International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial and the appropriateness of revascularization

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Abstract

The recently published ISCHEMIA trial which is a prospective randomized multi-centre trial has concluded that there was no evidence that an initial invasive strategy of revascularisation in patients with stable angina reduced the risk of ischaemic cardiovascular events or death from any cause. The trial has confirmed that patients with stable angina do not greatly benefit from revascularisation and optimal medical treatment (OMT) is an acceptable alternative. The trial has also confirmed that in patients with stable angina and end-stage renal impairment, OMT is once again an equally effective initial strategy. While the ISCHEMIA trial is one of the most rigorously and meticulously conducted trial, exclusion of symptomatic patients, recruitment of patients who are not known to derive significant benefit from revascularisation and those who were at low risk of clinical events, along with a short follow-up period, may all have contributed to the lack of difference seen between the groups. The fact that the ISCHEMIA trial does not represent the entire cohort of real-life patients requiring revascularisation should be borne in mind, and care should be taken in extrapolating these results to the wider group of patients requiring revascularisation for coronary artery disease.

Keywords ISCHEMIA · CABG · Stable angina · Stable ischaemic heart disease · Stable coronary artery disease

The rationale of carrying out coronary artery bypass grafting (CABG) in patients with coronary artery disease (CAD) has been to improve survival, relieve angina and reduce the incidence of nonfatal outcomes. This rationale has been challenged by the findings of the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial. It concluded that there was no study evidence that the initial invasive strategy of revascularisation reduced the risk of ischaemic cardiovascular events or death from any cause [1].

The findings have been the subject of interpretation and discussion among medical as well as non-medical community who have been quick to point out the irrationality of the medical profession in treating patients with CAD and even casted

veiled aspersions of greed and unethical practices among doctors. It therefore becomes mandatory from a clinical point of view as well as a moral imperative to evaluate our practice in the light of the findings of the ISCHEMIA trial.

The ISCHEMIA trial was a prospective randomized parallel multi-centre trial carried out across 37 countries and 320 centres that included 3 centres from India. This is by far the largest study of its kind [1]. Patients with stable ischaemic heart disease (SIHD) were screened for eligibility to the trial. Stress imaging (nuclear perfusion, echocardiography or cardiac magnetic resonance) was carried out, and patients were invited to participate if they had moderate to severe ischemia. In the latter part of the study, non-imaging exercise tolerance testing (ETT) was also used to recruit patients to ensure that the trial was more relevant to the real world practice. However, on expert advice when inducible ischaemia was assessed on ETT, only patients with severe ischaemia were included, unlike stress imaging where both moderate and severely ischaemic patients were included.

Following this the patients underwent a blinded coronary computed tomographic angiography (CCTA) to identify those

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with unprotected left main disease (defined as $\geq 50\%$ stenosis) as well as those without obstructive CAD. Both these categories of patients were subsequently excluded. The cut-off for defining obstructive lesions in a coronary artery was 50% for patients screened with stress imaging and 70% for patients recruited with ETT. After confirming anatomical eligibility, 5179 patients were randomized in a 1:1 ratio into an initial invasive strategy [optimal medical therapy (OMT) + angiography + revascularization] and initial conservative strategy (OMT alone). In the invasive-strategy group, the type of revascularization to be carried out [percutaneous coronary intervention (PCI) or CABG] was decided by the local heart team. The goal of revascularization in ISCHEMIA was complete “ischaemic revascularization” rather than complete anatomic revascularization. Thus, angiographic diameter stenosis of $\geq 70\%$ but with a Fractional Flow Reserve (FFR) > 0.80 did not require treatment. Primary and secondary definitions for myocardial infarction (MI) were developed for both procedural (based on third universal definition) and non-procedural MI. Primary outcome was defined as a composite of the rate of death from cardiovascular causes, myocardial infarction or hospitalization for unstable angina, heart failure or resuscitated cardiac arrest. Secondary outcome included death from cardiovascular causes and myocardial infarction and angina-related quality of life. OMT consisted of intensive secondary prevention using lifestyle and pharmacologic interventions and was applied to both arms equally. In the invasive-strategy group, PCI was carried out in majority (74.2%) of the patients, and second-generation drug-eluting stents (DES) were used in 98.1% cases. In the CABG arm (25.8%), the internal mammary artery (IMA) usage was 91.9%.

