What is the Real Message of the ISCHEMIA Trial from a Clinician's Perspective?

Islam Y Elgendy[1] and Carl J Pepine[2]

1. Division of Cardiology, Weill Cornell Medicine-Qatar, Doha, Qatar;
2. Division of Cardiovascular Medicine, University of Florida, Gainesville, FL, US

Disclosure: The authors have no conflicts of interest to declare.
Received: 28 May 2020 **Accepted:** 30 June 2020 **Citation:** *European Cardiology Review* 2020;15:e63. **DOI:** https://doi.org/10.15420/ecr.2020.27
Correspondence: Carl J Pepine, Division of Cardiovascular Medicine, University of Florida, 1329 SW 16th St, PO Box 100288, Gainesville, FL 32610-0288, US. E: carl.pepine@medicine.ufl.edu

Management goals in patients with stable coronary disease or chronic coronary syndrome include controlling symptoms and reducing the risk of future cardiovascular events.[1,2] Randomised trials conducted in the bare metal stents era have indicated that an invasive management strategy, which includes coronary angiography, followed by percutaneous or surgical revascularisation, if indicated, was not superior to optimal medical therapy (OMT) alone in reducing the risk of cardiovascular death or MI.[3] However, there have been many advances in revascularisation therapies, as well as medical management, in the past decade. In addition, patients with any degree of ischaemia on functional assessment were eligible for enrolment, which might have led to underenrolment of patients with moderate-to-severe ischaemia who might derive the most benefit from revascularisation.[4] Moreover, as coronary angiography was performed prior to randomisation, patients with coronary anatomy that might be associated with high risk for adverse outcomes were likely not randomised, but sent directly to revascularisation. These concerns led to continuing controversy regarding the optimal management strategy for patients with stable coronary disease.

In this context, the International Study of Comparative Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial sought to determine whether an invasive strategy with coronary angiography and contemporary coronary revascularisation, if indicated, would be superior to OMT alone in patients with moderate-to-severe ischaemia on stress imaging, including echocardiogram, nuclear scan, cardiac magnetic resonance or exercise testing (an option added late in the trial to improve recruitment).[5] Most patients (73%) underwent CT coronary angiography (CTCA) analysed by the core lab to exclude those with left main obstruction or non-obstructive coronary disease. Key exclusions included unprotected left main obstruction >50%, advanced kidney disease (estimated glomerular filtration rate <30 ml/min/1.73m^2), New York Heart Association class III or IV heart failure, left ventricular dysfunction, angina refractory to medical therapy, acute coronary syndrome within 2 months and percutaneous coronary intervention or coronary artery bypass grafting within the past year.[5] The primary outcome was the first occurrence of cardiovascular death or resuscitated cardiac arrest, non-fatal MI or hospitalisation for either unstable angina or heart failure.[5] Secondary outcomes included cardiovascular death or MI and quality of life (QOL).[5,6] A parallel trial compared both strategies in patients with advanced kidney disease or those receiving dialysis.[7,8]

Between 2012 and 2018, 8,518 patients were screened; 3,339 of these were excluded. The main reasons for exclusion (and their frequencies) were mild ischaemia, non-obstructive coronary disease (~14%) on CTCA and unprotected left main disease (5.1%). Finally, 5,179 patients were randomised from 320 centres in 37 countries. Their median age was 64 years, 77% were men and 35% did not have any angina symptoms at baseline. In the invasive group, 96% of the patients underwent coronary angiography, whereas 26% of patients randomised to the conservative group crossed over to coronary angiography because of inadequate angina control or an ischaemic event. Loss of follow-up was remarkably low (~1%). During a median follow-up of 3.2 years, the rates of the primary outcome (12.3% versus 13.6%) and of cardiovascular death or MI (10.7% versus 12.1%) did not differ significantly between the randomised groups. All-cause mortality was low in both groups (5.6%).[5] The invasive group had greater improvement of QOL, but this benefit was observed mainly in those with angina at baseline.[6] In the parallel trial for patients with advanced kidney disease, an invasive strategy neither reduced cardiovascular mortality or MI, nor improved the QOL.[7,8]

The ISCHEMIA trial is the largest trial to date comparing an invasive strategy versus OMT in patients with stable coronary artery disease and moderate-to-severe ischaemia on functional testing. Key strengths included the following:

- A rigorous design requiring the presence of obstructive epicardial coronary arteries on CTCA, without left main obstruction, prior to enrolment, reviewed by an independent core lab. This is important, as prior trials randomised patients after the coronary anatomy was identified, so many patients believed to have a high-risk anatomy were likely not randomised.[3]
- The trial was not industry funded.
- Very few patients were lost to follow-up.
- A rigorous assessment of outcomes, including QOL measures.
- Control of cardiovascular risk factors, including systolic blood pressure and low-density lipoprotein levels, and adherence to medical therapy was high in both groups (~80% at the end of follow-up).

