Multivessel coronary artery disease: current revascularization strategies

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Introduction

The clinical presentation, extent and severity of coronary artery disease, left ventricular function and associated co-morbid conditions influence the choice of initial management of a patient with coronary artery disease. In 1964, Garrett, Dennis, and DeBakey first used coronary artery bypass grafting (CABG) to treat coronary artery disease[1]. Subsequently, in the 1970s, the indications for coronary revascularization, CABG vs medical therapy, were the major focus of investigation[2–6]. These data enabled the development of comprehensive guidelines for indications of coronary revascularization[7]. Percutaneous transluminal coronary angioplasty (PTCA) was introduced by Dr Andreas Gruentzig in 1977 as a technique for the treatment of proximal, non-calcified, concentric lesions involving a single coronary artery[8]. With improvements in angioplasty equipment and techniques, the use of PTCA was expanded to more complex lesions and in patients with multivessel disease. In the mid-1980s and 1990s, the focus of investigation shifted toward the preferred method of revascularization — CABG vs PTCA. In recent years, there have been major improvements in both surgical and medical treatments. For instance percutaneous and surgical revascularization, the use of stents, arterial bypass conduits, minimally invasive coronary artery surgery have all progressed. Medical treatment, too, such as adjunctive pharmacotherapy (glycoprotein IIb/IIIa inhibitors) and aggressive lipid lowering have reached optimum levels. The purpose of this review is to discuss the current role of various modes of revascularization in multivessel coronary artery disease.

Coronary artery bypass graft surgery compared with medical therapy

Shortly after the introduction of CABG, three large, multicentre, randomized trials began enrolling patients to compare a strategy of initial CABG with a strategy of initial medical therapy in stable angina pectoris. These are the largest randomized trials of revascularization vs medical therapy to date and they have maintained their major clinical role in evidence-based decision making regarding coronary revascularization. These trials are summarized in Table 1.

The meta-analysis[9] of seven randomized trials, comparing CABG and medical therapy, contains the majority of patients from three large trials[2–4]. These patients represent a small proportion of patients screened from randomizing sites in different trials. Most (91.1%) of these patients had either multivessel or left main coronary artery disease. They were predominantly middle-aged male patients, while a few were women (3.2%), some were elderly (7.3% over 60 years of age) and some had left ventricular dysfunction (7.2% with ejection fraction less than 0.40). Only 10% of the patients received internal mammary grafts and only 20% were treated with antiplatelet agents. There was a significant crossover in the medical treatment group during the long-term follow-up, with 41% of these patients undergoing CABG surgery within 10 years.

The meta-analysis[9] supports the general concept that the greater the amount of myocardium jeopardized, due to more extensive or proximal coronary disease, the greater the improvement in prognosis with surgery. The CABG group had significantly lower mortality than the medical treatment group (Fig. 1) at 5 years (10.2 vs 15.8%, \( P=0.0001 \) and at 10 years (26.4% vs 30.5%, \( P=0.03 \)). The benefit of CABG surgery was greater in patients with extensive coronary disease, such as left...
main coronary artery disease, three- and two-vessel disease with left anterior descending coronary artery involvement. Factors such as left ventricular dysfunction, advanced age, abnormal exercise test, and previous myocardial infarction, did not individually affect the relative benefit. Since the mortality rate was higher in patients with lower ejection fractions, those with abnormal left ventricular function derived greater absolute benefit.

There is no evidence from randomized trials that bypass surgery reduces the subsequent occurrence of Q wave myocardial infarction compared with medical therapy. The Veterans Affairs (VA) investigators speculated that, the survival benefit of CABG was due to improved survival in patients who suffered a myocardial infarction during long-term follow-up in surgical patients (possibly with patent grafts functioning as collaterals) as compared to medically treated patients. The benefit of surgery diminished with time in all patient subsets, possibly as a result of graft attrition, progression of disease in un bypassed vessels and cross-overs from medical to surgical therapy.

There are four randomized trials comparing PTCA and medical therapy in patients with stable angina. These trials have included predominantly single vessel disease patients. The second Veterans Affairs ACME trial of double vessel disease has included 101 patients randomized into two groups; however, the number is too small to draw any conclusion. In the RITA-2 trial, 40% of a total of 1018 patients had multivessel disease; however, there is no separate subgroup analysis of multivessel disease in this trial. So the data from trials comparing PTCA and medical therapy is limited and inconclusive for multivessel disease. These trials are summarized in Table 2.

In the Asymptomatic Cardiac Ischemia Pilot (ACIP) study, 588 chronic stable angina patients with suitable coronary anatomy for revascularization were randomized to three strategies: angina-guided drug therapy, angina plus angina plus ischemia-guided drug therapy and revascularization (angioplasty or bypass surgery). Two years after randomization, total mortality (P<0.02), combined death and
myocardial infarction ($P<0.04$) and a composite of death, myocardial infarction and recurrent cardiac hospitalization ($P<0.001$) were significantly lower in the revascularization group than other two groups. The benefit of revascularization was concentrated in those with proximal left anterior descending coronary artery stenosis ($P=0.013$ for difference between relative risks). There was similar benefit in patients with three-vessel disease compared with those with one- or two-vessel disease ($P=0.015$ for difference between relative risks).

**PTCA vs CABG in multivessel disease**

The trials comparing CABG with medical therapy[^2–4] have established a role for revascularization in the treatment of multivessel coronary artery disease. But, the preferred method of revascularization remains a major issue of debate. There are several observational studies[^15–18], seven randomized trials[^19–25], and two meta-analyses[^26,27] comparing PTCA and CABG in multivessel disease. All the randomized trials included patients with two- or three-vessel disease, with the exception of the RITA trial which included 45% single-vessel disease patients. These trials enrolled predominantly male patients and there were a significant number with unstable angina. The majority of the patients in the surgical arm received internal mammary artery grafts. Most of these trials were conducted in the late 1980s and therefore stents were not used in the PTCA arm of these trials (summarized in Table 3). In these trials, only 5-2% of 91 730 patients screened were randomly assigned to a study group. Nearly two-thirds of patients were excluded for angiographic reasons, such as left main coronary artery disease, chronic total occlusion, diffuse disease or inability to achieve ‘functional’ complete revascularization. In addition, most of the patients had well-preserved left ventricular systolic function. As a result, patients who had previously been shown to benefit most from surgical revascularization were excluded[^28,29].

