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Initial Invasive or Conservative Strategy for Stable Coronary Disease: The ISCHEMIA Trial and Its Clinical Implications

Breda Hennessey

Ivan J Nuñez-Gil

Pedro Villablanca
Henry Ford Health, PVillab1@hfhs.org

Harish Ramakrishna

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Editorial

Initial Invasive or Conservative Strategy for Stable Coronary Disease: The ISCHEMIA Trial and Its Clinical Implications

WHETHER OR NOT one should take an initial invasive or conservative approach in the management of stable coronary artery disease, lately named as chronic coronary syndrome (CCS), has long been the subject of much debate.

The results of the recently published and highly anticipated International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial[1] have added fuel to this debate and have challenged the value of an initial invasive strategy in patients with stable coronary artery disease (CAD). The results of this trial have the potential to be far-reaching and likely will influence future clinical practice guidelines. Current recommendations from the European Society of Cardiology for the management of CCS reenforce the importance of optimal medical therapy (OMT) in the management of stable CAD, primarily for symptom reduction and slowing the disease process, while recommending myocardial revascularization in specific CCS.[2]

The evolution of management strategies for patients with stable CAD has called into question the long-term benefits of an initial invasive strategy versus OMT on clinical outcomes. Before the ischemia trial, arguably the most robust data addressing this question came from the COURAGE and the BARI 2D studies, and both of these trials failed to show significant differences in death and major adverse cardiovascular events between the groups managed with an initial invasive approach versus OMT.[3,4] It should be noted, however, that both of these trials have received criticism over perceived selection bias and the lack of clarity in myocardial ischemia thresholds for inclusion of patients in these trials.

The ISCHEMIA trial set out to address this with the intention of determining the effect of an invasive strategy (angiography and revascularization where feasible) in addition to OMT in patients with stable CAD in patients with moderate-to-severe ischemia. To date, this is the largest trial that has been conducted to address this issue. Eligible patients were randomized in a 1:1 fashion to either the initial invasive strategy in conjunction with OMT versus an initial conservative group. This study ultimately randomized 5,179 patients. The primary outcome was a composite of death from cardiovascular causes, myocardial infarction, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest. A key secondary outcome was death from cardiovascular causes or myocardial infarction.[1]

Patients included in this trial had to have at least moderate ischemia on a qualifying stress test. Originally, this was moderate ischemia demonstrated on a stress echocardiogram, a nuclear perfusion with single-photon emission computed tomography or positron emission tomography, or cardiac magnetic resonance imaging; however, an amendment to the protocol was made in 2014 to include exercise stress testing without imaging to improve recruitment. Most patients in this trial (73%) underwent computed tomography coronary angiography (analyzed by the core-lab) to exclude left mainstem stenosis. The main exclusion criteria for this trial were: significant left mainstem stenosis, those with New York Heart Association Class III-to-IV symptoms, percutaneous coronary intervention (PCI) or coronary artery bypass surgery within the last year, unacceptable angina despite medical therapy, patients with an ejection fraction (EF) <35%, acute coronary syndrome (ACS) within two months, and patients with an estimated glomerular filtration rate <30 mL/min or on dialysis. It is also important to highlight some of the baseline characteristics of the patients randomized in the trial. The median age was 64 years (interquartile range, 58-70), more than 75% of the patients were male, and 41.8% of patients overall were diabetic. The median EF was 60% (interquartile range, 55-65). It is also important to note that when it came to the Seattle angina questionnaires, just over one-third of patients in both groups reported no anginal symptoms in the last four weeks, and one-fifth of patients reported daily or weekly angina. Overall, the patients included in this trial could be considered low-risk patients. It is also prudent to mention that among patients in the invasive strategy group, 96% underwent angiography and 79% underwent revascularization. In the conservative-strategy group, 26% of the patients underwent angiography and 21% underwent revascularization.[1,5]

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The results of this trial are clinically striking.[1,6] To summarize, over a median of 3.2 years, 318 primary outcome events occurred in the invasive-strategy group and 352 occurred in the conservative-strategy group. At six months, the cumulative event rate was 5.3% in the invasive-strategy group and 3.4% in the conservative-strategy group (difference, 1.9 percentage points; 95% confidence interval [CI], 0.8-3.0); at five years, the cumulative event rate was 16.4% and 18.2%, respectively (difference, −1.8 percentage points; 95% CI, −4.7 to 1.0). Results were similar with respect to the key secondary outcome. The incidence of the primary outcome was sensitive to the definition of myocardial infarction (MI), and a secondary analysis yielded more procedural MIs of uncertain clinical importance. There were 145 deaths in the invasive-strategy group and 144 deaths in the conservative-strategy group (hazard ratio, 1.05; 95% CI, 0.83-1.32).[1]

While discussing improvements in anginal symptoms, again, it is important to remember that 35% of patients is this study reported no anginal symptoms in the preceding four weeks. Having said that, patients randomly assigned to the invasive strategy had greater improvement in angina-related health status than those assigned to the conservative strategy. Differences were larger among participants who had more frequent angina at baseline (8.5 *v* 0.1 points at three months and 5.3 *v* 1.2 points at 36 months among participants with daily or weekly angina compared with no angina).[6] In both arms, the control of cardiovascular risk factors and compliance with OMT were high, and very few patients were lost to follow-up.[1,6]

It is clear that this was a robust, expensive, and large trial that required patients to undergo a comprehensive noninvasive evaluation to demonstrate moderate-severe ischemia, with tight control of cardiovascular risk factors, appropriate OMT with few patients lost to follow-up. With a trial of this magnitude, however, one must ask what the caveats are and bear these in mind when interpreting the results before applying them to clinical practice. First and perhaps most important, is patient selection. This trial only included low-risk patients with stable CAD. It excluded those patients with complex anatomic features such as left mainstem disease.