Despite these notable strengths, some areas warrant further mention. First, the trial was an 'open design'. Although outcomes were assessed by an independent committee masked to randomised group assignment, the lack of a sham control for the OMT strategy remains a limitation. Given the results of the Objective Randomised Blinded Investigation with Optimal Medical Therapy of Angioplasty in Stable Angina (ORBITA) trial, which found that revascularisation did not increase exercise time compared with the sham-controlled OMT, the absence of a sham-controlled OMT arm in the ISCHEMIA trial might have diminished any gradient between the OMT and revascularisation arms for angina.[9]

Second, slow recruitment may have reflected the practice pattern of some sites to limit enrolment of the more symptomatic patients, thus contributing to the low event rates observed and reducing the power of the study.

Third, the prevalence of significant left main stenosis was 5.1%, which is higher than 'all-comer' studies with chest pain (~1%), and could reflect selection bias towards the inclusion of only patients with moderate-to-severe ischaemia on non-invasive stress testing.[10]

Fourth, although CTCA was performed prior to randomisation to ensure that patients who only had obstructive epicardial coronary artery disease that did not involve the left main artery were enrolled, approximately 16% of patients in the invasive arm did not undergo revascularisation because they had only non-obstructive disease on invasive angiography.

Fifth, a considerable proportion of enrolled patients (35%) did not have any angina at baseline, thus they were unlikely to derive any symptom benefit from either revascularisation or OMT. However, angina relief was not a component of the primary end-point but rather a pre-specified secondary endpoint of the study.

Finally, women represented only 23% of enrollees. While this could be a result of excluding patients with non-obstructive coronary disease, it also suggests considerable bias against recruiting women in landmark trials. This is important because the US population is predominantly women >64 years, and that was the median age for the ISCHEMIA trial. That is, a large group of older women with coronary artery disease were not included. In an exploratory analysis of the ISCHEMIA trial, women were more likely to have more frequent angina independent of the extent of disease on CCTA or ischaemia.[11] It is unclear if this underenrolment of women was recognised and/or if attempts were made to better recruit women during the trial. Importantly, the interaction of sex on the outcomes has not been addressed. By inadequately enrolling women, an opportunity to better understand the sex differences in the efficacy of interventions was missed.[12]

What is the Real Message from the ISCHEMIA Trial?

The ISCHEMIA trial confirmed that younger patients (mostly men) with stable symptoms, normal ejection fraction, normal or slightly impaired renal function and evidence of moderate-to-severe ischaemia on stress testing could be risk stratified with CTCA to exclude significant unprotected left main disease, and then managed with OMT alone. Invasive coronary angiography could be reserved for those who have refractory angina despite medical therapy. The ISCHEMIA trial also suggested that, in this patient population, an upfront invasive strategy reduces angina frequency and improves QOL, especially in highly symptomatic patients. Interestingly, the Kaplan–Meier curves for cardiovascular mortality or MI were initially in favour of the OMT strategy because of higher rates of peri-procedural MI, but later the curves trended in favour of an invasive strategy driven by lower spontaneous MI. Shared decision-making between treating physicians and patients in light of these findings could help to better provide more personalised care to our patients. However, patients with advanced kidney disease or those receiving dialysis who have stable coronary disease could be best managed with a strategy of OMT alone. The ISCHEMIA trial findings stress the importance of adherence to medical therapy and risk factor control, irrespective of the management strategy.

Some frequently encountered groups of patients in clinical practice were excluded from the ISCHEMIA trial, thus the findings should not be extrapolated to them. These include patients with recent acute coronary syndrome, for whom randomised trials have shown benefits of a routine invasive strategy, as well as patients with reduced ejection fraction; although contemporary randomised data are scarce for such patients, observational data suggest revascularisation benefits.[13–15]

In the ISCHEMIA trial, there was no evidence of interaction of the degree of ischaemia on the outcomes.[5] This challenges the routine use of functional testing for assessing stable coronary disease patients, and suggests that an anatomical test, such as CTCA, could be performed to exclude obstructive epicardial coronary artery disease. However, this approach will result in missing the opportunity to evaluate for microvascular and vasospastic angina, which could be diagnosed with functional invasive testing.[16] These syndromes are prevalent (~40–50% of patients undergoing invasive angiography for angina), especially in women, and they result in poor QOL.[17,18] Importantly, evidence-based management approaches for these syndromes exist.