Despite differences in study designs, inclusion and exclusion criteria, the results of these trials are remarkably consistent. Two meta-analyses, including five of six trials (excluding BARI) have been completed. One was on multivessel disease only with a follow-up of 1 to 3 years[^26] (Fig. 2); the other was on predominantly multivessel disease, with a mean follow-up of 2.7 years[^27]. The overall risk of death was similar between the CABG and the PTCA patients (3.7% vs 3.9%, $P=0.67$). The

### Table 2 Comparative trials of PTCA and medical therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number</th>
<th>Diseased vessels</th>
<th>Unstable angina (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACME[^10]</td>
<td>212</td>
<td>SVD</td>
<td>0</td>
<td>PTCA more effective in angina relief and improving exercise time but with higher cost and complications</td>
</tr>
<tr>
<td>ACME-DVD[^11]</td>
<td>101</td>
<td>DVD</td>
<td>0</td>
<td>Lack of superiority of PTCA as compared to medical therapy</td>
</tr>
<tr>
<td>RITA-2[^12]</td>
<td>1018</td>
<td>40% MVD</td>
<td>10</td>
<td>PTCA more effective in angina relief and improving exercise time, excess early hazard due to procedural complications</td>
</tr>
<tr>
<td>MASS[^13]</td>
<td>214</td>
<td>Prox LAD</td>
<td>0</td>
<td>Randomization to IMA bypass surgery, PTCA and medical therapy, no difference in primary end-point between PTCA and medical therapy</td>
</tr>
</tbody>
</table>

ACME=Angioplasty compared to Medicine; ACME-DVD=ACME trial in double vessel disease; RITA-2=Second Randomized Intervention Treatment of Angina; MASS=Medicine, Angioplasty or Surgery Study; SVD=single vessel disease; MVD=multivessel disease; Prox LAD=proximal left anterior descending coronary artery; IMA=internal mammary artery.

### Table 3 Comparative trials of PTCA and CABG in multivessel disease

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number</th>
<th>% of screened</th>
<th>Mean age (years)</th>
<th>Male (%)</th>
<th>Unstable angina (%)</th>
<th>Ejection fraction (mean)</th>
<th>IMA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOULOUSE[^19]</td>
<td>152</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>ERACI[^20]</td>
<td>127</td>
<td>17</td>
<td>58</td>
<td>85</td>
<td>83</td>
<td>61</td>
<td>na</td>
</tr>
<tr>
<td>GABI[^21]</td>
<td>358</td>
<td>4</td>
<td>59</td>
<td>81</td>
<td>20</td>
<td>56</td>
<td>37</td>
</tr>
<tr>
<td>EAST[^22]</td>
<td>392</td>
<td>8</td>
<td>62</td>
<td>73.5</td>
<td>65.9</td>
<td>61</td>
<td>90</td>
</tr>
<tr>
<td>RITA[^23]</td>
<td>1011</td>
<td>&lt;5</td>
<td>57</td>
<td>81</td>
<td>55</td>
<td>na</td>
<td>76</td>
</tr>
<tr>
<td>CABRI[^24]</td>
<td>1054</td>
<td>4-6</td>
<td>61</td>
<td>78</td>
<td>14-5</td>
<td>63</td>
<td>81</td>
</tr>
<tr>
<td>BARI[^25]</td>
<td>1829</td>
<td>7</td>
<td>62</td>
<td>73.5</td>
<td>64</td>
<td>57</td>
<td>82</td>
</tr>
</tbody>
</table>

ERACI=Argentine trial of PTCA versus CABG; GABI=German Angioplasty Bypass Surgery Investigation; EAST=Emory Angioplasty versus Surgery Trial; RITA=Randomized Intervention Treatment of Angina Trial; CABRI=Coronary Angioplasty versus Bypass Revascularization Investigation; BARI=Bypass Angioplasty Revascularization Investigation; IMA=internal mammary artery graft; na=not available.
combined risk of death and non-fatal myocardial infarction was also similar between CABG and PTCA groups (10.1% vs 9.8%, P=0.81). The rate of additional interventions (PTCA and/or CABG) in the first year of follow-up was 33.7% and 3.3% in patients randomized to PTCA and CABG, respectively[27]. The surgical patients had a long initial hospitalization; the PTCA patients were discharged early and resumed work early, but were subsequently hospitalized more often.

The BARI trial[22] is the largest trial comparing PTCA and CABG in multivessel coronary artery disease and the only trial empowered to detect differences in mortality. The technically suitable patients with clinically severe angina or objective evidence of ischaemia were randomly assigned to an initial treatment strategy of CABG (n=914) or PTCA (n=915) and were followed for an average of 5.4 years. The 5-year survival rate was 89.3% for those assigned to CABG and 86.3% for those assigned to PTCA (P=0.19). The respective 5-year survival rates free from Q wave myocardial infarction were 80.4% and 78.7% (P=0.84). By 5 years after study entry, 8% of the patients assigned to CABG had undergone additional revascularization procedures, as compared with 54% of those assigned to PTCA (P<0.001); 69% of those assigned to PTCA did not subsequently undergo CABG.