Primary outcome events were similar (5.3% versus 3.4%) at 6 months as well as 5 years (16.4% versus 18.2%) in the invasive and the conservative strategy. Secondary outcome event rate was 4.8% in the invasive-strategy group and 2.9% in the conservative-strategy group at 6 months and 14.2% and 16.5% at 5 years. Death from any cause at 5 years was 9% in the invasive and 8.3% in the conservative group. With regard to angina, participants in the invasive-strategy group had greater improvements; however, the probability of being angina-free was larger among participants who had angina at baseline but was minimal among those who were asymptomatic [2]. PCI and CABG were not compared head to head to assess if the strategy of revascularisation influenced outcomes.

So does the trial confirm that revascularisation does not improve outcomes in patients with stable ischaemic heart disease?

This is perhaps the question the cardiac surgical community is most interested in. To answer this question, we have to do two

things. Firstly, we have to critically evaluate the overall trial. Secondly, we have to examine the trial in the specific context of revascularisation with a particular focus on the patients undergoing CABG.

ISCHEMIA trial is the largest trial so far to compare revascularisation with OMT patients with stable angina. Even though this was a meticulously thought-out and rigorously conducted trial, certain issues or findings of the trial need highlighting. To start with one has to note the change in sample size and the primary outcome during the trial period. The sample size which was 8000 at the start of the study was subsequently reduced to 5179 to complete the recruitment within prescribed time frames and led to a reduction in the power of the study. The original sample size calculation was based on a five-component composite primary outcome but was later changed to a composite of death from cardiovascular causes or myocardial infarction. This was once again reverted to the originally proposed five-component composite outcome because of slower recruitment and low event rates.

In the trial, 20.6% patients randomized to invasive strategy did not actually undergo PCI/CABG. In majority of cases, this was because no obstructive CAD could be seen on the pre-procedure angiography despite a positive stress test and presence of obstructive disease on CCTA. On the other hand, in the conservative-strategy arm, 21% ended up crossing over as they required revascularisation of which 15% underwent revascularization before occurrence of a primary event.

Apart from changes in primary outcome and patients' crossing over to the other treatment arm, the trial excluded patients who are known to benefit from CABG. It is well known that patients with significant coronary artery stenosis and angina with poor or no response to OMT constitute a class IA recommendation for revascularisation [3]. However, in the ISCHEMIA trial, these patients were excluded. In fact, one-third of the patients (34%) had no angina for 30 days prior to revascularisation. This was because patients with Canadian Cardiovascular Society Class III–IV angina, unstable angina and patients with acute coronary syndrome within 2 months were all excluded. The trial also excluded patients who had LVEF $< 35\%$, who were in NYHA III–IV or who had a history of heart failure requiring admission in the preceding 6 months. Patients with unprotected left main stenosis $\geq 50\%$, with history of PCI or CABG in previous 12 months or with stroke in the last 6 months along with patients with non-ischaemic dilated cardiomyopathy or hypertrophic cardiomyopathy and those with end-stage renal disease on dialysis or estimated glomerular filtration rate < 30 ml/min were all excluded.

Thus, the population undergoing revascularisation in the ISCHEMIA trial does not seem to be representative of patients presenting for CABG in real life. The evidence of how unrepresentative this group was is evident from the fact that 26,000 patients were screened to recruit 5179 patients. Thus, almost

80% of the screened patients were actually not considered for the study for one reason or the other [4].

Closer scrutiny of the data on patients undergoing early revascularisation reveals some other interesting facts. PCI was the primary mode of revascularisation, and CABG was performed in only 25.8% cases. Of the patients randomized to the invasive strategy, 63.8% did not have a proximal left anterior descending (LAD) artery lesion, and almost one in four (23.5%) patients in the invasive-strategy group had no LAD lesion at all. Of the patients undergoing CABG, only 3.8% had left main stem stenosis, and only 39.6% had triple vessel disease.

