

Treatment of Multi-Vessel Coronary Artery Disease. What Is the Optimal Revascularisation Approach? What Do We Know, What Will We Learn?

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Key words:

Multi-vessel disease, stent implantation, coronary artery bypass grafting.

Coronary artery bypass grafting (CABG) has long been the definitive, but nevertheless aggressive therapeutic approach for the treatment of patients with multi-vessel coronary artery disease. On the other hand, continuous improvement of devices and percutaneous techniques in interventional cardiology has led from the limited treatment of single, simple lesions to the extensive management of multiple and severely complex stenoses.

Historical data from the early trials comparing percutaneous coronary intervention (PCI) with bare metal stent implantation and surgical revascularisation showed that there were no differences in terms of mortality and myocardial infarction. However, a more favourable outcome was observed in the CABG arm regarding repeat revascularisation and long-term relief from angina.

The largest multi-centre, randomised studies were conducted in the mid to late 1990s. The Angina With Extremely Serious Operative Mortality Evaluation (AWE-SOME) trial was one of the first randomised, multi-centre studies to show that there is no significant difference in the global survival or the combined endpoint of survival free of unstable angina among patients with multi-vessel disease treated with CABG or PCI with stent implantation.¹ These results were sustained up to three years'

follow up. However, survival free of unstable angina and repeat revascularisations was observed to be generally greater in the surgical group than in the PCI group.¹

The ERACI II study (Argentine Randomised Study: Coronary angioplasty with stenting vs. coronary bypass surgery in multi-vessel disease) included 450 patients.² ERACI II showed better survival and freedom from myocardial infarction in the PCI arm compared with the surgical cohort. This difference in favour of the PCI strategy was mainly observed during the first 30 days, when more patients died in the surgical group, and disappeared after one month. The surgical hospital mortality in the ERACI II study was higher than in other trials,³⁻⁵ but was mainly observed in patients with severe unstable angina. On the other hand, freedom from the need for new revascularisation procedures and major adverse cardiovascular events were significantly better with CABG patients.^{2,6}

The SoS (Stent or Surgery) trial was conducted in 53 centres in Europe and Canada and randomised 988 patients.⁷ Of the patients initially randomised to PCI, 21% required one or more additional revascularisation procedures, whereas in the surgical cohort only 6% underwent additional PCI or CABG ($p < 0.0001$). The incidence of death or non-fatal Q-wave myocardial infarction was similar in both groups,

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but survival was significantly lower in the PCI arm. Excess mortality in the PCI cohort was mainly due to the increased rate of cancer-related deaths in the particular study group.⁷

The Arterial Revascularisation Therapies Study (ARTS) was designed to compare CABG and stenting in patients with multi-vessel disease.⁸ In total, 1205 patients from 67 participating centres were randomised to either stent implantation or CABG. Both one-year⁹ and five-year¹⁰ follow-up results confirmed the findings of the previous studies. In the ARTS study overall freedom from death, stroke, or myocardial infarction was not significantly different between groups, whereas the incidence of repeat revascularisation was significantly higher in the PCI group than in the CABG group.^{9,10}

Similar results were demonstrated in a recent meta-analysis of the trials mentioned above.¹¹ The meta-analysis confirmed that those patients with multi-vessel disease undergoing surgical revascularisation or stent implantation were protected against death, myocardial infarction, or stroke to a similar degree. In contrast, repeat revascularisation procedures were higher after PCI than after CABG.¹¹

Drug-eluting stents seem to address the majority of the disadvantages that restrict the unlimited use of bare metal stents. Several studies and registries have consistently shown promising results regarding high-risk populations with complex lesions.¹²⁻¹⁵ However, concerns have been raised recently regarding the long-term safety of drug-eluting stents, as a consequence of the reported potentially increased risk of late thrombosis.¹⁶⁻²⁰ Furthermore, drug-eluting stents are more expensive than conventional stents²¹ and prolonged, costly, anti-platelet regimens are required. In the drug-eluting stent era these questions have re-emerged: Which is the best way to treat patients with multi-vessel coronary artery disease? Which patient will benefit most from stent implantation and which is more eligible for surgical revascularisation? In order to answer these question and determine the safety, the long-term efficacy and the cost-effectiveness of drug-eluting stents in this particular population, it is mandatory to design and implement new large-scale, randomised trials, comparing drug-eluting stents with CABG.