The follow-up angiographic substudy of GABI shows some interesting results[30]. Follow-up angiograms were available in 102 CABG patients and 117 PTCA patients. The saphenous vein bypass grafts had an occlusion rate of 12.6% at 6 months, which is comparable to other studies[31,32]. Although the protocol excluded patients with total occlusion, 37% of the native arteries were occluded 6 months after bypass grafting compared to only 2.5% after PTCA. The rate of occluded native arteries was higher in the case of patent grafts than in the case of occlusion of the corresponding bypass graft. This kind of progression of disease to total occlusion has generally occurred proximal to the site of graft insertion. Native arteries with high grade lesions (>70%) were only at a slightly higher risk of progressing to total occlusion after bypass surgery than were native arteries with less severe lesions. Thus, a bypass to an artery with minimal disease might be potentially harmful, as it accelerates the progression of native disease; in cases of graft attrition, it will be undoubtedly harmful.

Thus combined evidence comparing PTCA with CABG shows no difference in prognosis (death and myocardial infarction) between these two revascularization strategies. However, the treatments differ markedly in the subsequent requirement for additional revascularization procedures and in the relief of angina. CABG patients were significantly more likely to be angina-free as compared to PTCA (80.7% vs 73.1%; OR 1.57, 95% CI 1.32 to 1.87, P<0.0001)[29]. The objective evidence of less ischaemic burden in CABG patients as

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**Table 1** Overall risks of death and a composite of death and non-fatal myocardial infarction at 1 to 3 years of follow-up from a meta-analysis of five randomized trials comparing CABG and PTCA for multivessel coronary artery disease. CABRI=Coronary Angioplasty versus Bypass Revascularization Investigation; EAST=Emory Angioplasty versus Surgery Trial; ERACI=Argentine trial of PTCA versus CABG; GABI=German Angioplasty Bypass Surgery Investigation; MI=myocardial infarction; OR=odds ratio; PTCA=percutaneous transluminal coronary angioplasty; RITA=Randomized Intervention Treatment of Angina Trial (Reprinted from Sim I, Gupta M, McDonald K, Bourassa M, Hlatky MA. A meta-analysis of randomized trials comparing coronary artery bypass grafting with percutaneous transluminal coronary angioplasty in multivessel coronary artery disease. Am J Cardiol 1995; 76: 1025–29. Copyright (1995) Reproduced with permission from Excerpta Medica, Inc.).
compared to PTCA, as provided by thallium scintigraphy in the Emory Angioplasty vs Surgery trial supports the subjective reports of angina relief[33]. The late follow-up of these trials is of considerable importance because restenosis after PTCA is a relatively early phenomenon, whereas graft attrition, especially with vein grafts after CABG produces its major effects several years after the initial operation[33].

**Important issues in multivessel PTCA**

**Completeness of revascularization and culprit lesion dilatation approach**

Functionally complete revascularization is defined as the successful dilatation of all significant stenoses in vessels that are of sufficient size (>1.50mm in diameter) and supplying viable myocardium. The definition of significant stenosis varies from 50% to 70% in surgical and PTCA literature, respectively. Vessels serving either infarcted territory, as demonstrated by akinesis on the left ventricular angiogram, or that were too small were not considered functionally important. Anatomically complete revascularization is defined as no residual significant stenosis in any major epicardial vessels[34]. Thus, functionally complete revascularization can be anatomically complete or incomplete. The impact of completeness or revascularization in multivessel disease is more obvious from surgical series.

The coronary artery surgery study (CASS) registry[35] is the largest observational study comparing 4-year cumulative survival patterns in multivessel disease involving 20 088 medically treated patients. Survival varied according to the severity of coronary artery disease, from 92% in the single-vessel disease to 60% in three-vessel disease, with significant obstruction of the left main coronary artery. Survival also varied according to left ventricular function: with survival of 92% with an ejection fraction greater than 50%, and 58% with an ejection fraction of less than 35%. In a further analysis of the impact of the extent of coronary artery disease and left ventricular function on survival, it was concluded that left ventricular function is a more important predictor of survival than the number of diseased vessels.

In the retrospective analysis of 3372 non-randomized surgical patients from the CASS surgical registry[36] who had three-vessel disease, adjusted event-free survival was not influenced by completeness of revascularization in a group with Canadian class I or II angina. In patients with class III and IV angina, those with more complete revascularization were more likely to be asymptomatic or free of severe angina, and a trend towards improvement in event free survival ($P=0.074$) was observed. The effect of complete revascularization was particularly evident in patients with severe angina and an ejection fraction <55%. In these patients, complete revascularization, defined as grafts to three or more vessels, was associated with both improved survival and event-free survival ($P=0.04$). Moreover, the mortality rate among patients experiencing a myocardial infarction during follow-up was significantly higher for patients with less complete revascularization. The beneficial effects in a subset with severe angina and a low ejection fraction were attributed to the improvement in myocardial perfusion and function from complete revascularization in hibernating myocardium. One important item to note from this study was that the survival curves diverge after around 2–3 years of follow-up. In another surgical study[37], it was concluded that postoperative residual lesions in the left anterior descending or left circumflex coronary artery were the most important predictors of mortality. In the same study, it was concluded that postoperative survival correlated better with the extent of residual disease than with the pre-operative extent of coronary disease. The 5-year survival rates of all well-revascularized patients with good left ventricular function were similar, about 90% regardless of the extent of pre-operative disease.

In the case of PTCA, revascularization is less complete as compared to a surgical series. In the NHLBI PTCA registry[38], complete revascularization was achieved in 23% of patients with double-vessel disease but in only 9% of those with triple-vessel disease. The most common causes of incomplete revascularization were culprit lesion dilatation strategy and chronic total occlusion.

