Complete myocardial revascularization: between myth and reality

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Myocardial revascularization in patients with multi-vessel coronary artery disease may be accomplished, by percutaneous interventions or surgery, either on all diseased lesions or directed to selectively targeted coronary segments. The extent of planned revascularization is often a major determinant of treatment strategy. Revascularization of all diseased coronary segments—complete myocardial revascularization—has a potential long-term benefit, but is more complex and may increase in-hospital untoward events. Revascularization may otherwise be incomplete, either because of the operator’s inability to treat all diseased coronary segments or by choice of deciding to selectively revascularize only large areas of myocardium at risk. Although incomplete revascularization may negatively affect long-term outcomes, it may be, when wisely chosen, the preferred treatment strategy in selected patient categories because of its lower immediate risks. The patient’s clinical status, ventricular function, and the presence of co-morbidities may orient clinical decisions in favour of incomplete revascularization.

KEYWORDS
Revascularization; Coronary artery bypass surgery; Angioplasty; Stents

Introduction
Patients with multi-vessel coronary artery disease may undergo revascularization with either coronary artery bypass graft (CABG) surgery or percutaneous coronary interventions (PCI). When compared in randomized trials, these two strategies have shown overall similar long-term rates of irreversible events, such as death or myocardial infarction (MI)1-2 A greater protective effect of CABG was traditionally attributed to a more complete revascularization or to the fact that epicardial vessels are bypassed distally, regardless of disease extent and progression.3 This hypothetical superiority of surgery does not, however, translate into tangible benefits in most patients.4 In recent years, the development of arterial conduits for CABG5,6 and the use of stents for PCI7-8 have dramatically improved the results of both strategies. A more aggressive pharmacological approach with statins9 and full antiplatelet therapy10,11 has ameliorated the outcome of candidates to percutaneous revascularization, and differences between CABG and PCI have considerably blurred, currently persisting only for non-fatal events and favouring surgery mostly for a lower rate of reinterventions.12-14

Therefore, the cardiologist has both options available in the vast majority of cases. What is mostly lacking today is the solid ground to decide to what extent pursuing revascularization. The guidelines currently available for treatment of coronary artery disease15-18 do not formally discuss the issue on adequacy of myocardial revascularization. For both PCI and surgery, there is still a substantial uncertainty on the definition and evaluation of the ‘adequacy’ of myocardial revascularization. Theoretically, complete anatomical revascularization should provide benefits in terms of recovery of myocardial function or protection from intervening events that should translate into a better survival. This comes, however, at the price of longer procedures and higher immediate risk. Thus, have we to accept the myth that completeness is always the goal or should we be ready to come to some compromise? Is the price to reach the ‘ideal’ goal too high for the individual patient? We will try to answer these questions on the basis of the existing literature.

Methods
We reviewed published reports from January 1994 to August 2004 in English on revascularization strategies in patients with multi-vessel coronary artery disease using the PubMed database and through personal communication with experts in the field. We used the keywords ‘multi-vessel coronary disease’, ‘complete’ and ‘revascularization’. We also searched through the references of all the studies found from previous sources to locate additional references that might be useful for the purpose.

Definitions and historical background
There is a large variability in the criteria adopted to define the completeness of myocardial revascularization. By
interpolation of existing knowledge, we provide here a comprehensive definition that takes into account the size of the vessel, the severity of the lesion, and the viability of the myocardial territory (Table 1). An ‘anatomically complete’ revascularization is accomplished when all vessels with clinically significant stenoses (>1.5 mm vessel diameter and per cent diameter stenosis ≥50%) are treated, irrespective of the underlying myocardial function. A ‘functionally complete’ revascularization instead refers to cases in which only lesions supplying a viable myocardium are treated. Revascularization may, therefore, also be anatomically incomplete but still functionally adequate. Such definitions are relevant to compare outcomes of different strategies over time.

In most trials comparing the relative efficacy of PCI and CABG in patients with multi-vessel coronary artery disease, the adequacy of revascularization was judged on an anatomical basis, owing to the unavailability of systematic data on myocardial viability. No trial was specifically designed to compare patients’ outcome according to the completeness of the revascularization, with either PCI or CABG. Most comparisons of complete vs. incomplete revascularization are based on observational series or on trials comparing CABG vs. PCI among patients with multi-vessel disease, without any specific design to test the hypothesis that the adequacy of revascularization could have prognostic relevance. Selection bias can only be overcome with a randomized trial, which is challenging and likely difficult to fund. Therefore all considerations here are based on reasoning and interpolation of data from indirect sources.