The patients typically were younger, with good left ventricular EFs and with high Seattle anginal questionnaire scores. This trial also explicitly excluded the most symptomatic patients (precisely those who were more likely to derive symptomatic benefits from OMT and revascularization) and those with a recent ACS. Therefore, there appears to be an element of selection bias.

Slow recruitment rates in certain centers could be interpreted as a tendency for these centers to exclude highly symptomatic patients. When looking at the gender balance of patients in this trial, it is evident that female patients were underrepresented. More than three-quarters of the patients in this trial were male, with female patients comprising 23% of the total; and when considering the median age of 64 years and that female patients typically present at an older age, this trial missed the opportunity to include this important subgroup.[1,6]

Although not part of the primary endpoint, it is worth pausing and looking further into the prespecified secondary endpoint of angina reduction. Slightly more than one-third of patients overall in this study reported no episodes of angina within the preceding four weeks. Therefore, it may be extrapolated that these patients were unlikely to have a major improvement in anginal symptoms with either OMT or revascularization.[1,6]

This was an important trial that furnished us with important data on the initial management of stable CAD. One must not forget to consider the crossover between the groups in this study. It should be noted that 20% of patients in the invasive group did not actually receive revascularization, and 21% of the patients in the conservative group crossed over to receive revascularization. The strategies of revascularization included both PCI and surgical revascularization, with slightly more than one-fourth of the revascularization patients undergoing surgical revascularization. The ISCHEMIA study also did not assess lesions with angiographic stenosis of >50% with invasive coronary physiology to confirm functional significance of said stenosis, and this could be considered a limitation. This is particularly relevant when interpreting the result of the ISCHEMIA trial in the context of the FAME-2 trial results in which fractional flow reserve (FFR) was performed on all lesions. If the lesion was significant, the patients were randomized to PCI plus OMT versus OMT, and FAME-2 reported lower even rates in the PCI arm.[1,6,7]

The authors concluded that this trial did not reveal evidence that an initial invasive strategy in comparison with an initial conservative strategy reduced the risk of ischemic cardiovascular events or death from any cause over a median of 3.2 years. Overall, the event rates in this trial were low. It is unsurprising that the initial conservative strategy had a lower risk of periprocedural MI. Over time, the divergence of the curves of spontaneous MI and of the primary endpoint supported revascularization, and this was in the context of the crossover of 21% of patients in the conservative group receiving revascularization. The conservative group also had lower rates of heart failure admission with greater symptomatic control, and improved quality of life was noted in the initial invasive strategy, particularly in those with a high burden of angina.[1,6]

So How Does This Fit into Daily Clinical Practice?

First and foremost, one needs to remember to keep individual bias in check when it comes to interpreting these results, before applying them to day-to-day practice. Clinicians also must be vigilant in not taking a ‘one size fits all’ approach, and individualization is of the upmost importance. Full disclosure and presenting both treatment options to patients is paramount, and involving them in the decision-making process is key. The lack of mortality benefit demonstrated in this trial may be influential in the decision-making process for both patients and the physicians. Indeed, this study reenforced the importance of upfront aggressive OMT in patients presenting with stable CAD in the context of stable angina symptoms without

necessarily proceeding directly to a revascularization strategy. These treatment options should not be seen as competing but rather as complementary to each other. This is particularly applicable to younger patients (predominantly male) with preserved EFs. One must be mindful of the patients excluded from this study, particularly those with left main disease, reduced EF, New York Heart Association Class III to IV, and those with unacceptable angina and recent ACS, and not apply an upfront conservative approach in these patients. In addition, this study likely will cause a shift away from diagnostic coronary angiography in these patient groups and increase the use of computed tomography coronary angiography to confirm the presence of CAD, with invasive strategies reserved for those who do not respond to OMT or have a high symptom burden. This may change the profile of the patients ultimately ending up in catheterization laboratories and have the effect of reducing the number of those lower-risk patients without obstructive epicardial stenosis ultimately having an invasive angiography.

Overall, this practice-changing study has enhanced significantly the understanding of the management of stable CAD, challenges clinicians to involve patients in the decision-making process, and likely will influence future clinical practice guidelines.

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Conflict of Interest

The authors have no conflict of interest to disclose.

Breda Hennessey, MD*
Ivan J. Nuñez-Gil, MD, PhD, FESC*
Pedro Villablanca, MD, MSc, FACC, FSCAI†
Harish Ramakrishna, MD, FACC, FESC, FASE‡,1
*Division of Interventional Cardiology, Cardiovascular Institute, Hospital Clinico San Carlos, Madrid, Spain
†Division of Cardiology, Henry Ford Hospital, Detroit, MI
‡Division of Cardiovascular and Thoracic Anesthesiology, Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN

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