Should extensive myocardial ischaemia prompt revascularization to improve outcomes in chronic coronary artery disease?

Raymond J. Gibbons* and Todd D. Miller

Division of Cardiovascular Diseases, Mayo Clinic, 200 1st Street SW, Rochester, MN, USA

Received 13 April 2015; revised 18 May 2015; accepted 1 June 2015; online publish-ahead-of-print 16 June 2015

Introduction

A 44-year-old man presents with a 1-month history of substernal chest pressure. His only risk factor is hypercholesterolaemia. His physical exam, electrocardiogram (ECG) and chest X-ray are normal. The patient undergoes an exercise treadmill test. He exercises for 6.5 min on a Bruce protocol to a peak heart rate of 150 beats/min and a blood pressure of 212/112 mmHg. He stops due to angina. His exercise ECG shows 1 mm of ST segment elevation in lead V1. The patient is offered either exercise single photon emission computed tomography (SPECT) or coronary angiography. He chooses exercise SPECT. This demonstrates a large area of apical, anterior, and septal ischaemia. Subsequent coronary angiography demonstrates a 95% stenosis in the middle of the left anterior descending coronary artery and insignificant disease elsewhere. Does the patient merit early revascularization to improve his prognosis?

The existing clinical dogma is that stress-induced myocardial ischaemia is important in the management of chronic coronary artery disease (CAD) because it can identify patients with a worse prognosis who are more likely to benefit from revascularization. R.J.G. has presented this case vignette to multiple audiences of cardiologists and cardiovascular surgeons in Europe and the USA over the last 5 years. The audiences have overwhelmingly favoured treatment with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). The potential impact of coronary revascularization on patient outcome was assessed in three large trials performed in the 1970s that randomized patients to CABG or medical therapy. Overall, results were inconsistent. In the USA, both the Veterans Administration (VA) Study and the Coronary Artery Surgery Study (CASS) reported no significant difference over 5 years between surgery and medical therapy. In contrast, the European Cooperative Surgery Study (ECSS) reported a highly significant benefit with CABG at 5 years (P < 0.0001) that was attenuated and only modestly significant at 12 years (P = 0.02).

The patients enrolled in these early randomized trials were substantially different from contemporary practice. They were overwhelmingly middle-aged men with stable angina. Medical management consisted primarily of β blockers in almost half of patients at baseline. The published advice to investigators for the CASS trial was devoted solely to how to properly use sublingual nitroglycerin. Compared with contemporary medical therapy, statins, and ACE inhibitors were not available, and there were limited options for control of hypertension.

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

* Corresponding author. Tel: +1 507 284 2541, Fax: +1 507 266 9142, Email: gibbons.raymond@mayo.edu

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2015. For permissions please email: journals.permissions@oup.com.
The use of risk to select patients for revascularization was supported by a systematic overview of individual patient data from the seven available randomized trials comparing CABG with initial medical therapy. This overview showed a significant reduction in mortality with CABG at 5 years (odds ratio 0.61; P = 0.0001) that was attenuated but still significant at 10 years (odds ratio 0.83; P = 0.03). At 1 year after randomization, only 66% of medical therapy patients were taking β blockers and even fewer (19%) were taking anti-platelet agents. Although the relative risk reduction in most subgroups was similar, the benefit of surgery was greatest in patients at highest clinical and angiographic risk. An abnormal exercise test appeared to identify patients who were more likely to benefit from surgery (odds ratio 0.52; P < 0.001), but the formal test for treatment interaction was not significant (P = 0.37).

Several single-centre studies applied exercise radionuclide angiography to examine the potential role of stress-induced ischaemia to identify higher risk patients within anatomic subsets. Bonow et al. studied patients with three-vessel disease and normal resting left ventricular ejection fraction (LVEF). Patients with the ischaemic triad of decrease in LVEF, ST segment changes, and low exercise capacity had significantly worse survival (Figure 2). A Mayo Clinic study reported similar results in patients with one- or two-vessel disease and abnormal resting LVEF. These studies suggested that among patients with higher risk anatomy, stress-induced ischaemia might identify those who could benefit from revascularization. However, in patients with more favourable anatomical features consisting of one- or two-vessel CAD and normal LVEF, the ischaemic triad did not identify those with worse outcome.