Thus, the patients undergoing revascularisation were a low-risk unrepresentative patient population. Despite this, it was seen that while in the first 6 months greater number of MI (predominantly procedural) occurred in the invasive-strategy group, as the trial proceeded, the curves crossed, and with time more MI (predominantly spontaneous) occurred in the conservative-strategy group. At 5 years, the cumulative incidence of death from cardiovascular causes or myocardial infarction (based on the primary definition) was higher in the conservative-strategy group than in the invasive-strategy group (16.5% vs. 14.2%). It is therefore possible that the trial ended before a substantial difference in favour of the invasive strategy emerged and a longer follow-up may show a significant difference in favour of the initial intervention strategy [5].

Thus, exclusion of symptomatic patients, recruitment of patients who are not known to derive significant benefit from revascularisation and those who were at low risk of clinical events, along with a short follow-up period, may all have contributed to the lack of difference seen between the groups.

What did we already know about role of revascularization in management of stable ischaemic heart disease before the ISCHEMIA trial?

Several meta-analyses in the past have reported that compared with OMT, PCI in patients with stable coronary artery disease (SCAD) offered none or only modest benefits in terms of survival or MI [3].

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial also confirmed that PCI in patients with SCAD did not reduce the risk of death, myocardial infarction or other major cardiovascular events compared with optimal medical therapy [6]. More recently the ORBITA (Objective Randomized Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina) trial which compared PCI with placebo (sham procedure) in low-risk patients with SCAD found that the primary endpoint was similar in both arms [7].

With regard to CABG in stable angina, a similar picture emerges. It has now been known for over quarter of a century that in patients with stable angina, a strategy of initial CABG surgery is associated with lower mortality than medical management in high- and medium-risk patients. However, *in low-risk patients*, there is a non-significant trend towards greater mortality with CABG [8]. The overall superiority of CABG over initial medical therapy and evidence of early and sustained improvement for both PCI and CABG in patients with multi-vessel disease has been confirmed in some very large studies [3, 9].

What about patients with renal impairment?

To answer this question, another 777 patients who had advanced chronic kidney disease were included in a separate trial (ISCHEMIA-CKD) [1, 10]. Advanced chronic kidney disease was defined as an estimated glomerular filtration rate of < 30 ml per min per 1.73 m² or requiring dialysis. A 3-year cumulative event rate was similar between the groups (invasive vs. conservative) with regard to the primary outcome (37.4% vs. 37.6%). There was no difference in the secondary outcome (death from any cause, MI, hospitalization, for unstable angina or heart failure) between the groups. In ISCHEMIA-CKD, there was also no benefit with regard to angina-related health status with the invasive strategy. One important finding that needs to be stressed is the very high mortality in these patients irrespective of the treatment strategy. The all-cause mortality at 3 years was 27.2% with the early invasive strategy and 27.8% with the initial conservative strategy [10]. Therefore, it can be argued that patients with stable ischaemic heart disease and chronic kidney disease can be treated with an initial conservative strategy.

Summary

The role of revascularisation in low-risk patients with stable angina has always been questionable. The ISCHEMIA trialists in this excellent trial have confirmed long known but often ignored evidence that low-risk patients with stable angina do not greatly benefit from revascularisation and OMT may be an acceptable alternative. In patients with stable angina and end-stage renal impairment compared with revascularisation, OMT is once again an equally effective initial strategy. In the subgroup of patients who had angina at baseline, the probability of being angina-free was higher with the invasive strategy, and spontaneous MI was more common in the conservative arm at a 5-year follow-up.

Exclusion of symptomatic patients, recruitment of patients who are not known to derive significant benefit from revascularisation and those at low risk of clinical events along

with a short follow-up period may all have contributed to the lack of difference seen between the groups. Considering that the ISCHEMIA trial has consent from the patients to follow them up for 20 years, a longer follow-up may help in clarifying some of the issues.

Lastly, the un-intended fall out of the findings of the ISCHEMIA trial was inappropriate extrapolation of data by the lay media that led to concern among the patients regarding the appropriateness of revascularisation in CAD as a whole. This information needs to be stressed and disseminated that the ISCHEMIA trial does not represent the entire cohort of real-life patients requiring revascularisation and majority of revascularizations carried out are appropriate and life-saving.

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