

### **Will stent revascularisation replace CABG? Lessons learnt from landmark trials**

Revascularization outcomes include three major endpoints, namely death, myocardial infarction, and symptom control (often requiring reintervention). With respect to death, surgical revascularization benefits patients who have severe multivessel disease and left ventricular dysfunction or other physiologic indicators of high risk. This evidence comes from three seminal trials performed in the 1970s and 1980s, namely the CASS randomised<sup>14</sup> and registry<sup>15</sup> trials and the Veterans trial,<sup>16</sup> and from many observational studies. When angioplasty was introduced the hope was for a method of revascularization that would rival coronary artery bypass grafting.<sup>17</sup> Angioplasty worked well in patients with no major risk factors, but failed in diabetic patients. The BARI trial demonstrated that the use of PCI in diabetics is potentially harmful when compared with a LITA to the LAD.<sup>5</sup> In stable coronary disease the Courage trial, published in 2007, showed that the addition of PCI was unsuccessful in proving a positive impact over optimal medical therapy alone.<sup>18</sup> The bare-metal stent was developed as a metallic buttress to overcome restenosis after angioplasty. The use of stents drastically reduced the probability of emergent surgery after attempted PCI from 1 to 0.3%, increased angiographic success from 89 to 97%, increased freedom from six-month major events, from 77 to 85%, and drastically lowered six-month reintervention rate, from 20 to 8%.<sup>19</sup>

The drug-eluting stent was developed to cure restenosis. However the probability of new lesion formation or late restenosis after intervention did not decrease. This figure was quoted as 10.1% restenosis requiring revascularisation during a three-year follow-up in the J-Cypher registry trial.<sup>20</sup> Stent-in-stent repeat revascularisation was better than balloon angioplasty at preventing further revascularisation, with a hazard ratio of 0.44 favouring stenting, but two-year mortality was similar, at 10.4% after stent-in-stent and 10.8% after balloon angioplasty. Drug-eluting stents with their promise of no restenosis failed to deliver.

### **Guidelines and local trends**

The current European Society of Cardiology/ European Association for Cardio-Thoracic Surgery

(ESC/EACTS) guidelines are for a 1A recommendation for CABG in all patients with low predicted surgical mortality in all but one scenario, that of single or double vessel disease, not involving the proximal LAD. The other recommendation, at class 1C, is that, in patients with multivessel disease, the appropriate revascularization strategy should be discussed by the Heart Team.<sup>21</sup>

CABG trends in the US showed a decline of 38% from a peak in the year 2001 to 2008. During the same period PCI decreased by 4%.<sup>22</sup> During a corresponding 7-year period locally, this time starting from peak CABG rates in 2004, the decline in CABG equates to 49%. Local PCI rates increased by 63% during this same period and 26.5% of these were ad hoc procedures, where an investigational angiogram led directly to a PCI. In 2004, 463 patients were referred for CABG, of which 347 (75%) received 3 or more grafts for multivessel disease. In 2011 although the number of angiograms increased by 23% over the 2004 figure, only 150 operations were performed for multivessel disease. Had referral patterns remained unchanged this figure would have reached 427. The real decline in referral of patients with multivessel disease for surgery over this period was of 277 patients in 2011, or 65% of the projected figure. Local PCI numbers increased from 520 in 2004 to 845 in 2011, an increase of 62.5%.

The SYNTAX score is a recognised, computer-based tool for evaluating the risk of complications or failure after PCI. There are other risk stratification systems for estimating mortality after surgery. These estimates enable cardiologists to objectively advise patients regarding the revascularization method that has the best short- and long-term probability of success. In patients with non-life-threatening disease, those without significant LV dysfunction, 3VD or LMS disease, stent revascularization has become an alternative to surgery. However, this is true only if stenting is confined to patients whose anatomy is suited to it, a consideration that is well quantified in the SYNTAX score. With regard to the choice of revascularization, in a patient with multivessel disease, a reasoned approach must be taken, using these predictive tools and considering the patient's wishes. Treatment decisions should include all parties, the patient and the heart team, including the cardiologist and the cardiac surgeon. Thus the ESC/EACTS guidelines recommend that patients be adequately informed about the potential benefits and short- and long-term risks of a revascularization procedure and enough time should be allowed for informed decision making. This is a class 1C recommendation. In this setting there is virtually no recommendation for ad hoc angioplasty.

### Inappropriate stenting

Inappropriate stenting is a term that includes the placement of a coronary stent in a vessel when the lesion is not clinically important, as well as the placement of stents in patients who would benefit more from surgery. In a recent multicentre, prospective study the appropriateness of PCI was assessed in the acute and non-acute clinical scenario.<sup>23</sup> 500,154 PCI patients were recruited from 1091 US hospitals and these were classified as acute (71.1%) (ST-segment elevation MI 20.6%, non-ST-segment MI 21.1% or unstable angina 29.3%) or non-acute (28.9%). In the acute group 98.6% were deemed appropriate. In the non-acute group 50.4% were deemed appropriate, 38% uncertain due to lack of adequate data, and 11.6% inappropriate. Appropriate PCI in the non-acute situation was defined as that performed in the presence of angina, high-risk ischaemia on stress testing, or optimal medical treatment. 95.8% of inappropriate PCI's were performed in the absence of optimal medical treatment. Lack of adequate data in the patient's file may be interpreted as a corresponding deficiency during the decision-making process leading to PCI, in which case the uncertain/inappropriate cohort reached a disturbing level of 49.6%. This study poses important implications on our local practice where non-acute PCI's represent 59.1% of the total program, more than twice that in the study by Chan. Moreover, because of long local PCI waiting times the patient's clinical state may be unknown or may have changed from the time of referral to intervention.

### Conclusions

Local referral patterns for multivessel disease have changed drastically over the years 2004-2011. During this period surgery for multivessel disease decreased by 65% and PCI increased by 62.5%. Syntax scoring is not performed and treatment plans for patients with multivessel disease are not discussed in a multidisciplinary heart team, as proposed by ECS/EACTS guidelines. Ad hoc procedures, which allow little opportunity for informed consent, reached 26.5%. The incidence of non-acute PCI is very high, a cohort in which the incidence of inappropriate stenting is increased. Clearly much can be improved.

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