Impact of ISCHEMIA Trial on Clinical Practice

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ISCHEMIA (Initial Invasive or Conservative Strategy for Stable Coronary artery disease) trial was a large, international, multi center, prospective, randomized controlled clinical trial comparing initial invasive plus optimal medical therapy (OMT) strategy versus conservative management plus OMT strategy in stable coronary artery disease patients with moderate to severe ischemia. It is still too early to describe the overall impact of ISCHEMIA trial partly because the result is still in the process of slowly being digested in the cardiology and general communities, but also because COVID-19 pandemic has greatly altered recent cardiology practices in the US and worldwide. However, one thing is very likely. Based on the result of this trial, cardiologists will be asked more often to be cautious about indications for revascularization. A proof of ischemia alone cannot be justified for initial invasive strategy in a stable coronary artery disease patients who are optimally medically managed and asymptomatic or minimally symptomatic. In the early days of angioplasties, “Oculo-stenotic reflex” was frowned upon as a too premature attitude of angioplasty treatment for an anatomically significant coronary stenosis but otherwise unknown hemodynamic or clinical importance. After the ISCHEMIA trial, cardiologists may be asked to shy away from “Ischemia-invasive reflex” in the appropriate context in stable coronary artery disease patients who are optimally medically treated and asymptomatic or minimally symptomatic. According to the result of this trial, proof of significant ischemia is not a “Carte Blanche” for early invasive management strategy. On the other hand, this trial did show durable improvement of angina symptoms in the invasive arm compared to conservative arm, thus, as long as the goal of the management is clearly stated to reduce angina and to improve quality of life, early invasive strategy for stable coronary artery disease patients is justifiable in the post ISCHEMIA era.

KEY WORDS: CABG, Ischemia, OMT, PCI, stable coronary artery disease

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I. Background

The traditional holy grail of coronary artery revascularization in stable coronary artery disease patients are not only to reduce angina symptoms and improve quality of life but to reduce risk of death and future ischemic events compared to medical therapy alone. However, previous trials including COURAGE trial showed PCI did not reduce the risk of death, myocardial infarction, or other major cardiovascular events when added to optimal medical therapy in stable coronary artery disease patients. On the other hand, recent FAME2 trial showed fractional flow reserve (FFR) guided percutaneous coronary intervention (PCI) decreased the incidence of composite endpoint of death, myocardial infarction, and ischemia driven urgent revascularization compared to OMT alone in 5 years’ follow up. ISCHEMIA trial was done to answer the question of if initial strategy of invasive management of coronary angiogram on top of OMT can reduce the risk of future death or myocardial ischemic events in stable coronary artery disease patients with moderate to severe ischemia.

II. Introduction

ISCHEMIA (Initial Invasive or Conservative Strategy for Stable Coronary artery disease) trial was a large, international, multi center, prospective, randomized controlled clinical trial comparing initial invasive plus optimal medical therapy (OMT) strategy versus conservative management plus OMT strategy in stable coronary artery disease with moderate to severe ischemia. This trial enrolled a total of 8,518 patients and randomized 5,179 patients at 320 sites in 37 countries. The study was sponsored by National Heart, Lung, and Blood Institute of the United States. Primary outcome was a composite of cardiovascular death, myocardial infarction, or hospitalization due to angina, heart failure, or resuscitated cardiac arrest. A key secondary outcome was cardiovascular death or myocardial infarction and angina related quality of life. Patients were enrolled if clinically indicated stress imaging test was positive for moderate or severe ischemia or if severe ischemia was present on exercise EKG testing without imaging. The majority of the patients had blinded coronary CT
angiogram performed before randomization to exclude unprotected left main disease and non-obstructive coronary artery disease. Severe left ventricular systolic dysfunction with ejection fraction <35%, chronic kidney disease patients with GFR below 30 ml/min/1.73 m², recent acute coronary syndrome patients, decompensated heart failure, and unstable angina patients were also excluded.

Eligible patients were randomized in 1:1 fashion to an initial invasive strategy of OMT plus angiography, followed by revascularization either by coronary artery bypass graft (CABG) or PCI if feasible, or initial conservative management with OMT alone. In the invasive arm, angiogram was performed within 30 days after randomization and complete revascularization of all ischemic territories if feasible were encouraged. They were provided guidelines including the usage of FFR measurements, but the method of revascularization including choice of CABG vs PCI were deferred to local heart team.

III. Results

Over a median of 3.2 years of follow up, 318 primary outcomes occurred in the invasive arm, while 352 occurred in the conservative arm (non significant difference). At 6 months, the cumulative event rate was 5.3% in the invasive arm as opposed to 3.4% in the conservative arm. At 5 years, the cumulative event rate was 16.4% and 18.2%, respectively. There were 145 deaths in the invasive arm and 144 deaths in the conservative arm (Hazard Ratio=1.05, CI: 0.83 to 1.32). Thus authors concluded that among stable coronary artery disease patients with moderate or severe ischemia, initial invasive plus OMT management strategy did not improve the risk of ischemic cardiovascular events or death compared to initial conservative plus OMT management strategy (Fig. 1).