In the observational series of PTCA[34,38–41], the completeness of revascularization and long-term outcome varied depending on the improvement in angina and reduced the need for repeat revascularization, with complete revascularization in some studies[39–41]. But there was no survival advantage with complete revascularization, as in surgical series. The reason maybe the shorter length of follow-up and the comparatively low-risk of the PTCA patients as compared to the surgical series. In the randomized trials of PTCA and CABG[19,25], the revascularization strategies also varied. In some trials the objective was complete anatomical (GABI), complete functional (ERACI), or equivalent (RITA) revascularization, but in EAST and CABRI an initial strategy of partial revascularization was permitted. The rates of complete revascularization were significantly higher in CABG patients than PTCA patients in all trials. For example, in the BARI trial[25], complete revascularization was achieved in 57% and 91% of patients in the PTCA and CABG arms, respectively. However, in none of the trials was there any difference in the hard endpoints, such as death or myocardial infarction. One of the explanations given by EAST investigators was that even though in the EAST trial, successful index segment revascularization (<50% residual stenosis) was more common at 3 years with CABG as compared to PTCA (89% vs 76%; $P<0.01$), the index segments free of severe disease with physiological priority (>70%) did not differ between two groups (95% vs 93%, $P=ns$).

In spite of these conflicting data, complete revascularization remains a desirable goal, and a satisfactory
outcome may be obtained with functionally complete revascularization. This may not apply, however, to patients with limited reserve, such as left ventricular dysfunction and severe ischaemia. Similarly, significant residual disease in the left anterior descending coronary artery, as part of an incomplete revascularization strategy, is not an acceptable approach [43]. The use of stents in multivessel coronary artery disease may not cause a substantial increase in the rate of complete revascularization [44], reflecting the continued practice of functionally complete revascularization and the fact that the acute procedural success rate of chronic total occlusion is not affected by stents.

Even though dilatation of the culprit lesion is part of an incomplete revascularization strategy, which may be less than ideal, this approach, may be of value in some cases. Among patients with stable angina pectoris and multivessel disease, only in 50% of patients can a culprit lesion be identified [45]. The long-term effect of this approach in these patients is unknown [44,45]. However, in order to achieve symptomatic relief, in chronic stable angina, this strategy may be valuable in some selected patients.

The natural history of unstable angina varies with the risk stratification based on the severity of angina and the underlying clinical circumstances. The risk of death and non-fatal myocardial infarction at 3 months follow-up ranges from 5% in the lowest risk group to 25% to 35% in the highest risk group [46,47]. Similarly major complications following percutaneous interventions vary according to the baseline clinical severity of the patients [48,49]. In one study [46], the composite risk of death and myocardial infarction after PTCA was 2.2%, 3.5% and 5.1% in unstable angina Braunwald class I, II and III, respectively. Among all patients with unstable angina, multivessel disease is found in approximately 60% of patients [48]. In the VANQWISH (Veterans Administration Non-Q Wave Infarction Strategies In Hospital) trial comparing ‘invasive’ and ‘conservative’ strategies, the bypass surgery mortality of 15% was unacceptably high [50]. So in patients with acute coronary syndrome, dilatation of only the ischaemia-causing vessel (the ‘culprit’ lesion) has been recommended as an initial approach to stabilize the patient’s condition [44,45].

In another study comparing an early invasive with an early non-invasive strategy in the unstable coronary artery disease FRISC II trial [52], 2457 patients were randomly assigned to invasive or non-invasive treatment and 3 months of diltiazem or placebo. The composite of death or myocardial infarction occurred in 10.4% vs 14.1% of patients (risk ratio = 0.74; 95% CI = 0.60–0.92; P = 0.005) at 1 year in the invasive and non-invasive strategies, respectively. In 100 patients with moderate to high risk unstable coronary-artery disease, at 1 year follow-up, an invasive strategy saves 1.7 lives, prevents two non-fatal myocardial infarctions and 20 readmissions, and provides earlier and better symptom relief at the cost of 15 more CABG and 21 more PTCA procedures. These results are particularly important considering that the in-hospital surgical mortality was approximately 1%, stents were used in around 65% of patients undergoing percutaneous interventions, the left internal mammary artery was used as a conduit in 95% of bypass surgery and multivessel disease patients constituted approximately 53% of the total trial population.

The culprit lesion can be identified by using the combined evidence of transient ECG changes during ischaemia and angiographic findings (complex ulcerated plaque with thrombus and severity of the lesion). Although these patients are incompletely revascularized, many will continue to be asymptomatic. Some patients will require subsequent interventions in the form of PTCA or CABG, but they will be at less risk on a more elective basis [43]. Similarly, in spite of differing coronary anatomy, the infarct-related artery is the only target in primary PTCA, except in patients whose haemodynamic status remains poor despite restoration of the patency of that artery [54].

### Diabetic patients

The risk of death from cardiovascular causes is three times higher for diabetic than non-diabetic men, even after adjustment for age and other cardiovascular risk factors [55]. The long-term event rates after PTCA and CABG are also higher than in non-diabetic patients [56–59]. The medically treated diabetic patients comprised 19.5% of the total BARI trial population [55]. Five-year survival (Fig. 3) was 65.5% among patients with treated diabetes who were assigned to PTCA, as compared with 80.6% among diabetics assigned to CABG, (P = 0.003). The 2-year results for 122 diabetic patients in the Coronary Angioplasty vs Bypass Revascularization Investigation (CABRI) [58] also suggest that CABG improved survival to the same extent as in BARI trial. The more extensive disease among diabetics and their greater tendency to have a restenosis after angioplasty were the mechanisms proposed by the BARI investigators. Late coronary occlusion causing fatal myocardial infarction is also one of the mechanisms proposed to explain the worse long-term survival in the PTCA group [59].

