Benefit of revascularization for stable ischaemic heart disease: the jury is still out

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Received 28 June 2012; revised 6 December 2012; accepted 4 January 2013; online publish-ahead-of-print 29 January 2013

Introduction

Patients with stable ischaemic heart disease (SIHD) and moderate to severe ischaemia are at increased risk of death and myocardial infarction (MI) when compared with those with no or mild ischaemia.¹,² Relatively old studies have shown that revascularization using coronary artery bypass grafting (CABG) improves survival in patients with high-risk anatomical features (such as left main coronary disease or triple vessel disease) compared with medical management.³ – ⁵ Since then, percutaneous coronary intervention (PCI) has progressively replaced CABG as the dominant method of revascularization for SIHD. While there have been important improvements in both percutaneous and surgical revascularization techniques, there has been simultaneous progress in medical therapy and to a certain extent, all comparisons of treatments are time-sensitive and plagued by the continuous technical advances which tend to render obsolete previous trial results. The ACIP study, a pilot randomized trial in the older medical therapy era, had suggested benefit of revascularization (using balloon angioplasty or CABG) over optimal medical therapy (OMT) in patients with SIHD.⁶ Furthermore, data from large retrospective cohorts have consistently shown that revascularization was associated with a lower risk of cardiac death in patients with >10% ischaemic myocardium as assessed by scintigraphy.⁷ – ⁹ Finally, a recent meta-analysis of randomized trials also concluded that PCI and CABG were associated with improved survival.¹⁰ Nevertheless, modern large randomized trials comparing PCI added to OMT vs. OMT alone for SIHD, such as COURAGE and BARI 2D, have found that PCI and OMT resulted in comparable clinical outcomes in terms of death or MI.¹¹,¹² Therefore, given the current evidence, one interpretation of COURAGE is that stable patients in whom coronary artery disease extent is known can be treated first with OMT, postponing a decision of revascularization to the time point when symptoms become refractory to OMT, which in the COURAGE trial resulted in crossover to revascularization in approximately one-third of the initial population at 5 years. This strategy avoids the need, risks, and costs of revascularization in the majority of patients. The discrepancy between results from older trials and observational studies on the one hand, and the more recent randomized COURAGE and BARI 2D on the other, has generated a heated debate in the cardiology community.¹³,¹⁴ We will review hereby some of the salient points regarding this issue.

Medical therapy has improved

The applicability to current practice of results from randomized studies performed 30 years ago is currently uncertain. Indeed, during this period, modern drug therapies (such as statins, angiotensin-converting enzyme inhibitors and antiplatelet therapy) in association with risk factor control and lifestyle modifications, which were either inexistent or minimally used at the time of these studies, have emerged and been shown to markedly improve outcomes of patients with coronary heart disease, with an expected risk reduction of up to 50%.¹⁵ – ²¹ Therefore, proving any benefit of revascularization apart from improved symptom control is more challenging than in the past.

Revascularization can only demonstrate benefit if patients are above a certain risk threshold

In the COURAGE trial, patients with ischaemia (demonstrated either by resting ECG changes or abnormal exercise or pharmacologic stress tests) underwent coronary angiography, and were then randomized to PCI in addition to OMT or OMT alone.¹¹ While such a design ensures that only patients with proven coronary artery disease were included, it also potentially raises the concern of selective non-enrolment of those with the most severe and treatable lesions, who were likely to benefit from PCI.
and who may have been preferably triaged to pre-emptive revascularization.

The BARI 2D trial included only patients with type 2 diabetes, a group with higher event rates.\(^\text{12}\) Patients were also enrolled after coronary angiography, and randomization to OMT or revascularization was stratified to PCI or CABG on the basis of coronary anatomy. Consequently, patients selected for the PCI stratum also appeared to be at low risk, as illustrated by the lower proportion of proximal left anterior descending coronary artery stenosis and triple vessel disease in comparison with the CABG stratum (10 vs. 19% and 20 vs. 52%, respectively). Therefore, the lack of benefit of PCI over OMT in terms of hard outcomes may also be related to some degree of selection in the PCI stratum of lower risk patients less likely to benefit from PCI.