The largest dataset on the issue of revascularization adequacy derives from post hoc analyses performed after the Bypass Angioplasty Revascularization Investigators (BARI) trial where, according to the subjective clinical judgment of the interventional cardiologist and the surgeon, lesions were rated as:

(i) clinically important, when deemed responsible for patient’s ischaemic symptoms or signs, with a distal territory sufficiently large and viable to warrant revascularization;
(ii) borderline, when revascularization was judged as not required or unnecessary;
(iii) not relevant, when the distal myocardial territory was small or non-viable.

During the early days of CABG surgery, an improved long-term event-free survival was documented when all stenoses ≥50% in diameter were bypassed. Similar results were obtained at the very beginning of PCI procedures. However, patients with incomplete revascularization were generally older and with a higher prevalence of severe comorbidities. Thus, the higher perioperative risk of patients not allocated to complete revascularization could flaw conclusions on the adopted strategy, owing to the existence of a systematic bias. Therefore, the evidence for a superiority of complete revascularization had to be based on other grounds.

Establishing the myth: evidence favouring complete revascularization

The advantages of complete revascularization emerge from long-term follow-up studies showing a direct relationship between the number of treated coronary segments and the reduction of cardiovascular events (Table 2). Large populations and long follow-up are necessary to demonstrate minor differences in survival or other important endpoints.

In the CABRI (Coronary Angioplasty vs. Bypass Revascularization Investigation) trial, incomplete revascularization was allowed in the PCI arm. Therefore, patients with total coronary occlusions were deemed eligible for the study, and this accounted for a lower procedural success rate and a less extent of complete revascularization in patients treated with PCI than with CABG. After 1 year of follow-up, subjects randomized to PCI showed a trend toward a higher mortality (3.9%) when compared with CABG (2.7%), and a significantly worse event-free survival (66 vs. 93.5%, P < 0.001).

On pooling data from 2047 patients undergoing PCI in the BARI randomized trial and the BARI observational registry, a strategy of PCI on all ‘clinically important’ or ‘borderline’
lesions was associated with a lower 5-year risk of death or MI when compared with an incomplete revascularization. 23 Among 2067 patients undergoing isolated grafting of the left internal mammary artery (LIMA) to the left anterior descending (LAD) coronary artery, the presence of an ungrafted diseased left circumflex or proximal right coronary artery as well as any degree of left main stenosis was associated with a reduced 20-year survival. 24 In a large database of 8409 patients undergoing elective PCI, age, the degree of creatine-kinase (CK)-MB elevation, baseline creatinine $\geq 2$ mg/dL, elevated C-reactive protein, low ejection fraction, and congestive heart failure were all identified as independent correlates of death within 4 months. 25 When only patients with untoward events were selected, and the cohort matched with subjects with CK-MB elevation who survived, the strongest independent correlate of death was the presence of an incomplete revascularization ($P < 0.001$), followed by congestive heart failure ($P = 0.005$), and hospital discharge without statin therapy ($P = 0.009$).

**Challenging the myth: evidence favouring incomplete revascularization**

Incomplete revascularization, however, limits peri-procedural risk, and can therefore be wisely used in high-risk patients, when the aim is to target vessels supplying large amounts of myocardium. In this case, attempts at treating small coronary arteries or occluded vessel supporting necrotic areas likely increases the duration of the intervention and procedure-related complications, 26,27 and are therefore deliberately avoided. Sometimes, a repeat procedure is judged as not to be such to affect long-term survival, and is an acceptable price to pay for a reduction in the immediate risk (Table 2). In such settings, surgical and non-surgical revascularization strategies have extremely different perspectives. With PCI, staged procedures may limit the patient’s exposure to radiation and contrast media, and the additional revascularization may be later performed only after a positive non-invasive functional testing. With CABG, additional surgery is a much more serious event, since patients with a short time interval between primary and redo CABG show a substantially higher in-hospital mortality rate (18 vs. 8%, $P < 0.05$, among patients undergoing redo CABG > 1 year after the index surgery). 28

Intentionally incomplete PCI revascularization in non-diabetic patients with multi-vessel disease does not compromise 5-year survival. 29 Only a trend towards a higher subsequent need for CABG (30 vs. 26%, $P = 0.08$) was observed with this strategy when compared with complete revascularization. 29 Among 1507 patients undergoing CABG in the BARI trial and registry, no survival advantage was documented for anatomically or functionally complete revascularization compared with incomplete revascularization, and actually the use of more than one graft into a non-LAD territory increased the long-term incidence of death or MI (relative risk = 1.37, $P = 0.03$) compared with the use of one or less graft to the right coronary or the left circumflex artery. 30