In a retrospective observational study at Emory University hospitals [59], involving diabetic patients with multi-vessel disease (PTCA, n=1057 and CABG, n=2088), in both groups, survival was approximately 50% by 10 years of follow-up. In the insulin-requiring subgroup, in contrast to the total group, therapy with PTCA was a risk factor for long-term mortality with a hazard ratio of 1.35 (95% CI = 1.01 to 1.79, P = 0.045) relative to CABG. In the patients treated with oral hypoglycaemic agents, the choice of revascularization was not a correlate of survival. The higher long-term mortality rate for insulin-requiring diabetic patients treated with angioplasty was explained by two possibilities in this study: (1) diabetes itself has pathophysiological effects that increase the mortality rate after PTCA as compared to CABG, or (2) insulin-requiring
diabetes may be a marker for more severe disease, in which surgery is a better option than angioplasty. However, in another large non-randomized Duke registry,[61] no advantage was observed with CABG as compared with PTCA among patients with diabetes. In the EAST trial there was no difference in 5 year survival between diabetic patients.[22]

So the survival advantage of CABG in diabetic patients with multivessel revascularization varied in different studies. There was a survival advantage for both insulin and oral hypoglycaemic treated patients in the BARI and CABRI trials. However, in the observational Emory registry only insulin-requiring patients had an advantage, and in the Duke registry there was no benefit. Diabetic patients constitute a separate subset of patients and the issue of multivessel revascularization needs to be addressed in prospective randomized trials in these patients. Until that time, it is advisable to maintain aggressive risk factor modification, tight glycaemic control, intensive non-invasive screening for asymptomatic restenosis and a lower threshold for CABG in these patients who require coronary revascularization.[59]

Staging

Multivessel coronary interventions not infrequently involve complex anatomy, such as long chronic total occlusions, severely calcified lesions requiring adjunctive rotational atherectomy or difficult bifurcation lesions requiring complex angioplasty techniques. The patient’s baseline characteristics may sometimes be unfavourable; they may be old and frail with poor left ventricular function, or renal impairment. In these situations it is better to follow the ‘dentist approach’ to the coronary revascularization by staging the procedure. It can be a true elective prospective staging or unintentional staging due to premature termination of the procedure due to unexpected problems.

The foremost reason for staging is patient safety. If the result of the first lesion in suboptimal, it is generally safer to tackle remaining lesions in another setting. In spite of the availability of better contrast media, such as on-ionic monomeric or dimeric and ionic low osmolar contrast agents, the amount of the contrast agent should not exceed 5 ml.kg⁻¹ due to possible undesirable
haemodynamic, electrophysiological or renal effects\textsuperscript{62,63}. Patient compliance and operator fatigue should also be considered especially in restless, uncomfortable patients and if the procedure is prolonged. If PTCA is a direct continuation of the diagnostic angiography, then staging is an attractive option. Due to differing reimbursing policies, and cost increment with staging, the decision to stage is also influenced by economic considerations.

When the staging strategy is chosen, the culprit lesion is obviously the first to undergo PTCA. The time interval for planning the second procedure varies from days to a few months, according to operator discretion, as there are no available data to support one particular timing. One approach is staging in the same hospitalization that can be either after 24 h, leaving the sheath in place, or towards the end of the hospital stay. This period is still within the time frame of subacute stent thrombosis. The second approach is to time the second procedure at around 4 to 8 weeks, well after the first lesion is stabilized with complete endothelization. Yet another approach is to stage the patient at 3–6 months, if the patient is reasonably asymptomatic after the first procedure, with the proposed goal of detecting and treating the restenosis in the same setting. However, in following these approaches, caution should be exercised in terms of the doubling of the reinterventions due to an ‘oculostenotic reflex’ in the angiographic follow-up arm, as compared to the clinical follow-up arm in the BENESTENT II trial\textsuperscript{65,66}.

In the BARI trial, 17\% of patients underwent staged PTCA for the initial PTCA. In the preliminary report of the Arterial Revascularization Therapies Study (ARTS)\textsuperscript{65,66}, 10\% of the first 482 patients were staged. The reasons given for staging were, patient fatigue in 60\%, amount of contrast used in 30\%, operator fatigue in 19\%, long fluoroscopic time in 19\% and ‘other’ in 24.5\% (in some patients more than one cause).

In a recent comparison between staged and non-staged procedures, it was shown that staging at an interval of 4–8 weeks is safe and results in more complete revascularization vs a non-stop approach\textsuperscript{65}.

\section*{Cost}

Even though the clinical efficacy of any treatment modality is the most important factor in choosing among the multiple options, cost-effectiveness remains the important factor. The RITA trial indicates that although PTCA is initially less expensive, the cost of the PTCA strategy rises over 2 years to around 80\% of the cost of a strategy of CABG\textsuperscript{28}. Similar findings were reported for GABI\textsuperscript{29}. In the BARI trial, the cost of the initial procedure was 35\% lower for angioplasty than surgery. However, the long-term cost at the 3 year follow-up, was only 4\% lower than bypass surgery, predominantly due to additional revascularization procedures required among patients with three-vessel disease\textsuperscript{67}. Two-vessel disease identifies patients likely to incur lower costs after angioplasty, whereas age, heart failure, co-morbid conditions and diabetes identify patients likely to have higher costs after either angioplasty or bypass surgery\textsuperscript{68,69}.

\section*{Unconventional indications}

Patients with left main coronary artery (LMCA) disease have a poor prognosis\textsuperscript{62} with medical treatment and they derive maximum benefit from coronary artery surgery\textsuperscript{4,44}. A report of the American College of Cardiology/American Heart Association task force regards unprotected left main stenosis as an absolute contraindication for PTCA\textsuperscript{70}. The proximity of this vessel to the aorta, its large calibre and lack of tortuosity makes it an inviting target for PTCA\textsuperscript{71}. In Gruentzig’s original report of the initial five patients undergoing PTCA, three underwent dilatation of the left main coronary artery\textsuperscript{49}. However, early reports of PTCA of the left main demonstrated a high procedural complication rate and short-term mortality. The initial NHLBI Registry\textsuperscript{72} reported 19 patients with PTCA to LMCA with a success rate of only 68\%. In the largest report\textsuperscript{73} of PTCA to LMCA in 127 patients, the procedural mortality was 9.1\% and 3 year survival was 36\% in the unprotected left main (not protected by previous CABG to one or more branches or from extensive right-to-left collaterals). The need for subsequent revascularization was 42\%.