One important explanation for the inability of revascularization to improve prognosis in low-risk patients is that the hypothetical benefit of the revascularization procedure over OMT alone is counteracted by the risk of harm induced by the revascularization procedure (such as peri-procedural MI, stroke, or stent thrombosis). Hence, it is possible that for revascularization to be superior to OMT in terms of mortality and MI, patients have to be above a certain risk threshold, related mainly to extent of ischaemia, coronary anatomy, and possibly clinical characteristics (Figure 1). Moreover, whenever event rates are low during follow-up, it becomes more difficult to improve hard outcomes. For example, in the COURAGE trial, the composite 4.6-year event rate for death, MI and stroke was 20.0% in the PCI group and 19.6% in the OMT group.\(^\text{11}\) Similarly, in the PCI stratum of the BARI 2D trial, the 5-year incidence of these events were 23.0 and 21.1% for PCI and OMT, respectively.\(^\text{12}\) However, in the CABG stratum where patients had a higher risk profile, the major adverse cardiovascular events occurred in 22.4% of patients who underwent CABG and 30.5% in patients treated with medical therapy. Furthermore, given the event reduction only in the CABG stratum in the BARI 2D trial and the benefit of CABG over PCI in the recent FREEDOM trial, it may be considered that not all revascularization techniques achieve the same results, and this may be particularly true for diabetic patients.\(^\text{22}\) Nevertheless, comparisons of PCI and CABG should take into account several limitations. Indeed, patients enrolled in the CABG stratum were clearly at higher risk in comparison to the PCI stratum in BARI 2D, and therefore the potential benefit from revascularization was higher.\(^\text{12}\) Moreover, in the FREEDOM trial, the external validity of the results is somewhat limited by the highly selective nature of inclusion criteria, since patients had to be amenable to both revascularization techniques to be eligible for enrolment, thereby resulting in less than 10% of screened patients ultimately being enrolled.\(^\text{22}\)

### Importance of the presence and extent of ischaemia

Large retrospective studies have found that revascularization was associated with a lower risk of events in patients with >10% ischaemic myocardium.\(^\text{7–9}\) In COURAGE, there was a low proportion of patients (≈30%) with more than 10% of the myocardium demonstrating ischaemia on perfusion imaging, most likely limiting the power of the study to detect significant differences between both treatment modalities.\(^\text{11,23}\) In the nuclear substudy from the COURAGE trial, extensive myocardial ischaemia was associated with adverse prognosis, and outcomes were improved in patients with proven ischaemia reduction by nuclear perfusion scans performed at baseline and 6–18 months (for both groups combined), with PCI patients experiencing ischaemia reduction more frequently.\(^\text{24}\) The findings from this substudy, which are often interpreted as demonstrating clinical benefit from PCI, are somewhat limited by the results from a subsequent analysis, which

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**Figure 1** Hypothetical representation of the outcomes of revascularization and optimal medical therapy according to patient risk. While low-risk patients have better outcomes with optimal medical therapy (OMT), those with a risk above a certain threshold may benefit more from percutaneous coronary intervention in terms of mortality and subsequent myocardial infarction.
evaluated outcomes according to treatment group for patients with at least moderate ischaemia. Ultimately, the authors concluded that the extent of ischaemia did not predict adverse events and did not alter treatment effectiveness, thereby suggesting uncertainty as to whether the extent and severity of ischaemia impact on therapeutic effectiveness. It should be noted however that both of these post-hoc analyses were largely underpowered to detect any significant difference between both treatment modalities.

