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The controversies of ISCHEMIA

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Take Home Messages

- Recent evidence has challenged the historical concept of employing invasive coronary intervention strategies to manage stable coronary artery disease.
- The preliminary results of the major landmark ISCHEMIA trial suggest that invasive treatment appears no better than optimal medical therapy (OMT) for preventing cardiovascular events in patients with stable coronary artery disease not involving the left main stem (LMS).
- The ISCHEMIA trial results are yet to be published in a peer reviewed medical journal.
- OMT should form the mainstay of treatment for patients with stable coronary artery disease.
- Coronary intervention should be reserved for patients with angina despite OMT.
- The results raise the question as to what benefit is gained by undertaking coronary revascularization in patients with stable coronary disease, when significant LMS disease is excluded.

Introduction

The management of stable coronary artery disease (CAD) or ischemic heart disease (IHD) traditionally focused on identifying patients who may benefit from coronary intervention strategies to 'unblock' or 'bypass' diseased arteries. However recent evidence has challenged this approach.[1-7]

In 2007, the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial showed that percutaneous coronary intervention (PCI) in patients with stable CAD did not reduce the risk of death, myocardial infarction or other major cardiovascular (CV) events compared with optimal medical therapy (OMT).[3,4]

In 2009, the Bypass Angioplasty Revascularisation Investigation 2 Diabetes (BARI 2D) trial looked at an initial strategy of coronary revascularisation followed by OMT compared to initial OMT with the option of subsequent revascularisation. This study showed that there was no significant difference in the rates of death and major CV events between diabetic patients in both groups.[5]

However, in 2012, the Fractional flow reserve versus Angiography for Multivessel Evaluation 2 (FAME 2) trial showed that in patients with angiographic evidence of CAD, fractional flow reserve-guided PCI in addition to OMT was superior to OMT alone in the management of patients with stable angina.[6] Conversely, in patients without haemodynamically significant stenoses, the outcome was favoured by OMT.

In 2017, the Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA) trial used a sham control and reported that PCI did not increase exercise time or improve symptoms for people with stable coronary disease and at least one angiographically significant lesion.[7] However, all

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these previously mentioned trials did not include sufficient numbers of participants with significant ischemia, and only included participants in whom the coronary anatomy had been established prior to randomisation. Furthermore in all these trials, randomisation occurred after coronary angiography and therefore was subject to selection bias. Additionally, coronary artery bypass graft (CABG) surgery was not undertaken in COURAGE or FAME 2.

The ISCHEMIA Trial

The $100 million International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial sought to answer the question of whether an invasive approach offers significant improvement over OMT for patients with stable CAD.[8] The results of the long-awaited ISCHEMIA trial were presented at the annual American Heart Association meeting in Philadelphia, November 2019, but are yet to be published.[9] This National Heart, Lung, and Blood Institute sponsored study compared an initial invasive strategy with PCI or CABG plus OMT against a conservative treatment strategy of OMT alone in stable patients with moderate-to-severe ischemia on stress testing.

ISCHEMIA was an international, non-blinded, multicentre, randomised trial. In total, 8518 patients were screened of whom 3319 were deemed unsuitable due to either insufficient ischemia (n=1350), no obstructive CAD (n=1218) or unprotected left main stem disease (n=434). Following screening 5,179 patients (mean age 64 years) with stable IHD and moderate-to-severe ischemia were randomised to routine invasive therapy (n=2588) versus medical therapy (n=2591). In the routine invasive therapy group, patients underwent coronary angiography and PCI or CABG as appropriate. In the medical therapy groups, patients underwent coronary angiography only for failure of medical therapy.

The primary aim of the ISCHEMIA trial was to determine whether an initial invasive strategy of cardiac catheterisation followed by optimal revascularisation (if feasible) in addition to OMT, compared with an initial conservative strategy of OMT alone with catheterisation reserved for failure of OMT would reduce the primary composite endpoint (defined as CV death, non-fatal myocardial infarction, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure). The main inclusion and exclusion criteria are summarised in **Table 1**. The planned follow-up period was 3.5 years.

Table 1. Inclusion and exclusion criteria for the ISCHEMIA trial (adapted from [8])

Inclusion	Exclusion
Age >21 years	≥50% left main stenosis (from blinded computed tomography)
Evidence of moderate-to-severe ischemia on non-invasive stress imaging*	Advanced chronic kidney disease (estimated glomerular filtration rate <30 ml/min)
Subjects willing to give written informed consent	Recent myocardial infarction
Subjects willing to comply will all aspects of the protocol	Left ventricular ejection fraction <35%
	Unacceptable angina at baseline
	New York Heart Association class III-IV heart failure
	Prior PCI or CABG within the last year

* nuclear imaging ≥10% ischemia; echocardiography ≥3 segments of ischemia; cardiac magnetic resonance imaging ≥12% ischemia and/or ≥3 segments with ischemia; exercise treadmill test ≥1.5 mm ST depression in ≥2 leads or ≥2 mm ST depression in single lead at <7 metabolic equivalents of task with angina. CABG coronary artery bypass graft, PCI percutaneous coronary intervention.

Secondary aims were to determine whether an initial invasive strategy compared to a conservative strategy would improve:

- the composite of CV death or MI;
- angina symptoms and quality of life (assessed by the Seattle Angina Questionnaire);
- all-cause mortality;
- net clinical benefit (assessed by including stroke in the primary and secondary composite endpoints); and
- individual components of the composite endpoints.