One hundred and seven patients from 25 centres were reported in the ULTIMA registry\textsuperscript{74}. They were treated either electively (n=91) or for acute myocardial infarction (n=16) for unprotected left main (ULMT) coronary stenoses. Of patients treated electively, 25\% were considered inoperable, and 27\% were considered at high risk for bypass surgery. Primary treatment included stents (50\%), directional atherectomy (24\%), and balloon angioplasty (20\%). Results varied considerably, depending on presentation and treatment. For patients with acute myocardial infarction, technical success was achieved in 75\%, and for elective patients, technical success was achieved in 98.9\%. Longer-term event (death, infarction, or bypass surgery)-free survival was correlated with ejection fraction (P<0.001) and was inversely related to presentation with progressive or rest angina (P<0.001). Surgical candidates with ejection fractions ≥40\% had an in-hospital survival of 98\% and a 9-month event-free survival of 86.5\%, whereas patients with ejection fractions <40\% had 67\% and 22±12\% in-hospital and 9-month event-free survivals, respectively. Nine hospital survivors (10.6\%) experienced cardiac death within 6 months of hospital discharge; they were primarily patients with unstable angina and the authors suggested follow-up angiography 6 to 8 weeks after PTCA to prevent early post-hospital discharge cardiac death. Forty out of a patient total of 277, who underwent an emergency percutaneous coronary intervention of unprotected left main stenosis for acute myocardial infarction were discussed in a further report of this registry\textsuperscript{75}. Most of these patients
were in cardiogenic shock, requiring aggressive mechanical support. The in-hospital death rate was 55% and the 12-month survival rate was 42%. However, for a similar clinical presentation of acute myocardial infarction, left main stenosis and shock (left main shock syndrome) the in-hospital mortality of medical therapy and CABG is very high and comparable, respectively [76–78]. Hence the authors concluded that percutaneous revascularization can be a preferred strategy in this setting.

Recently there have been several reports of left main stenting with 100% procedural success and no in-hospital mortality [71,79,80]. In these studies, the clinical restenosis rate was 20% [71] and 17% [79] and event-free survival 80% [71]. However, considering the small number of patients in these studies, and their non-randomized nature, left main interventions can be advocated only to protect the left main coronary artery and in patients with unacceptable surgical risks or severe co-morbid conditions. There is concern about late sudden death after unprotected left main stenting [74,81].

**Current trends**

**Percutaneous revascularization**

**Stents**

Coronary stent implantation has become the major mode of myocardial revascularization after the STRESS and BENESTENT landmark trials [82,83], which proved the efficacy of Palmaz-Schatz stents in the prevention of restenosis. The target lesions in these trials were discrete (<15 mm), large vessels (>3 mm) with certain anatomical exclusions, such as multiple lesions, diffuse disease, thrombus, ostial location and tortuous vessels. There was a higher clinical success, reduced restenosis (around one third) and a reduction in the need of target vessel revascularization in the stent patients as compared to the angioplasty patients. While these trials were critically important in shaping our current revascularization strategies, they included highly selected lesions, constituting less than 20% of lesions in current clinical practice. In the BENESTENT II trial [64–65], with the heparin-coated Palmaz-Schatz stent, the restenosis rate was reduced to 16% as compared to 30% in the balloon group, even though this trial included 56% of ACC/AHA type B2 and C lesions. As the studies in small vessels [84,85], saphenous vein grafts [86], restenotic lesions [87], chronic total occlusions [88], and acute myocardial infarctions [89,90] are showing the superiority of stenting over balloon angioplasty, the stent indications are growing, and currently up to 80% of interventions in many centres are accomplished by stent placement [91].

There are several recent non-randomized studies [92–96] of multivessel stenting. They are summarized in Table 4. The multivessel coronary stenting in these studies was associated with a high angiographic success rate, a low periprocedural complication rate, and a high event-free survival rate. The rate of emergency CABG was lower in these trials, (ranging from 0% to 2%) as compared to 6.3% in the BARI trial [25] and 9.6% in EAST trial [23]. Severe dissection is the most common cause of abrupt vessel closure, and stents are the most effective bailout device, significantly reducing the need for emergency CABG. These series included a relatively high proportion of complex lesions, and ACC/AHA type B2 and C lesions constituted 45% to 74.5% in different studies. In one study [91], 53% of patients had undergone saphenous vein graft stenting. However, in these studies there was no increase in completeness of revascularization. In one study [94], complete revascularization was achieved in only 57.1%; the reasons given were chronic total occlusion and a policy of functionally adequate revascularization. In another study [95], out of 377 multivessel disease patients, only one vessel was treated in 321 patients, due to a significant number with unstable angina (33%) of a culprit lesion and chronic total occlusions (40–3%). However, repeat revascularization during follow-up was very low (10-8%).

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>Mean follow-up months</th>
<th>ACC/AHA type B2/C %</th>
<th>Emergency CABG %</th>
<th>Procedural success %</th>
<th>Repeat revascularization %</th>
<th>Event free survival %</th>
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<td>21</td>
<td>60</td>
<td>2</td>
<td>97</td>
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<tr>
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<td>97</td>
<td>17</td>
<td>80</td>
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<td>12</td>
<td>74:5</td>
<td>0</td>
<td>98:3</td>
<td>18:3</td>
<td>79:8</td>
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ACC/AHA = American College of Cardiology/American Heart Association; revasc = revascularization; event free survival = free of death, myocardial infarction and revascularization; na = not available.

**Table 4 Non-randomized studies of multivessel stenting**

The ARTS trial[97] shows that with multivessel stenting, incidence in MACCE rates in favour of the surgical arms. Intervention have shown, on average, a 30% follow-up. Previous trials of CABG vs percutaneous stroke) with either revascularization technique at 1-year.