The use of overall risk to identify patients who would benefit from coronary revascularization was embedded in the clinical practice guidelines from that era, which included a Class I recommendation for ‘PTCA or CABG for one-vessel or two-vessel disease without proximal LAD disease but viable myocardium and high risk’. Parameters that were considered high risk (Table 3) included many descriptions of stress-induced ischaemia. At the end of the 20th century, the value of stress-induced ischaemia to identify higher risk patients who were more likely to benefit from coronary revascularization was generally accepted.

## New evidence in the 21st century challenging the dogma

### Randomized trials

Recent randomized trials examining treatment strategies in patients with chronic CAD have challenged the dogma. The Clinical Outcomes Using Revascularization (COURAGE) trial randomized patients with Class I–III angina, many with evidence of ischaemia, to PCI plus intensive medical therapy vs. intensive medical therapy alone. There was no difference in subsequent hard events. The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) trial enrolled diabetic patients who were asymptomatic...
or had mild angina and objective evidence of ischaemia to revascularization with PCI or CABG vs. medical therapy alone, and reported no advantage with revascularization. The Surgical Treatment for Ischemic Heart Failure (STICH) study randomized patients with CAD and LVEF ≤ 35% to medical therapy plus CABG or medical therapy alone. Similar to COURAGE and BARI 2D, there was no difference in the primary endpoint of overall mortality between treatment arms. The surprisingly negative results from these three large trials raise concerns about how to best identify patients who benefit from coronary revascularization.

**Imaging substudies**

Many but not all patients in these three trials underwent stress imaging. The need to identify patients who are most likely to benefit from revascularization has focused attention on the imaging substudies from these trials (Table 4). Although all three trials were performed in a randomized manner, the imaging substudies were not...
randomized. There were two separate nuclear cardiology substudies from COURAGE with conflicting results. The most widely quoted study was based on objective core laboratory quantitative measurements from 314 patients who had stress SPECT at baseline (pre-treatment) and again at 6–18 months. Stress-induced ischaemic myocardium was reduced by >5% in a greater proportion of patients treated with PCI than with medical therapy alone (33 vs. 19%, $P = 0.0004$). Additional analyses of outcome beginning at the time of the follow-up scan reported that patients who had >5% reduction in ischaemia (regardless of randomization) had lower event rates. However, these post-randomization analyses were no longer significant after adjustment for differences in baseline variables. The authors concluded that ‘our outcome comparisons were limited to a small subset of enrolled patients and should be viewed for purposes of hypothesis generation’. Unfortunately, these findings have been misinterpreted as showing a survival advantage for PCI, even though the prognostic analysis that began at the time of the follow-up scan combined patients from both randomized groups. A subsequent second substudy from COURAGE examined the relationship between ischaemia on the baseline SPECT study (interpreted at the individual sites) and outcome in a larger group of 1381 patients. The extent of ischaemia was not associated with clinical events. In 468 patients with moderate-to-severe ischaemia, there was no difference in death or MI according to randomized treatment ($P = 0.72$).

The nuclear cardiology substudy from BARI-2D tested the association between outcome and the findings on a 1-year follow-up SPECT scan in a much larger group of 1505 patients. Patients treated with revascularization had less ischaemia on the 1-year scan. Abnormal myocardium predicted subsequent death and myocardial infarction but this association was due to scarred myocardium (adjusted odds ratio 1.16; $P = 0.002$) rather than ischaemic myocardium (adjusted odds ratio 1.04; $P = 0.468$). This much larger nuclear substudy was unable to replicate the results of the first COURAGE nuclear substudy.

