Expert Perspective

Strategies for the Invasive Treatment of Multivessel Coronary Artery Disease

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There are two main challenges that cardiology faces with regard to the invasive treatment of multivessel coronary artery disease: the management of acute coronary syndromes and, more importantly, the choice between angioplasty and aortocoronary bypass.

Acute coronary syndromes

The management of an acute myocardial infarction with primary angioplasty is absolutely indicated (category I) in accordance with the guidelines of the European Society of Cardiology and the American Heart Association/American College of Cardiology. In the case where multivessel coronary artery disease is found on the preprocedure coronary angiogram the traditional approach is to treat the culprit lesion. Treatment of any but the culprit lesion is absolutely contraindicated,[1] and may be carried out in a second phase if necessary (staged procedure). However, invasive cardiology is constantly developing, its results have improved and it now provides a greater degree of safety, even during the acute phase of infarction, mainly because of the use of stents and platelet glycoprotein IIb/IIIa inhibitors. This has raised the question as to what extent multivessel disease could be treated in total, even during the acute phase of infarction. Information about this subject in the literature is rare. Roe et al[2] published findings from 79 cases of multivessel angioplasty from 8 international centres, using as a control group patients who had angioplasty only of the lesion related to the infarction. At 30 days, the difference between the controls and the multivessel disease group in terms of mortality (11.5% versus 22.1%) and major events (14.8% versus 25%) was not statistically significant. At 6 months, mortality (16.4% versus 25%), major events (27.9% versus 35.3%) and reinfarction (1.6% versus 8.8%, $p<0.07$) again did not differ significantly between the two groups. One can easily see that, given the small number of patients in the study, it is difficult to draw clear conclusions. Multivessel angioplasty may be carried out acutely with a high rate of success, but it may be accompanied by a higher risk later on. Prospective, randomised studies are needed to determine the ideal strategy for reperfusion in patients with an acute myocardial infarction who are found to have multivessel disease.

The TACTICS-TIMI 18 study focused on the value of early angiography and appropriate reperfusion, compared with conservative drug treatment with elective angiography and reperfusion, in patients with an acute coronary syndrome without ST-segment elevation who were taking tirofiban. That study provided an opportunity for comparing multivessel angioplasty with angioplasty of just the culprit lesion in the group who underwent early (within 4-48 hours) angiography and intervention during the same session.[3] At 6 months the

Table 1. Aortocoronary bypass surgery (CABG) versus angioplasty (PCI) as methods of reperfusion in the treatment of multivessel coronary artery disease.

CABG		PCI	
Advantages	**Disadvantages**	**Advantages**	**Disadvantages**
• Full reperfusion • Result duration • Improvement of symptoms • Improved survival (Diabetes LIMA=>LAD)	• Operating theatre • Venous grafts • Vascular and cerebral episodes • Length of hospitalisation • Reproducibility • Progress of disease in native vessels	• Less invasive • Avoidance of surgery • No stroke • Repeatable	• Incomplete reperfusion • Radiation • Restenosis

combined endpoint (death, reinfarction, new hospitalisation) was similar in the multivessel and culprit lesion groups, 21.2% versus 23.2%, respectively. However, the need for a further intervention in the multivessel group was less than in the culprit lesion group: 10.6% versus 13.8% in the culprit vessel (p: NS) and 1.5% versus 6.3% ($p<0.04$) in the non-culprit vessel.

Angioplasty or aortocoronary bypass

The guidelines for the treatment of coronary artery disease include special proposals for revascularisation strategy based on extensive review of the literature, expert opinions and meta-analyses.[4,5] A rough comparison of the two invasive reperfusion techniques is given in table 1. In comparing the methods and choosing which is preferable one must bear in mind that the rather rapid progress of the disease, especially in some subgroups of patients, such as diabetics, may have an unfavourable influence on the patients who are treated using angioplasty compared with those who undergo surgery. The late protective outcome of aortocoronary bypass surgery is traditionally attributed to the fuller reperfusion it achieves or to the fact that the proximal diseased sections of the epicardial vessels are permanently bypassed.

The pre-stent era

A direct comparison of the initial strategies of angioplasty and aortocoronary bypass in patients with multivessel disease is only possible through randomised studies. There are seven randomised studies comparing balloon angioplasty with aortocoronary bypass.[6-12] Those studies prove that in appropriately selected patients with multivessel disease an initial strategy of employing angioplasty produces similar overall results as regards death and infarction as does the initial strategy of aortocoronary bypass. There are more initial complications in aortocoronary bypass, which is also associated with a higher cost and a longer hospital stay. Aortocoronary bypass, however, provides greater relief from angina with a lesser likelihood of a need for reoperation. After angioplasty patients return to work sooner, but later on they need more frequent hospitalisation.