The main exclusion criteria were overt congestive heart failure and intention to treat >1 totally occluded major epicardial vessel. Two-thirds of patients in both groups had two-vessel coronary artery disease and a third had three-vessel disease; left ventricular function was preserved (mean LVEF 60%). One third of patients in both groups had unstable angina. There was a statistically significant reduction in MACCE in the CABG group at 1 year (12.2% vs 26.3%). This was primarily due to a marked difference in the repeat revascularization (3-5% in the CABG group as opposed to 16-9% in the stent group). The hard events such as death (2-8% vs 2-5%), myocardial infarction (4-0% vs 5-3%), and strokes (2-0% vs 1-7%) was not significantly different between the CABG and stent groups, respectively. The investigators performed a cost analysis of the two strategies. Initial costs were lower in the stent group, with the average cost in the surgical group amounting to 10 742 Euros (1 Euro=approximately 1 US$) as opposed to 6484 Euros to the stented group. Follow-up costs were higher in the stent group (4216 vs 2903 Euros). However, the overall cost was lower in the stent group by approximately 3000 Euros over the 1-year period. Thus in this trial, there was no significant difference in ‘hard events’ (death, myocardial infarction, stroke) with either revascularization technique at 1-year follow-up. Previous trials of CABG vs percutaneous intervention have shown, on average, a 30%–40% difference in MACCE rates in favour of the surgical arms. The ARTS trial[97] shows that with multivessel stenting, this difference can be narrowed to only 14%. The SOS (Stent OR Surgery) trial is another ongoing study comparing the two treatment modalities in multivessel disease.

**Adjunctive therapies and techniques**

Even through stents reduce the relative rate of restenosis in comparison with balloon angioplasty, the occurrence of stent restenosis is substantial due to frequent use of stents and its use in complex and long lesion subsets. When in-stent restenosis occurs, conventional treatments are of limited value and except for focal stent restenosis, repeat in-stent restenosis occurs in 54% to 66% of patients after treatment[98–100]. As the principal cause of in-stent restenosis is neointimal tissue proliferation in ultrasound studies[101], the speculation was that local radiation might be useful in this situation. The studies using 192Ir as a source of gamma radiation[98–100] for in-stent restenosis and studies using beta radiation to both de novo and in-sent restenosis[102–104] demonstrate impressive benefit in the reduction of repeat restenosis in the range of 50% to 60%. Thus intracoronary radiation is a step ahead in the percutaneous interventions.

The glycoprotein (GP) IIb/IIIa inhibitors have demonstrated a reduction in death, myocardial infarction, and the need for repeat revascularization in percutaneous coronary revascularization as a ‘class effect’ (trials with all of these agents show benefit): however, heterogeneity in the treatment effect is present with the strongest evidence for the use of abciximab. Kong et al.[105] reported a meta-analysis of 16 randomized controlled clinical trials of GP IIb/IIIa inhibitors to assess the effect on death, myocardial infarction and revascularization in 32 135 patients. For the composite end-point, there was highly significant benefit (P<0.001) favouring GP IIb/IIIa inhibitors. At 6 months there were 28 fewer events per 1000 patients undergoing interventions. In a pooled data of 1462 diabetic patients from EPIC, EPILOG and EPISTENT trials, mortality in diabetics who underwent multivessel intervention was reduced from 7-7% to 0-9% (P=0.018) with use of abciximab[106]. The primary benefit of IIb/IIIa inhibitors is in reducing the coronary events associated with the procedure, peri-procedural reduction of myocardial necrosis and abrupt closure. No additional benefit is apparent in the subsequent period from 2 days after intervention until 30 days[107]. Thus glycoprotein IIb/IIIa inhibitors are a major development in adjunctive pharmacotherapy enhancing the safety of the procedure.

With the introduction of sensor-tipped angioplasty guide wires, Doppler or pressure based information, such as coronary flow reserve and myocardial fractional flow reserve, can be derived regarding the significance of stenosis, facilitating physiologically based decisions regarding the need for intervention for an individual lesion during a multivessel-multileision procedure. As the number of lesions treated increases in multivessel disease, the chances of restenosis increases[92]. So, tackling only physiologically significant lesions should be an optimum policy. Recent studies suggest that intra-coronary physiological information complements information derived from coronary angiography in both decision making and to optimize the result of the coronary intervention[108], which should be more applicable to multivessel disease. Similarly intravascular ultrasound assists in optimizing acute gain, symmetry, and apposition of intracoronary stents even when post-stent high-pressure balloon inflation achieves an optimal angiographic result and may be associated with low rates for target vessel revascularization and major adverse cardiac events at follow-up[109].

**CABG**

Recently there has been significant improvement in myocardial protection techniques, less-invasive operative techniques and arterial conduits of CABG. The CABG is associated with myocardial stunning which is associated with morbidity and mortality, especially with acutely and chronically depressed myocardial function. It is demonstrated that some techniques, such as vented cardiopulmonary bypass and substrate enhanced...
sanguineous cardioplegia lead to improved survival in high-risk cases\(^{[110]}\). The choice of graft is very important in CABG because long-term graft patency is closely related to cardiac mortality. Barner et al.\(^{[111]}\) reported a superior graft patency of the internal mammary artery of 83% over saphenous vein graft patency of 41% at 10 years in 1000 patients. There is also a reduction in peri-operative mortality with internal mammary artery application and its use is recommended as myocardial protection in high-risk patients\(^{[112]}\). The employment of bilateral internal mammary artery grafts is associated with less recurrent angina, fewer reoperations and a trend towards better survival\(^{[113,114]}\). Use of free right internal mammary artery has also been shown to have excellent short and long-term results\(^{[115]}\). Acar et al.\(^{[116]}\) recently reported 84%, 5-year patency in the radial artery as a conduit. For other arterial grafts, such as gastro-epiploic and inferior epigastric arteries, long-term results are not available.