A blinded coronary computed tomography angiogram (CCTA) was performed in most participants with an estimated glomerular filtration rate ≥60 mL/min/1.73m^2 to identify and exclude participants with either significant unprotected left main disease (≥50% stenosis) or those without obstructive coronary artery disease (<50% stenosis in all major coronary arteries). Of the 8518 participants enrolled, those that had insufficient ischemia, ineligible anatomy demonstrated on CCTA or another exclusion criterion, did not go on to randomization. Of the patients randomised 34% had no angina at baseline, 44% had angina several times per month and 22% had daily or weekly angina. Based on the baseline assessment 54% of randomised patients had severe ischemia, 33% had moderate ischemia, 12% had mild or no obvious ischemia and 1% had unquantified ischemia.

The decision to undergo PCI or CABG was left to the discretion of the local heart team. A total of 80% of patients in the intervention arm underwent revascularisation. Of those, 74% underwent PCI (93% of stents were successfully placed) and 26% underwent CABG. Of the 20% who did not undergo revascularisation, around 2/3 of patients had insignificant coronary artery disease on invasive coronary angiography and 1/3 had extensive disease deemed unsuitable for any mode of revascularisation.

Principal findings

Primary outcomes

Baseline demographics are included in **Box 1**. After a mean follow up of 3.3 years there was no significant difference in the primary outcome of CV death, myocardial infarction, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure (13.3% invasive group v 15.5% medical therapy group; p=0.34). Invasive therapy was associated with harm (2% absolute increase) within the first 6 months and benefit within 4 years (2% absolute decrease).

Box 1. Baseline demographics of patients included in the ISCHEMIA trial

Total number of participants	5179
Mean patient age, years	64
Female, %	23
Diabetes, %	41
Duration of follow-up, years	3.3

Secondary outcomes

CV death or myocardial infarction occurred in 11.7% of the routine invasive group compared with 13.9% of the medical therapy group (p=0.21). All-cause death occurred in 6.4% of the routine invasive group compared with 6.5% of the medical therapy group (p=0.67). Routine invasive therapy was associated with harm within the first 6 months with an increase in peri-procedural myocardial infarctions (adjusted hazard ratio (HR) 2.98, 95 % confidence interval (CI) 1.87-4.74; p<0.01) but with overall benefit within the 4 year follow up period with a reduction in spontaneous myocardial infarction, (adjusted HR 0.67, 95 % CI 0.53-0.83; p<0.1).

Quality of life outcomes

Improvement in symptoms was observed among those with daily, weekly or monthly angina but not in those without angina. In patients experiencing weekly angina, at 3 months 45% of patients in the invasive group experienced no angina compared to 15% in the conservative arm.

Interpretation

One important consideration was that high-risk patients were excluded from this study. Namely, patients with severe left ventricular systolic dysfunction (left ventricular ejection fraction <35%), New York Heart Association class III/IV

heart failure symptoms or advanced kidney disease were excluded from the study. This raises the question of whether the cohort of patients in the study was truly representative of the patients seen in clinical practice. Furthermore, one third of subjects did not even report angina symptoms on enrolment into the study.

Another important factor to consider is the definition of 'moderate-to-severe' ischemia and the modalities of functional imaging used to define this. By employing different modalities of functional imaging in the trial, a reference value for practicing physicians can be established, as some modes of imaging may not be available in certain centres depending on available resources. Although stress echocardiography, nuclear perfusion and cardiac magnetic resonance imaging are well-established modalities of assessing functional ischemia, exercise stress testing can be an unreliable modality[10,11] particularly in certain subgroups e.g. women.[12] A meta-analysis of 24,047 patients in 147 studies found exercise stress tests to have a pooled sensitivity of 68% and specificity of 77% for detection of CAD.[10,11] The pooled sensitivity and specificity in 3,721 women from 19 studies were 61% and 70% respectively, compared with 68% and 77% in men.[12]

In January 2018, the primary endpoint of the ISCHEMIA trial was changed from its 2012 version. The endpoint was extended from CV death and non-fatal myocardial infarction to include three further endpoints; resuscitated cardiac arrest, hospitalisation for unstable angina and hospitalisation for heart failure.[13] The endpoints of hospitalisation for heart failure and unstable angina are subjective. The diagnosis of unstable angina in itself is subjective, and the decision to admit a patient on the basis of these variables could be subject to bias. As this study was non-blinded, a clinician may have been more inclined to admit a patient who had not been revascularised and therefore subject to bias. Had this been a blinded study, it would have been more reliable. Although there are instances where a primary endpoint in a trial can be changed,[14] it is often at the consequence of favouring the intervention arm and can amplify type 1 errors of a study. In this particular case it does not seem to have favoured the intervention arm, however it may have affected the reliability and validity of the study.

Conclusion

It is important to note that, even with its limitations the ISCHEMIA trial is the largest study to date comparing an invasive and conservative treatment strategy in patients with stable CAD. Whilst accepting that the full results of the study are yet to be published in a peer reviewed medical journal, I believe we can reasonably draw some conclusions from the long-awaited ISCHEMIA trial. Firstly, OMT should be the mainstay of treatment for stable CAD. Secondly, revascularisation in this subgroup should be offered when medical therapy fails. Finally, we may need to rethink the benefit we gain by offering patients with stable coronary artery disease invasive treatment; are we causing more harm than good?

Disclosures

None.

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