In the Arterial Revascularization Therapies Study (ARTS), a complete revascularization was more frequently obtained with CABG than with PCI (84% vs. 70.5%, $P < 0.001$). Incomplete revascularization did not affect the 1-year event-free survival among CABG patients, while PCI patients with incomplete revascularization showed a lower 1-year event-free survival compared with patients treated with PCI on all diseased vessels (69% vs. 77%, $P < 0.05$), mainly due to a higher rate of subsequent CABG (10% vs. 2%, $P < 0.05$). 31

One has to acknowledge, however, that none of the aforementioned large-scale trials took into account the presence of a previous MI, wall motion score, or data on myocardial viability, and therefore the ‘completeness’ of myocardial revascularization was judged only on an anatomical basis.

**High-risk patients**

Patients with acute coronary syndromes frequently feature multiple complex coronary plaques: ~40% of patients admitted with an acute MI have ulcerated plaques or evidence of thrombus in other than infarct-related segments, and this multi-focal pattern is associated with adverse clinical outcomes. 31 In patients with non-ST elevation acute coronary syndromes, an early stratification based on clinical, electrocardiographic, and serum biomarker criteria is of utmost relevance. Patients with intermediate-to-high risk should be managed in a timely and aggressive fashion, as they benefit from intensive anti-platelet therapy, the use of heparin, and early angiography for a prompt decision-making. 32 Here, incomplete revascularization with PCI of the sole culprit lesion may be an attractive option for a timely management. Indeed, in one study, the extent of revascularization did not apparently influence the risk of adverse events in patients undergoing PCI for an acute coronary syndrome, despite the fact that those with an incomplete revascularization had a worse baseline left ventricular function. 33 Here only diabetes and the presence of a thrombus predicted the 1-year outcome after PCI. 33 In patients with multi-vessel disease and ST-elevation MI, management of non-culprit lesions is controversial. The most common approach is to defer revascularization of territories served by a non-culprit lesion away from the unfavourable immediate condition of acute MI. This practice is supported by the notion of possible overestimation of non-culprit lesion severity in the setting of acute MI due to enhanced vascular tone, often resistant to nitrate administration. 34,35

In most trials comparing surgery with PCI, diabetic patients experience an increased long-term survival if allocated to CABG. 2,12 A better 10-year survival after CABG compared with PCI (60 vs. 46%, $P < 0.001$) was documented also among 1938 diabetics analysed in a two-centre database project; here incomplete revascularization was the major determinant of adverse events after PCI. 36 The higher rate of adverse events observed in diabetics after PCI has to be ascribed to the increased occurrence of restenosis and the accelerated disease progression, the latter appearing mostly throughout the entire length of the instrumented artery. 37,38

There is still controversy on whether complete revascularization ameliorates prognosis in the elderly patients, although exposed to an increased procedure-related mortality. 39,40 Among 5003 subjects aged $\geq 70$, incomplete revascularization was found to be an independent risk factor for death as early as 6 months after CABG. 41 Among patients with a reduced life expectancy,
however, aiming at a complete revascularization may cer-
tainly increase immediate risks, and this is hardly balanced
by the hypothetical long-time survival benefit. The survival
benefit of a complete surgical revascularization seems
evident, in general, only for subjects having a predicted
life expectancy of >10 years.42 Thus, whenever life expect-
ancy is shorter, there is no solid ground for a choice of com-
plete revascularization at all prices. For elderly patients,
beating heart CABG is an attractive option, limiting unto-
ward events related to extracorporeal circulation and
aortic manipulation. In a limited series of patients aged
>75, matched for pre-operative risk and left ventricular
function, subjects operated with cardiopulmonary bypass,
although receiving more grafts and more likely to have com-
plete revascularization, had a higher mortality rate (15.9 vs.
4.5%, \( P = 0.029 \)), a higher rate of perioperative compli-
cations, and a worse 1-year survival (\( P = 0.022 \)) than
patients operated off-pump.43