A STICH substudy reported on the relationship between stress-induced ischaemia and outcome in 399 patients. There was no relationship between ischaemia and subsequent CV mortality (hazard ratio 1.10; $P = 0.632$). However, this study had multiple limitations. It had even less power than the main STICH study, did not account for 22% of patients who were treated with ICDs, combined both stress SPECT and stress echo to identify ischaemia, and included very few SPECT patients with moderate-to-severe ischaemia. Thus, these four imaging substudies from contemporary trials are inconsistent with respect to the prognostic value of stress-induced ischaemia and fail to support the existing dogma that the magnitude of ischaemia identifies patients who will benefit from revascularization.

### Observational studies

Contemporary studies on the exercise ECG also raise doubts about the importance of ST segment changes and symptomatic angina during exercise testing. Lauer et al. developed a detailed mortality prediction rule that included both clinical and exercise ECG parameters on 33,268 patients from the Cleveland Clinic, and validated it on 58,211 HMO patients from Colorado. Their model had better discrimination and calibration than the Duke treadmill score. Exercise capacity adjusted for age was significantly associated with death ($P < 0.001$), but ST segment depression ($P = 0.23$) and angina with exercise ($P = 0.25$) were not.

The current best evidence supporting the use of stress-induced ischaemia to identify patients with chronic CAD who are most likely to benefit from revascularization is based on a large single-centre observational study of 10,627 patients with no prior CAD who underwent stress SPECT. The authors computed the log hazard ratio for cardiovascular mortality for different values of % ischaemic myocardium for patients treated with revascularization and patients treated with medical therapy. The log hazard ratio for mortality was greater in patients treated with revascularization compared with medical therapy when the amount of ischaemic myocardium was...
small. In contrast, this hazard ratio was greater in patients treated with medical therapy compared with revascularization when there was a large amount of ischaemic myocardium. The ‘cross-over point’ occurred at $\sim 10\% - 12.5\%$ of ischaemic myocardium. This 10% estimate is widely quoted.

In a subsequent analysis, the same investigators$^{26}$ studied a broader population of 13,969 patients and included patients with prior CAD, longer follow-up, and total mortality as an endpoint. For the overall population, the % myocardium ischaemic was associated with mortality but specific ischaemic thresholds were not provided. Several patient subsets were analysed. For 8791 patients without prior CAD, the hazard ratio for mortality in patients treated with revascularization was still $>1$ (indicating no survival benefit with PCI/CABG) in patients with 10% ischaemic myocardium and was only $<1$ (indicating survival benefit with PCI/CABG) if the ischaemic myocardium was 15% (Figure 3). Similar findings were noted for 11,880 patients with fixed myocardial perfusion defects $\leq 10\%$ of the left ventricle. The percent ischaemic myocardium was of only modest significance ($P = 0.089$) in 1675 patients with fixed defects $\geq 10\%$ myocardium.

These analyses from Cedars-Sinai are based on well-validated methodology using the summed stress score and summed difference score from stress and rest images graded as 0–4 in each of 20 segments. These summed scores therefore reflect both the extent and severity of the perfusion abnormality. The maximum summed score is therefore 80 ($4 \times 20$), and 10% ischaemia is defined as 10% of the maximum summed difference score of 80, or a summed difference score of 8. This requires 8 of 20 LV segments to change by one grade or at least four segments to change by two grades, which is much more ischaemia than is generally appreciated. Most laboratories currently utilize a 17-segment model, where 10% ischaemia is defined as a summed difference score of 7.

**Clinical practice guidelines and appropriate use criteria**

The evolving evidence with respect to the interpretation and clinical application of stress-induced ischaemia has led to inconsistencies within and across clinical practice guidelines (Table 5). In the ACCF/AHA Stable Ischemic Heart Disease Guideline,$^{27}$ there is no longer a Class I recommendation to improve survival with revascularization on the basis of extensive ischaemia. Coronary artery bypass grafting is assigned a Class IIa recommendation for two-vessel disease without proximal LAD disease with extensive ischaemia and a Class IIb recommendation without extensive ischaemia. Percutaneous coronary intervention is a Class IIb recommendation in such patients regardless of the presence or absence of ischaemia. In contrast, the European Guidelines on Stable Angina$^{28}$ include a Class I indication for revascularization to improve prognosis in the presence of $>10\%$ ischaemia. The references listed for this recommendation are the first study by Hachamovitch, and the first hypothesis-generating COURAGE substudy.