The biggest of all the above studies was the BARI study,[11] in which 1829 patients with multivessel disease were randomised in 18 centres to balloon angioplasty or aortocoronary bypass. The 5-year survival was 86.3% in the angioplasty group compared with 89.3% in the bypass group ($p=0.19$) and the 5-year survival free of Q-wave infarction was 78.7% versus 80.4%, respectively. However, at 5 years 54% of patients in the angioplasty group had undergone an additional intervention, compared with only 8% in the bypass group. During a mean follow up of 7.8 years[13] aortocoronary bypass was shown to be superior to angioplasty in terms of survival (84.4% versus 80.9%, respectively, $p<0.043$). The difference was clearly due to the diabetic patients, whose survival rate was 76.4% after surgery and 55.7% after angioplasty ($p<0.0011$). The respective survival rates in non-diabetics were 86.8% and 86.4%.

The BARI study has been criticised for not using stents, as is the modern practice nowadays. One could maintain, however, that the earlier studies of aortocoronary bypass may also not have reflected the results of modern surgical practice, in which arterial grafts are used whenever feasible. At the time of the BARI study platelet glycoprotein IIb/IIIa inhibitors were unavailable and full reperfusion could not be achieved using angioplasty (in contrast to aortocoronary bypass). Also, the group of patients who were suitable for the study but were not randomised (BARI

registry)[14] probably provide a better picture of the practices followed outside of studies and their results. Thus, in the BARI registry the 7-year mortality was similar for angioplasty (13.9%) and aortocoronary bypass (14.2%). The 7-year mortality in diabetics was equally high (26%) for both procedures. In the angioplasty group the mortality was lower in the patients who were not randomised (13.9%) than in those who were (19.1%, $p<0.01$). Such a difference did not exist in the bypass patients. The most important limitation of all randomised studies is related to the extent to which conclusions may be generalised. The findings are not applicable to all patients with multivessel disease for two main reasons: first, only around 5% of the patients with multivessel disease who were screened finally took part in the study; second, the judgement of the treating physician appears to be a significant factor that is absent from randomised studies. This is shown by the slightly better survival among 450 patients suitable for the EAST study[15] who refused randomisation, compared with the 392 patients who were randomised into the study, as well as by the similar mortality among diabetic patients in the BARI registry who underwent either angioplasty or aortocoronary bypass, as mentioned above.

The stent era

Conventional stents

In recent years the use of stents has become common practice in almost all percutaneous reperfusion procedures. There are 3 randomised studies comparing angioplasty with stenting and aortocoronary bypass.[16-18] The largest of these is the ARTS study (Arterial Revascularization Therapy Study), which included 1205 patients with multivessel coronary artery disease for whom the cardiac surgeon and the invasive cardiologist agreed that they could achieve a similar degree of reperfusion. At 1 year there was no difference in the combined probability of death, infarction and stroke between the two reperfusion strategies. However, a repeat procedure was needed significantly more often in the angioplasty group (16.8%) than in the aortocoronary bypass group (3.5%). At 3-year follow up,[19] survival free of infarction or stroke was similar in the two groups – 87.2% and 88.4% for angioplasty and bypass, respectively – but the likelihood of a repeat procedure during 3 years was 26.7% for angioplasty compared to 6.6% for bypass. The latter difference was mainly due to the large probability of a repeat procedure in diabetic patients who were treated with angioplasty.

Cost/benefit of reperfusion

The ARTS study[19] provided particular information concerning the cost-effectiveness of the two kinds of reperfusion. The total cost in Euros of angioplasty with stenting at 1 year was 11,111, compared with 13,896 for aortocoronary bypass. This difference decreased at 3 years, but the cost of angioplasty remained significantly lower (14,302 versus 16,100, $p<0.0001$). The additional cost of surgery aimed at producing a patient who would be event-free at 3 years reached 10,492 Euros, while if reperfusion procedures are excluded this increases to 142,391 Euros.

Meta-analyses

Several meta-analyses of randomised studies have tried to obtain clearer conclusions regarding the relative position of angioplasty and aortocoronary bypass. In the most recent of these, Hoffman et al[20] carried out a meta-analysis of 7 studies that used balloon angioplasty and 3 that used angioplasty plus stenting. They found superior survival rates for aortocoronary bypass compared with angioplasty at 5 and 8 years, with a risk reduction of 2.3% and 3.4%, respectively. This difference arose from the older studies, without the use of stents. In the studies with stents there was no such difference, at least during 3 years of follow up. Angioplasty was associated with a 3.3% lower risk of infarction at 3 years. Patients randomised to angioplasty had more revascularisations (difference 24-38%), but this difference was reduced to 15% by stenting. As regards the survival of diabetic patients, aortocoronary bypass had advantages over angioplasty at 4 years, but not at 6.5 years, while in non-diabetics there was no difference in survival at 4 or at 6.5 years.