Less invasive surgery has been used recently to reduce the morbidity of conventional CABG. It is of three types\(^{[110]}\). (1) Off-bypass surgery is performed with median sternotomy, reducing cardiac motion by mechanical and pharmacological means. (2) Minimally invasive direct coronary artery bypass (MIDCAB) is performed through a small left anterior thoracotomy without cardiopulmonary bypass. Usually only left anterior descending coronary artery and diagonal branches, but occasionally two vessels, are grafted by this approach. It is associated with rapid recovery and less morbidity, but long-term patency remains to be determined. (3) Closed chest, port access, video-assisted CABG can be performed with femoro-femoral cardiopulmonary bypass and cardioplegic arrest with limited incision. All these innovations may improve short-term morbidity, but the long-term results, in terms of graft patency need to be carefully assessed in the future.

**Medical treatment**

There have been significant advances in lipid lowering therapy, antiplatelet therapy, beta-blocker therapy and gene therapy. Clinical trials in patients with coronary heart disease and with and without high cholesterol have demonstrated consistently that statins reduce coronary events by ~30% and also reduce mortality significantly. The angiographic follow-up trials of lipid lowering show the slowing of progression, induction of regression, reduction of new lesion formation and most importantly ‘plaque stabilization’\(^{[117]}\). In one trial of 341 asymptomatic or mild to moderately symptomatic chronic stable angina patients randomized to high dose atorvastatin (80 mg) and PTCA, the atorvastatin group had a 36% lower event rate than PTCA patients \(P=0.048\) at 18 months follow-up\(^{[119]}\). Aspirin is currently the standard secondary prevention therapy in all subsets of patients with established heart disease\(^{[119]}\). The addition of ticlopidine and clopidogrel to aspirin along with optimum stent deployment had significantly reduced the incidence of subacute thrombosis\(^{[120]}\). As aspirin itself is a weak antiplatelet agent, the other potent antiplatelet drugs, GP IIb/IIIa inhibitors, are major advances in pharmacotherapy.

The feasibility of the use of recombinant genes or growth factors to enhance myocardial collateral blood vessels has been proved in animals. It will be interesting to see the results of the large prospective trials of these factors in humans of both direct intramyocardial injection or catheter based transendocardial injection\(^{[123]}\).

**Newer modalities**

Both surgical (transmyocardial revascularization) and catheter based myocardial laser revascularization (percutaneous myocardial revascularization) are potential alternatives that are currently being evaluated in patients in whom conventional methods fail\(^{[122]}\). Both types result in a reduction in anginal symptoms in patients with intractable medically refractory angina pectoris not amenable to CABG and PTCA, most likely related to myocardial inflammation, secondary stimulation of growth factors and denervation of the myocardium. There are three randomized published trials\(^{[123–125]}\) prospectively comparing transmyocardial revascularization and medical treatment in 655 patients. There was significant improvement of subjective endpoints such as angina class and quality of life with transmyocardial revascularization in all trials. There was no significant difference in survival between medically treated and transmyocardial revascularization patients. There were differing results of objective end-points in different trials. There was improvement of exercise tolerance in one trial\(^{[125]}\), whereas treadmill exercise time and 12 min walk distance were not different in another trial\(^{[123]}\). There was improvement of perfusion defects in one trial\(^{[124]}\), but no improvement in another trial\(^{[125]}\).

In general, the improvement in angina appears to be out of proportion to any demonstrable improvement in myocardial perfusion\(^{[126]}\).

The percutaneous myocardial revascularization approach applies laser energy to create channels from the endocardial side of the left ventricular wall. The early results of percutaneous myocardial revascularization indicate that the reduction in anginal symptoms are similar to that with transmyocardial revascularization and improvement in exercise duration\(^{[127–129]}\). However, recently a study with Direct Myocardial Revascularization (DMR), randomizing laser to placebo treatment could not detect a beneficial effect for DMR in comparison to the placebo group.

**Conclusion**

The gold standard for multivessel revascularization remains conventional coronary artery bypass surgery, as
it offers more complete revascularization with long lasting symptom relief and with fewer reinterventions than after PTCA. The surgical approach has a wide applicability, such as left main disease, chronic total occlusions, diffuse disease and anatomically complex disease that would have been problematic and technically demanding with PTCA. However, surgery has its own limitations, such as the use of general anaesthesia, extracorporal circulation, ventilation and associated morbidity of major surgery. It is also less easily implemented in acute coronary syndromes, less easily repeatable and associated with longer hospital stay and difficulties in work resumption.[86]

In contrast, PTCA has many advantages. It is less invasive, and more readily applicable to acute coronary syndromes and sick patients. In addition, it is more easily repeatable (dentist approach) with shorter hospitalization. However, it is associated with less symptomatic relief, more repeat procedures and possibly less favourable outcomes in diabetic patients. Recent developments in stents have introduced this device as an important tool for revascularization provided the vessel is larger than 2-75 mm. Longer follow-ups with the current randomized trials of CABG, comparing stents in multivessel disease, will define in detail how the difference between surgical and percutaneous techniques are modified by the introduction of the stent.

In recent years, neither mode of revascularization has been utilized in a mutually exclusive way. Often, they can be complementary. The ‘hybrid’ procedure, such as MIDCAB to left anterior descending coronary artery and PTCA to other vessels in patients with multivessel disease may be safer and more effective than either alone.[131]

Finally the importance of risk factor reduction and medical treatment, including aggressive lipid lowering, cannot be over-emphasized. Long-term follow-up provides scarce evidence[122] for a reduction in future acute coronary events with revascularization. However, there is ample evidence in the literature for a reduction with medical treatment. Comprehensive medical therapy vs revascularization is a re-challenge to our current practice. Current practice may need reevaluation due to the recent important developments in both medical therapy and revascularization procedures.

References