ARTS II (Arterial Revascularisation Therapies Study II) compared the effectiveness of sirolimus-eluting stent implantation with the historical two arms of ARTS.²² ARTS II enrolled 607 patients (53.5% with 3-vessel disease) from 45 centres. The study met its primary end-point; the composite major adverse cardiac and cardiovascular events at one year were low (10.5%)

and were within the same range as the historical surgical arm of ARTS. Even if the re-intervention rates in the drug-eluting group were still higher than those of the surgical group, this was counterbalanced by a higher incidence of death / stroke and myocardial infarction.²² However, it was notable that diabetic patients in the drug-eluting group, though having lower event rates than those in the bare metal group, still experienced an almost twofold greater need for repeat revascularisation in the first year compared with non-diabetic patients.

The SYNTAX trial (SYNergy between percutaneous coronary intervention with TAXus™ and cardiac surgery) is a multi-centre, randomised study, designed to evaluate the optimum revascularisation treatment for patients with *de novo* 3-vessel disease and/or left main disease (either isolated or with 1-, 2-, or 3-vessel disease) by randomising patients to either PCI with paclitaxel-eluting stents or surgery.²³ Additionally, the trial incorporates two registries that enrol patients who are not eligible for either PCI or CABG. A local Heart Team (consisting of an interventional cardiologist, cardiothoracic surgeon and study coordinator) screen all the patients and decide whether the screened patient fulfils the inclusion and exclusion criteria. If both PCI and CABG could achieve comparable revascularisation, the patient is assigned to the randomised cohort; otherwise the patient is included in one of the nested registries. Randomised patients are stratified at each site, based on the presence or absence of left main disease and medically treated diabetes mellitus (requiring oral medication or insulin). A total of 1500 patients have been randomised from approximately 90 participating centres in Europe and in the USA. The primary endpoint is freedom from major adverse cardiac and cerebral events at one year. The CABG registry data may determine the complex, high-risk subsets that are not suitable for PCI with drug-eluting stents. Similarly, the PCI registry data may define the population for which CABG is inappropriate.²³ In the SYNTAX study a scoring system (SYNTAX score) has been introduced.²⁴ The SYNTAX score intends to provide a measure of coronary artery disease complexity, taking into account both the number of significant lesions (>50% by visual estimation) and the complexity of each lesion independently.²⁴ It has been hypothesised that higher scores will correspond to more severe coronary artery disease and will identify patients with therapeutic challenge and potentially worse prognosis.

The FREEDOM multi-centre trial (Future REvascularisation Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease) will randomize 2400 diabetic patients with 2- or 3-vessel disease to either surgical or percutaneous revascularisation with drug-eluting stents. The study will be conducted in North America and Europe. The primary endpoint is mortality at 5 years. There will also be nested registries to capture patients treated with either PCI or CABG only.

The CARDia (Coronary Artery Revascularisation in Diabetes) trial is a UK and Ireland based trial. It will randomise 600 diabetic patients with either complex one-vessel disease or multi-vessel disease to CABG or PCI.²⁵ The primary endpoint is the composite incidence of death, non-fatal myocardial infarction or non-fatal stroke at one year. Also, in this trial a PCI and a CABG registry are incorporated, with the ultimate goal to compare their results with the randomised group.

The optimal therapeutic strategy for multi-vessel coronary artery disease still remains a controversial issue. The promising results demonstrated in small-scale studies and registries suggest that drug-eluting stents may abolish the limitations encountered with bare metal stent implantation. Currently, in Europe and the United States, the use of PCI for 3-vessel disease ranges from 10% to 58%.²⁶ The results of SYNTAX, FREEDOM and CARDia are anticipated with great interest and will almost certainly expand the indications for percutaneous revascularisation procedures in more complex and high-risk lesions. The aforementioned trials will provide a reliable dataset for assessing the various issues in patients with multi-vessel disease and will potentially set new guidelines for these patients in the future.

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