Left ventricular dysfunction is one of the major determi-
nants of perioperative risk,25 and a strong association has
been documented between revascularization and improved
survival among patients with left ventricular dysfunction
who have evidence of myocardial viability on imaging
tests.44 Currently available non-invasive testing techniques
assess distinct features of viable myocardial cells: \( ^{201} \)Tl
single photon emission computed tomography reflects cell
membrane integrity; dobutamine echocardiography assesses
the contractile reserve; positron emission tomography with
\( ^{18} \)F-fluoro-deoxyglucose assesses myocyte glucose utiliz-
ation; contrast-enhanced magnetic resonance imaging
detects the transmural extension of both the scar and
viable myocardium. Differences among techniques in pre-
dicting the recovery of regional contractile function after
revascularization, although reported in some studies,35 gen-
erally involve relatively small regions of the myocardium
and such small differences impact little on late survival.44
In a large single-centre study on 11 830 surgical candidates,
27% of whom had an ejection fraction <50%, incomplete
revascularization was identified as one of the independent
predictors of long-term mortality, together with pre-
operative angina class, congestive heart failure, and
number of diseased vessels.46 Among 908 patients under-
going CABG for ischaemic cardiomyopathy, viable myocar-
dium in the targeted areas and a complete revascularization
were independent predictors of the 5-year event-free survival.47 Among 105 subjects with poor
left ventricular function treated medically or submitted to
PCI or CABG, the most powerful prognostic determinant of
death or MI was the number of non-revascularized arterial
segments serving viable territories. Here, survival was sig-
ificantly better among patients treated with complete
revascularization when compared with those assigned to
medical therapy (\( P < 0.0002 \)) or to an incomplete revascu-
larization (\( P < 0.03 \)).48 In patients with ischaemic left ven-
tricular dysfunction, the severity of baseline contractility
defects, the extent of myocardial viability, and, again, the
completeness of revascularization were the main determi-
nants of post-revascularization functional recovery.49 Here,
a complete revascularization, however achieved, seems
the preferred alternative.

In patients with renal dysfunction, CABG and PCI are
similarly affected by an extremely high in-hospital mor-
tality, up to 14% after PCI and 30% after surgery.50,51 Here,
whenever possible, a strategy of PCI targeted to the single
culprit lesion seems to be associated with a better long-
term survival.52 All efforts should be done to minimize peri-
procedural risks: among 170 patients with serum creatinine
\( \geq 2.0 \) mg/dL undergoing PCI, CK-MB elevation was the most
relevant independent predictor of late mortality.53

In candidates for major vascular surgery, the prevalence
of coronary artery disease is high. Not surprisingly, perio-
perative and long-term cardiac events are accurately pre-
dicted by pre-operative myocardial perfusion imaging.44,55
The recently published Coronary Artery Revascularization
Prophylaxis trial56 has raised some concerns on the benefit
deriving from coronary revascularization before major vas-
cular surgery. Patients scheduled for elective vascular oper-
ations were randomly assigned to either myocardial
revascularization or medical therapy. At a median follow-
up of 2.7 years, the mortality was 22% in the revasculariza-
tion group and 23% in the conservative group (\( P = NS \)).
However, in that trial, patients with unstable angina, left
main disease, severe left ventricular dysfunction, or aortic
stenosis were excluded. The enrolment criteria of the trial
defined only 9% of the patients eligible for the randomiz-
ation out of more than 5000 subjects screened, and ~65% of
the study population had single- or double-vessel
disease. Therefore the absence of survival benefit for revas-
cularization when compared with medical therapy alone
does not necessarily apply out of the elective low-risk popu-
lation enrolled in that trial.57 Patients with documented
ischaemia on a pre-operative stress testing have significantly
improved long-term survival if they undergo a selective and
functionally adequate revascularization.58 The timing of this
staged approach is also critical. Whenever possible, non-
cardiac surgery should be delayed 6 weeks after stent PCI
in order to not discontinue full anti-platelet therapy
(aspirin plus a thienopyridine), which has been proved to
decrease the occurrence of stent thrombosis. A shorter
delay could expose the patient to an extremely high risk of
stent thrombosis and/or MI (from 3.8 to 7.1% per week).59

An educated opinion on the best revascularization strat-
egies in various clinical scenarios, putting together the
discussed pieces of evidence from the literature, is sum-
marized in Table 3.