Drug-eluting stents

During the last 4 years we have seen a real revolution in the field of invasive cardiology, with the use of drug-eluting stents (DES) that dramatically reduce restenosis, the acknowledged Achilles' heel of angioplasty. The first information about the use of DES in multivessel disease came from Lemos et al and the RESEARCH registry,[21] in which 338 patients with multivessel disease were treated with rapamycin-eluting DES and were compared with patients who had been treated with classical stents during the previous 6 months. At 6 months, survival free of major complications was 94.2% for DES versus 79.2% for the classical stent ($p<0.01$). The results of the ARTS II study, as announced by P. Ser-

ruys,[22] are also exceptionally favourable for angioplasty. In that study, 600 patients with multivessel disease who were treated with rapamycin-eluting stents were compared with the patients of the ARTS I study (600 had angioplasty with conventional stent and 605 aortocoronary bypass). The main endpoint of the study, which was the absence of major events including stroke at 1 year, was achieved in 93.6%, 91% and 80% of patients in the rapamycin-eluting stent, bypass, and conventional stent groups, respectively. There was no need for revascularisation in 97.3%, 94.5% and 84.7%, respectively. These results were seen in spite of the fact that in ARTS II more patients had diabetes, hypertension, dyslipidaemia, and three-vessel disease, while there were more lesions per patient than in ARTS I. It thus appears that the main problem of multivessel angioplasty, the need for target vessel revascularisation, has largely been solved by DES.

In the studies mentioned above involving balloon angioplasty or plain stents, the group with the least favourable results as far as target vessel revascularisation is concerned were the diabetics. More specifically, diabetic patients in the SIRIUS study showed a 70-80% reduction in the probability of clinical restenosis at 12 months when a rapamycin-eluting stent was used.[23] In the TAXUS IV study, also of diabetic patients, the use of a paclitaxel-eluting stent reduced the need for target vessel revascularisation during 12 months by 71%.[24] Important information about the ideal method of reperfusion in diabetics with multivessel coronary artery disease is still awaited from the FREEDOM study, in which 2600 patients will be randomised to angioplasty with rapamycin-eluting stent and abciximab administration or to aortocoronary bypass with or without cardiopulmonary bypass. Endpoints are 5-year survival and events during the first year.

Adjunctive therapy

Those involved with invasive treatment often forget the value of adjunctive therapy. In three randomised studies, the combined probability of death or infarction within 6 months following a percutaneous intervention was reduced by 45-62% by platelet glycoprotein IIb/IIIa inhibitors in the subgroup of patients with diabetes.[25] Recently, however, the ISAR-SWEET study showed no additional benefit as regards death or infarction from the use of abciximab in diabetics who underwent angioplasty after loading with a high dose of clopidogrel.[26] The long term administration of statins after a procedure is considered essential. In a sub-analysis of the 4S study,[27] the use of simvastatin in diabetic patients reduced major coronary events (RR=0.58, $p<0.001$) and target vessel revascularisation (RR=0.52, $p<0.005$) compared to placebo. Statin therapy after angioplasty with stenting also reduces the risk of major coronary events.[28] In diabetic patients the ideal glycaemic examination with HbA1c<7% is associated with a significantly lower probability of target vessel revascularisation.[29] The long term administration of clopidogrel and converting enzyme inhibitors appears to help in patients who have rapidly progressing coronary artery disease. Particularly important is a recent study by Cutlip et al,[30] involving the five-year follow up of 1228 patients after angioplasty with stenting. In the first year the risk of cardiac events was 18.3% from the target lesion and 12.4% from other lesions. Subsequently the annual risk was 1.7% and 6.3%, respectively. Diabetes and multivessel disease were associated with an increased risk of events either related or unrelated to restenosis. After the first year following stent implantation the clinical development was determined by a high risk of events related to the progress of the disease at points other than the site of stent implantation.

Expectations in 2005

It is expected that DES will be tried in all cases so far shown to have a high risk of restenosis, such as diabetics with multivessel disease. The spread of DES should have a significant effect on the surgical treatment of multivessel coronary artery disease over the coming decade and should turn the scale in favour of percutaneous interventions. Financial factors will continue to determine decision making to a significant degree. The true impact of DES, however, and the strategic limitation or prevention of restenosis, can only be fully appreciated in light of the fact that cardiac events often occur as a consequence of the progress of the disease in places other than sites of stent implantation.

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