**Proper selection of revascularization candidates is essential**

The hypothesis that a certain risk threshold has to be present for revascularization to be of potential benefit is also supported by the results of FAME. In that trial, patients with a stenosis >50% in at least two of the three major epicardial vessels were randomly assigned either to revascularization by PCI (therefore based solely on angiography) or to a strategy of PCI for lesions with a fractional flow reserve (FFR) ≤0.8 and deferral of PCI for lesions with an FFR >0.8. The latter strategy of more restrictive intervention guided by FFR resulted in a lower rate of death or MI after a 2-year follow-up. Therefore, the outcome of patients treated by PCI only for ischaemia-generating lesions (for which PCI-related adverse events will be outbalanced by the benefit) and for whom PCI was deferred for non-ischaemic lesions (presumably at low- or no-risk, for which PCI-related benefit would likely be outbalanced by the potential adverse events) was superior to the outcome of patients treated by PCI for all angiographically significant lesions regardless of the potential risk (with an overall higher proportion of PCI-related adverse events due to revascularization of lesions at low- or no-risk). Because angiography is notorious for being imprecise in assessing the ischaemic potential of a stenosis, one can raise the hypothesis that in patients treated with PCI for stenoses identified by angiography, genuine clinical benefit from treating ischaemia-generating stenoses is blurred by side-effects resulting from ‘treatment’ of ‘innocent’ non-ischaemia generating stenoses. This hypothesis is supported by the results from other FFR-guided studies, and such a limitation would potentially apply to all previous studies in which revascularization was primarily based on angiographic guidance. Furthermore, this phenomenon is less likely to be apparent after CABG because patients who undergo CABG have more extensive coronary artery disease, and higher likelihood of having a genuine extensive ischaemic burden.

While it is difficult to compare FAME to COURAGE and BARI 2D due to the absence of an OMT arm in the former, FAME does suggest that some patients benefit from PCI. More recently, the FAME 2 trial, which compared PCI with OMT for coronary disease proven haemodynamically significant by FFR, showed that the primary endpoint of death, MI and urgent revascularization was significantly reduced among patients treated with PCI. (Figure 2) This benefit was driven by a marked reduction in the need for urgent revascularization among patients treated with PCI, which led to the premature termination of the trial. These

![Figure 2](image-url) Concept and results of the FAME 2 trial. FFR, fractional flow reserve; PCI, percutaneous coronary intervention; OMT, optimal medical therapy; MI, myocardial infarction; UA, unstable angina.
trial results suggest that improved lesion and patient selection using FFR instead of angiography result in benefit of PCI compared to OMT alone. Importantly, although the trial was somewhat underpowered for demonstrating a difference in hard outcomes, approximately half of the urgent revascularization procedures were mandated by MI or unstable angina with evidence of ischaemia on ECG. Nevertheless, urgent revascularization as a component of the composite outcome is difficult to interpret in an open-label randomized trial testing the value of revascularization, as the hazard of a new revascularization is likely to differ in a patient recently revascularized in comparison with a patient known to have had a haemodynamically significant coronary stenosis and not to have been revascularized. Critics of the trial have also surmised that revascularization was ultimately performed with a rate of 103% in the PCI + OMT arm and 20% in the OMT arm since randomization, with no significant difference in terms of death or MI. Therefore, FAME 2 has advanced our knowledge, but has not definitively settled the issue of the role of revascularization in improving the hard clinical outcomes of death and MI in SIHD.

There is irrefutable evidence proving the benefit of revascularization in patients with coronary artery disease in high-risk settings such as ST elevation MI or high-risk non-ST acute coronary syndrome, where ischaemia is obvious and the culprit lesion almost always clearly identified. We speculate that patients with SIHD may also benefit from revascularization when there is proved extensive ischaemia and only lesions causing ischaemia are treated, but this remains to be proved, particularly as the pathobiology of acute coronary syndromes (in which rupture of mildly stenotic plaques is dominant) may differ from that of SIHD in which severely stenotic lesions play a dominant role.