Future directions

The literature evidence reviewed and the consequent
opinions come from patients with a variety of associated
clinical conditions and treated with a variety of rapidly
changing techniques (e.g. plain old balloon angioplasty,
bare-metal stenting, inadequate platelet inhibition). There
are interesting new developments that may change the
overall pattern in the near future. In the setting of CABG,
interest in beating heart (off-pump) surgery has rapidly
increased, as this technique avoids cardiopulmonary
bypass and reduces perioperative adverse events. Off-
pump complete revascularization can be now performed in
the majority of cases.60 However, although associated with
less perioperative myocardial damage,61 off-pump surgery
may come at the price of a lower 3-month graft patency
than on-pump surgery (88 vs. 98%, \( P = 0.002 \)).62 The
Disease will keep PCI economically competitive with use of these new devices in patients with multi-vessel disease, although it is still uncertain whether the liberal use of drug-eluting stents (DES) will significantly reduce the rate of restenosis. To extend the comparison between CABG and multi-vessel PCI to the current DES era, 607 patients who received DES where enrolled in the ARTS II trial; more complex lesions were treated, and more glycoprotein IIb/IIIa inhibitors were used than in the ARTS I trial; more complex lesions were treated, and more glycoprotein IIb/IIIa inhibitors were used than in the ARTS I trial. After 6 months, patients treated with DES-PCI in the ARTS II showed a trend toward lower mortality (0.5%) and less cardiovascular events (6.4%) when compared with the historical arms of CABG (1.8 and 9%, respectively) and PCI (2.3 and 20%, respectively) deriving from ARTS I. Whether DES reduce the occurrence of death or MI below the frequency seen with bare-metal stents is still unknown, as also with nonculprit lesion severity.44,35 Whenever revascularization is needed, delay major vascular surgery to allow stent re-endothelization (after PCI) or patient recovery (after CABG) is largely preferred because of its much greater acceptability by the patient and reduced hospital stay. Although current data indicate that PCI entails higher risks of subsequent interventions due to restenosis, the use of newer DES, which are extremely promising in reducing such complications, will likely further push preferences in this direction.

We maintain that clinical features should influence the choice of a complete or an incomplete revascularization strategy in selected patient categories. Diabetics benefit from a more complete revascularization, better performed, as of now, with CABG. In patients with left ventricular dysfunction, revascularization of all viable segments should always be at least functionally complete among patients with ischaemic heart disease. On the basis of the available evidence, revascularization with either CABG or PCI has similar benefits in terms of survival, but should always be at least functionally complete among stable non-diabetic patients with multi-vessel coronary artery disease and good left ventricular function. Here PCI is largely preferred because of its much greater acceptability by the patient and reduced hospital stay. Although current data indicate that PCI entails higher risks of subsequent interventions due to restenosis, the use of newer DES, which are extremely promising in reducing such complications, will likely further push preferences in this direction.

Conclusions
The extent of myocardial revascularization, accomplished by either CABG or PCI, is a major determinant of survival among patients with ischaemic heart disease. On the basis of the available evidence, revascularization with either CABG or PCI has similar benefits in terms of survival, but should always be at least functionally complete among stable non-diabetic patients with multi-vessel coronary artery disease and good left ventricular function. Here PCI is largely preferred because of its much greater acceptability by the patient and reduced hospital stay. Although current data indicate that PCI entails higher risks of subsequent interventions due to restenosis, the use of newer DES, which are extremely promising in reducing such complications, will likely further push preferences in this direction.

We maintain that clinical features should influence the choice of a complete or an incomplete revascularization strategy in selected patient categories. Diabetics benefit from a more complete revascularization, better performed, as of now, with CABG. In patients with left ventricular dysfunction, revascularization of all viable segments should also be accomplished in order to maximize benefit. Conversely, in subjects presenting with acute coronary syndromes, an incomplete revascularization with stent-PCI of the culprit lesion is extremely effective when performed in a timely fashion. In the elderly, or in patients with severe co-morbidities, every effort should be taken to reduce acute adverse events, and very often the additional perioperative risk entailed by attempts at complete revascularization appears to be unwarranted.

Table 3 Selection of the optimal revascularization strategies according to patient’s risk profile

<table>
<thead>
<tr>
<th>Features</th>
<th>Recommended revascularization strategy</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>ACS</td>
<td>Incomplete</td>
<td>NSTEMI: Provisional stent-PCI of culprit lesion proven effective</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Complete, preferably with CABG</td>
<td>Accelerated disease progression occurs in the vessel treated with PCI</td>
</tr>
<tr>
<td>Elderly</td>
<td>Complete when life expectancy &gt; 10 years</td>
<td>Off-pump CABG reduces peri-operative stroke</td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
<td>Functionally adequate</td>
<td>Accurate pre-operative functional evaluation to identify all viable segments</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>Incomplete</td>
<td>Consider preoperative hemodialysis</td>
</tr>
<tr>
<td>Candidates to major vascular surgery</td>
<td>Functionally adequate</td>
<td>Revascularization possibly not beneficial</td>
</tr>
<tr>
<td>Low-risk</td>
<td>At least functionally adequate</td>
<td>PCI preferred when technically feasible</td>
</tr>
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Please refer to Table 1 for definitions of revascularization strategies. NSTEMI, non-ST elevation myocardial infarction; ACS, acute coronary syndromes; STEMI, ST elevation myocardial infarction.

References refer to primary sources for the recommendation.
References