The CORonary MICrovascular Angina (CorMicA) trial showed that a stratified medical therapy approach based on the findings of invasive coronary functional assessment reduced angina and improved QOL in these patients.[16] Therefore, adopting a 'single-test' strategy to assess patients with stable coronary disease is premature. The ongoing Coronary Microvascular Function and CT Coronary Angiogram (CorCTCA) trial is investigating the merits of an initial CTCA approach, followed by invasive angiography, to guide therapies for patients with microvascular and vasospastic angina.[19]

Overall, the ISCHEMIA trial has clearly advanced our understanding of contemporary management options for patients with obstructive coronary artery disease, and should foster efforts to include the patient in management decisions. ■

1. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;41:407–77. https://doi.org/10.1093/eurheartj/ehz425; PMID: 31504439.
2. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease. *J Am Coll Cardiol* 2014;64:1929–49. https://doi.org/10.1016/j.jacc.2014.07.017; PMID: 25077860.
3. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;356:1503–16. https://doi.org/10.1056/NEJMoa070829; PMID: 17387127.
4. Hachamovitch R, Hayes SW, Friedman JD, et al. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003;107:2900–7. https://doi.org/10.1161/01.CIR.0000072790.23090.41; PMID: 12771008.

5. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med* 2020;382:1395–1407. https://doi.org/10.1056/NEJMoa1915922; PMID: 32227755.
6. Spertus JA, Jones PG, Maron DJ, et al. Health-status outcomes with invasive or conservative care in coronary disease. *N Engl J Med* 2020;382:1408–19. https://doi.org/10.1056/NEJMoa1916370; PMID: 32227753.
7. Bangalore S, Maron DJ, O'Brien SM, et al. Management of coronary disease in patients with advanced kidney disease. *N Engl J Med* 2020;382:1608–18. https://doi.org/10.1056/NEJMoa1915925; PMID: 32227756.
8. Spertus JA, Jones PG, Maron DJ, et al. Health status after invasive or conservative care in coronary and advanced kidney disease. *N Engl J Med* 2020;382:1619–28. https://doi.org/10.1056/NEJMoa1916374; PMID: 32227754.
9. Al-Lamee R, Thompson D, Dehbi HM, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet* 2018;391:31–40. https://doi.org/10.1016/S0140-6736(17)32714-9; PMID: 29103656.
10. Jang JJ, Bhapkar M, Coles A, et al. Predictive model for high-risk coronary artery disease. *Circ Cardiovasc Imaging* 2019;12:e007940. https://doi.org/10.1161/CIRCIMAGING.118.007940; PMID: 30712364.
11. Reynolds HR, Shaw LJ, Min JK, et al. Association of sex with severity of coronary artery disease, ischemia, and symptom burden in patients with moderate or severe ischemia: secondary analysis of the ISCHEMIA randomized clinical trial. *JAMA Cardiol* 2020;5:773–86. https://doi.org/10.1001/jamacardio.2020.0822; PMID: 32227128.
12. Elgendy IY, Van Spall HGC, Mamas MA. Cardiogenic shock in the setting of acute myocardial infarction: history repeating itself? *Circ Cardiovasc Interv* 2020;13:e009034. https://doi.org/10.1161/CIRCINTERVENTIONS.120.009034; PMID: 32151160.
13. Elgendy IY, Kumbhani DJ, Mahmoud AN, et al. Routine invasive versus selective invasive strategies for non-ST-elevation acute coronary syndromes: an updated meta-analysis of randomized trials. *Catheter Cardiovasc Interv* 2016;88:765–74. https://doi.org/10.1002/ccd.26679; PMID: 27515910.
14. Velazquez EJ, Lee KL, Deja MA, et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med* 2011;364:1607–16. https://doi.org/10.1056/NEJMoa1100356; PMID: 21463150.
15. Wolff G, Dimitroulis D, Andreotti F, et al. Survival benefits of invasive versus conservative strategies in heart failure in patients with reduced ejection fraction and coronary artery disease: a meta-analysis. *Circ Heart Fail* 2017;10:e003255. https://doi.org/10.1161/CIRCHEARTFAILURE.116.003255; PMID: 28087687.
16. Beltrame JF, Crea F, Kaski JC, et al. International standardization of diagnostic criteria for vasospastic angina. *Eur Heart J* 2017;38:2565–8. https://doi.org/10.1093/eurheartj/ehv351; PMID: 26245334.
17. Ford TJ, Stanley B, Good R, et al. Stratified medical therapy using invasive coronary function testing in angina: the CorMicA trial. *J Am Coll Cardiol* 2018;72:2841–55. https://doi.org/10.1016/j.jacc.2018.09.006; PMID: 30266608.
18. Shaw LJ, Merz CN, Pepine CJ, et al. The economic burden of angina in women with suspected ischemic heart disease: results from the National Institutes of Health–National Heart, Lung, and Blood Institute-sponsored women's ischemia syndrome evaluation. *Circulation* 2006;114:894–904. https://doi.org/10.1161/CIRCULATIONAHA.105.609990; PMID: 16923752.
19. Sidik NP, McEntegart M, Roditi G, et al. Rationale and design of the British Heart Foundation (BHF) Coronary Microvascular Function and CT Coronary Angiogram (CorCTCA) study. *Am Heart J* 2020;221:48–59. https://doi.org/10.1016/j.ahj.2019.11.015; PMID: 31911341.