There are several caveats that require attention. This trial result could only be applied to a specific population that is studied in this trial. For example, majority of the patients had coronary CT angio after enrollment but before randomization, which is not a typical practice in the US. Without this additional step of coronary CT angiogram, left main disease could have been missed at the time of randomization. This may have influenced the study outcome, favoring conservative strategy. Also, during the trial, due to slow enrollment, inclusion criteria was expanded to include positive stress test without imaging, which may have diluted the population to include less severe ischemia, which may also have contributed to the outcome, although authors stated that there were no heterogeneity of outcomes found among different degrees of ischemia severity.

It is important to point out that patients with severe kidney dysfunction with GFR less than 30 ml/min/1.73 m², recent acute coronary syndrome, EF less than 35%, NYHA class 3 to 4 CHF, or unstable angina despite medical therapy, and left main disease with >50% stenosis were all excluded and it is very important not to extend this study’s conclusion to patient population that
In the invasive strategy arm, 96% underwent angiography and 79% underwent revascularization (of these, PCI in 74% and CABG in 26%). The method of revascularization, i.e., CABG vs PCI was deferred to the local heart team. Thus, this trial was, contrary to a popular belief, NOT comparing PCI vs medical management. In the invasive arm, only 58% ($0.79 \times 0.74$) did actually receive PCI. The outcome difference between CABG group and PCI group was not reported and the decisions for one treatment vs other were deferred to local heart team and the reasons for the decisions were not provided.

In the conservative arm, there was significant crossover. During follow up, 26% of the patients in the conservative arm underwent angiography and 21% underwent revascularization. Thus more than 1 in 5 patients crossed over from conservative to invasive treatment during relatively short follow up period of an average of 3.2 years.

Moreover, at enrollment, 35.4% of patients had no angina symptoms and 44.3% had only several angina episodes per month, and only 20.3% had daily or weekly angina, thus the patients’ angina symptoms were relatively mild, which may also have favored initial conservative management strategy.

Patients in the invasive strategy arm had more procedural infarctions, and they had fewer non-procedural infarctions during late follow up. Therefore, overall, two arms were equal in primary and secondary endpoints at the end of trial. However, the time-to-event curves for primary composite outcome, cardiovascular death or MI, and myocardial infarction, all showed crossing point at about 2 years, initially favoring the conservative arm, but later favoring the invasive arm (Fig. 1). This crossing

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Fig. 2 Crude mean health status scores in the overall trial population. [Reproduced with permission from (Ref. 2), Copyright Massachusetts Medical Society.]
point and overall incidence of MI can change depending on the definition of myocardial infarction.

Patients with stable CAD and moderate to severe ischemia had significant, durable improvements in angina control and quality of life with an invasive strategy if they had angina (daily/weekly or monthly) (Fig. 2). This effect was seen during all through the duration of the study observation period up to 48 months. In patients without angina, an invasive strategy led to minimal symptom or quality of life benefits, as compared with a conservative strategy.

IV. Discussion

The two ISCHEMIA articles were published in NEJM on April 9, 2020, which was at the special historic time when COVID-19 pandemic was rampant in the US and worldwide. Therefore, it is difficult to assess the overall impact of ISCHEMIA trial partly because the result is still being discussed in the cardiology and general communities, but also because COVID-19 pandemic has greatly altered recent cardiology practice in the US and worldwide. Nevertheless, the ISCHEMIA was a huge, landmark trial which shed light to the relationship between myocardial ischemia and its revascularization treatment strategy and the authors of this trial should be greatly commended on the completion of this enormous worldwide endeavor and the subsequent lessons to be learned from it.

One other special note is that the median LDL-C was 64 mg/dl, systolic blood pressure was 129 mmHg, statin use was 95%, and aspirin usage was 97% at the last office visit, suggestive of exceptionally excellent OMT during this trial, which may have contributed favorably in the conservative arm. It is therefore unknown if “real world” management of stable coronary artery disease patients can reproduce the same low event rates as this trial.

V. Conclusion

From this trial, cardiologists are likely to be asked to be more cautious about indications for revascularization. A proof of ischemia alone cannot justify an initial invasive strategy in a stable coronary artery disease patients who are minimally symptomatic or asymptomatic and optimally medically managed. In the early days of angioplasties, “Oculo-stenotic reflex” was frowned upon as a too premature attitude of angioplasty treatment for an anatomically significant coronary stenosis but otherwise unknown hemodynamic or clinical importance. After the ISCHEMIA trial, cardiologists may be asked to shy away from “Ischemia-invasive reflex” in the stable coronary artery disease patients who are asymptomatic or minimally symptomatic and fulfills the inclusion/exclusion criteria of this trial. According to the result of this trial, proof of significant ischemia is not a “Carte Blanche” for early invasive management strategy. On the other hand, this trial did show durable improvement of angina symptoms in the invasive arm compared to conservative arm, thus, as long as the goal of the management is clearly stated to reduce angina and to improve quality of life, early invasive strategy is justifiable for stable coronary artery disease patients in the post ISCHEMIA era.

Conflicts of interest

None.

References

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