

ISCHEMIA trial: Back to the future or forward to the past?

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The ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial [1] is a publicly funded clinical trial with a complex design, elaboration, communication, and interpretation of the results. There were 5179 patients randomized worldwide in the study. The results of the ISCHEMIA trial showed that patients with significant stable coronary artery disease (CAD) that underwent invasive procedures, such as percutaneous coronary intervention or coronary artery bypass graft surgery plus optimal medical treatment fared no better than patients who received only optimal medical therapy. The initial invasive strategy was associated with a reduction in angina and improved quality of life, only in symptomatic patients.



The main finding was that, among stable patients who had evidence of moderate to severe ischemia on stress testing, an initial invasive strategy, when compared with an initial conservative strategy, was not associated with a reduction in the primary outcome of cardiovascular death, myocardial infarction (MI), hospitalization for unstable angina, hospitalization for heart failure, or resuscitated cardiac arrest over a median follow-up of 3.3 years. The primary composite endpoint occurred in only 15.5% of patients in the conservative arm and 13.8% of patients in the invasive arm ($p = 0.34$); an observed event rate which was lower than predicted. Similar results were also observed

for the pre-specified secondary endpoints of cardiovascular death or MI, and across the pre-specified sub-group analyses.

For inclusion into the study, documentation of at least moderate ischemia on stress testing was required. Ischemia severity was based on a core-laboratory interpretation. The chosen stress tests were markedly variable: 50% nuclear myocardial perfusion imaging via single-photon emission computed tomography or positron emission tomography; 25% exercise treadmill testing (without imaging), 20% stress echocardiogram and 5% stress cardiac magnetic resonance imaging. However, the stress core laboratories did not confirm whether the degree of ischemia was enough to qualify for the trial in 13.8% of patients who finally underwent randomization. Patients who were determined by the core laboratory to have moderate ischemia on a non-imaging exercise-stress test did not meet ischemia eligibility, yet some such patients underwent randomization. Non-imaging exercise test criteria were developed to approximate severe ischemia, taking into account the potentially higher false positive rate.

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In addition to an evaluation of ischemia, most patients underwent computed tomography angiography (CTA) in order to exclude the presence of left main stenosis ($\geq 50\%$ stenosis), as well as to exclude patients who had less than 50% stenosis in all arteries, in whom the presence of significant ischemia is less common, and events are generally lower [2]. A total of 1266 patients did not undergo core-laboratory-interpreted CTA for the trial and did not have an available previous CTA within 1 year before the trial for core-laboratory interpretation, and 923 patients had a CTA core-laboratory interpretation in which the number of diseased vessels could not be evaluated. When trial images could be interpreted for this variable, the number of diseased vessels on CTA was based on a 50% stenosis threshold. Data on CAD severity based on 50% stenosis excluded 4 patients with no diseased vessels. Stenosis of the proximal left anterior descending coronary artery was reported when the proximal left anterior descendant segment could be evaluated on CTA. For patients enrolled using a non-imaging exercise stress test, anatomic eligibility confirmation was required and CTA eligibility criteria were more stringent for them, requiring $\geq 70\%$ stenosis in the proximal or mid left anterior descending, proximal or mid right coronary artery, or proximal left circumflex (or circumflex equivalent).

The ISCHEMIA study highlights coronary anatomical assessment with cardiac CTA as an excellent tool to diagnose and evaluate the severity of coronary atherosclerosis. The assessment of the severity of a stenosis is facilitated using the CAD-RADS classification. In the ISCHEMIA study, a cardiac CTA scan was recommended, but was not required on randomization, which was based on the presence of moderate or severe ischemia in functional tests, as previously stated. Besides, cardiac CTA by itself did or did not indicate coronary revascularization, which relied on quantitative invasive coronary angiography. An optimal quality cardiac CTA was attained in more than 50% of patients, of which near 99% disclosed at least one major coronary artery with $\geq 50\%$ of luminal stenosis. In this regard, the SCOT-HEART study [3] showed that a conservative strategy in the treatment of stable angina based on cardiac CTA results compared with a conservative strategy guided by positive functional tests reduces coronary disease mortality and the incidence of MI. This benefit, observed after 5 years of follow-up, was associated with a 60% increase in the prescription of antiplatelet therapy and high potency statins. Undoubtedly, the effect

on plaque regression demonstrated with ambitious pharmacological therapy underlies the nexus that connects these observations.

The results of ISCHEMIA trial should be interpreted with caution and it may not be applicable to all patients. A selection bias cannot be excluded, and patients with very severe ischemia on the stress test might be less likely to be considered for study participation. Many patients with left main disease were also excluded with coronary CTA, and so the results are not applicable to them.

The question, at this point is: What is the role of functional testing and coronary computed tomography for patients with stable angina? Should all patients with stable symptoms be treated in a conservative manner, and reserve an invasive approach only if medical therapy alone fails? In light of results obtained, it might be wondered whether it was necessary for the patients with an evaluation for ischemia, if medical therapy would be used to treat nearly all stable patients who do not have left main disease. However, testing for ischemia will continue to have an important role in clinical cardiology. Sometimes, in routine clinical practice, it is unclear if patient symptoms represent angina or not, and an ischemic evaluation can be useful in these scenarios. Similarly, older patients or with long-standing diabetes frequently have silent ischemia, and functional studies could be required to identify the optimal diagnostic and therapeutic algorithm for them.

One of the strengths of the study is the usefulness of the CTA as a first line test to evaluate patients with stable symptoms and suspected CAD. This trial is another sample of the important role of the CTA as gate keeper of the diagnostic workflow, as reflected in the recent guidelines [4]. In patients who do not have known CAD, coronary CTA has an important role in identifying the need for aggressive medical therapy. CTA is also a key that can allow ruling out underlying high-risk coronary anatomy or left main disease, even though ischemia is present, particularly when symptoms are rare and conservative management is being considered. Indeed, one of the strengths of coronary CTA lies in its ability to identify a wide spectrum of CAD, ranging from mild non-obstructive plaque to extensive multi-vessel disease. Another advantage of using coronary CTA as a front-line test has to do with diagnostic efficiency: the majority of individuals with no history of CAD who are evaluated with coronary CTA will have either no CAD, or non-obstructive CAD, and will not need further testing.

In short, **the most relevant conclusion of this trial cannot be left in the absence of differences between the invasive and conservative treatment** [5]. At this point, one might think if all the available technology is being used for identifying which patients could benefit from each therapy [6, 7]. The answer to this question is given by the coronary CTA and the functional stress test, which can stratify risk and guide the algorithm. Trying to give an answer without them is to go back to the past, and not headed into the future. Going forward to the future is the only way to achieve the best individualized treatment for each patient.

Conflict of interest: None declared

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