Current ESC guidelines

The joint European Society of Cardiology and European Association for Cardiothoracic Surgery revascularization guidelines currently recommend revascularization with a class I indication and B level of evidence in patients with proven ischaemia >10% of the left ventricle, on the basis of the ACIP study, the COURAGE nuclear substudy and observational studies. Also, this recommendation is based on the strong evidence that revascularization of non-ischaemic lesions is inappropriate. Thus, although limited, available evidence supports the benefit of revascularization for SIHD, but stems from observational or underpowered studies, while more robust randomized trials have failed to demonstrate benefit in terms of reduction of death or MI of an invasive approach over medical therapy alone (which may be greatest in high-risk patients), possibly because enrolment was skewed towards selection of low-risk patients and evidence of myocardial ischaemia was lacking. There is uncertainty on which proportion of SIHD patients would qualify as ‘not low risk’ and possibly derive potential benefit from revascularization, but in studies linking the benefit of revascularization to the extent of myocardial ischaemia, the proportion of the entire patient population with ischaemia in >10% of the myocardium was clearly a minority, ranging from 12 to 32%.7,24

The ISCHEMIA trial: testing an invasive strategy rather than revascularization

In the presence of clinical equipoise, further evidence is urgently needed to define the proper role of revascularization in SIHD. The ISCHEMIA trial (ClinicalTrials.gov number NCT01471522) will prospectively randomize 8000 patients in ~400 sites worldwide to an invasive strategy in addition to OMT vs. a conservative strategy of OMT and cardiac catheterization and revascularization reserved for refractory angina or clinical events in patients with SIHD and objective moderate to severe ischaemia (>10% of myocardium). In contrast with the COURAGE and BARI 2D trials, randomization of patients will be performed before determination of coronary anatomy by angiography in an attempt to minimize any potential selection bias that would exclude higher-risk patients. So far, the only trial testing the value of revascularization which had randomized patients prior to performance of coronary angiography was the TIME trial.37 However, this resulted in enrolment of some patients with either too little angiographic disease to warrant revascularization or, conversely, of patients with too extensive disease to be amenable to revascularization. These concerns will be, in a large part, mitigated in the ISCHEMIA trial given the performance of coronary CT angiography prior to coronary angiography. This is designed to exclude patients with left main disease but also without obstructive CAD and therefore minimize the dilutional impact of randomizing patients to invasive treatment who are not candidates for revascularization. Furthermore, while there may be concern that treating physicians may be reluctant to randomize patients to an initial non-invasive strategy, a recent international survey found that up to 80% of referring cardiologists would be willing to enrol these patients in this type of trial.38 Therefore, the ISCHEMIA trial should provide robust evidence regarding the optimal management of patients with SIHD and the role of an invasive strategy in the modern era.

Acknowledgements

The authors gratefully thank Drs Judith Hochman and David Maron for their input and comments.

Conflict of interest: none declared.

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6. Davies R, Goldberg A, Forman S, Pepine C, Knatterud G, Geller N, Sopko G, Pratt C, Dearfield J, Conti CR. Asymptomatic Cardiac Ischemia Pilot (ACIP) trial.38 Therefore, the ISCHEMIA trial should provide robust evidence regarding the hard clinical outcomes of death and MI in SIHD.36 Also, this recommendation is based on the strong evidence that revascularization of non-ischaemic lesions is inappropriate. Thus, although limited, available evidence supports the benefit of revascularization for SIHD, but stems from observational or underpowered studies, while more robust randomized trials have failed to demonstrate benefit in terms of reduction of death or MI of an invasive approach over medical therapy alone (which may be greatest in high-risk patients), possibly because enrolment was skewed towards selection of low-risk patients and evidence of myocardial ischaemia was lacking. There is uncertainty on which proportion of SIHD patients would qualify as ‘not low risk’ and possibly derive potential benefit from revascularization, but in studies linking the benefit of revascularization to the extent of myocardial ischaemia, the proportion of the entire patient population with ischaemia in >10% of the myocardium was clearly a minority, ranging from 12 to 32%.7,24

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