Although the ACCF/AHA guideline includes a figure from the study by Lauer et al. for the interpretation of the exercise ECG that does not assign points for test angina or ST segment depression with exercise, the tables in the guideline that categorize intermediate and high risk include exercise-induced ST segment depression and symptoms with exercise. In the text, the European guideline

---

**Figure 3.** Hazard ratio for mortality for patients with stable coronary artery disease treated with early revascularization compared with those treated with medical therapy at Cedar Sinai Medical Center, shown as a function of the percent ischaemic myocardium on myocardial perfusion imaging. In the left panel (blue lines) are the hazard ratios and 95% confidence limits for 8791 patients with no prior coronary artery disease. In the right panel (red lines) are the hazard ratios for the 11,880 patients with fixed perfusion defects $\leq 10\%$ of the left ventricle. The circles highlight the hazard ratios for 10 and 15% ischaemic myocardium. The hazard ratio for mortality in patients treated with early revascularization was $>1$ (indicating no survival benefit with revascularization) in patients with 10% ischaemic myocardium in both groups. The hazard ratio was $<1$ (indicating survival benefit with revascularization) if the ischaemic myocardium was 15% (from Ref. 26, with permission).
incorrectly defines 10% ischaemia by myocardial perfusion imaging as ‘≥2 of the 17 segments’, and cites the paper by Hachamovitch. This definition considers the extent of ischaemia, but not its severity. Two abnormal segments with mild-to-moderate ischaemia would likely represent a summed difference score of only 2–4, far less than the summed difference score of 7 (using a 17-segment model) required for 10% ischaemia defined by Hachamovitch.

Both the ACCF-AHA and ESC Clinical Practice Guidelines recommend revascularization on the basis of coronary anatomy as well as the extent of ischaemia, potentially adding to clinical confusion when these approaches do not agree. For example, a patient with severe ischaemia may undergo angiography and have two-vessel disease without LAD disease. The presence of severe ischaemia would appear to justify revascularization despite the absence of high-risk anatomy.

Although the designation of ‘appropriate’ in the ACCF Appropriate Use Criteria (AUC) does not convey the same imperative (‘should do’ or ‘is usually indicated’) as a Class I guideline recommendation, the AUC do classify revascularization as appropriate in patients with a high-risk stress test, mild angina and one-, two-, or three-vessel CAD except for one-vessel CAD with a chronic total occlusion.29 In many other clinical scenarios, high-risk stress tests shift the rating of appropriateness to a higher level.

It seems plausible that optimal medical therapy in contemporary trials, which is far more intensive than the therapy in the early trials of the 1970s, may have blunted the prognostic impact of exercise-induced ischaemia. The use of aspirin, statins, blood pressure control, and ACE inhibitors, which all have proven prognostic benefit, is now far more widespread. However, this hypothesis needs to be tested.

The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial is an NHLBI-sponsored trial designed to test this hypothesis (https://www.ischemiatrial.org). Patients with moderate-to-severe stress-induced ischaemia on the basis of myocardial perfusion imaging, stress echocardiography, or stress magnetic resonance imaging undergo pre-randomization CT coronary angiography to exclude patients with left main CAD. Patients are then randomized to optimal medical therapy or optimal medical therapy plus coronary revascularization.

Conclusions

Until ISCHEMIA provides definitive evidence on the value of stress-induced ischaemia to select patients for revascularization, current clinical management is based primarily on judgement rather than evidence. In patients with severe ischaemia, matching coronary stenoses, and an acceptable risk of revascularization, who do not wish to participate in ISCHEMIA, we favour a shared decision-making approach, as current evidence supports clinical equipoise.


References

Extensive myocardial ischaemia prompt revascularization


