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Commentary - The ISCHEMIA trial

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The ISCHEMIA (International Study of Comparative Effectiveness with Medical and Invasive Approaches) trial was one of the most anticipated late breaking trials presented at the American Heart Association Scientific Sessions held in Philadelphia, November 16–18, 2019.

Prior to ISCHEMIA, evidence underlying the management of patients with stable ischemic heart disease was incomplete for several reasons. Most of the previous trials comparing revascularization by coronary artery bypass graft (CABG) with medical therapy did not include pharmacological agents that are currently known to improve clinical outcomes in these patients, i.e. aspirin, statins, beta blockers, and renin-angiotensin-aldosterone system inhibitors. Observational studies suggested that, compared to medical treatment, coronary revascularization with percutaneous coronary intervention (PCI) or CABG improved prognosis in patients with extensive myocardial ischemia. More recent randomized trials, however, showed a lack of prognostic benefit of myocardial revascularization, but these studies did not include patients at higher risk such as those with extensive obstructive coronary artery disease and severe myocardial ischemia [1–3].

The rationale for the ISCHEMIA trial was to ascertain if - added to optimal medical therapy (OMT) - a strategy involving routine cardiac catheterization and myocardial revascularization improves prognosis in higher-risk patients with moderate to severe ischemia. Inclusion criteria included evidence of moderate to severe ischemia based on non-invasive imaging as assessed by nuclear, echo, cardiac magnetic resonance, or ECG exercise stress testing. Patients with NYHA class III-IV, angina refractory to medical treatment, LV ejection fraction <35%, acute coronary syndrome within 2 months, PCI or CABG within 1 year, or impaired kidney function (eGFR <30 mL/min or on dialysis) were excluded (Fig. 1) [4].

The initial primary endpoint of the trial was a combination of time to cardiovascular death and myocardial infarction. However, for pre-specified reasons, including the enrollment rate falling behind timelines and a lower than expected initial event rate, the primary endpoint was changed as pre-specified to a 5-outcome major adverse cardiac event (MACE) of cardiovascular death, myocardial infarction, hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest. Secondary endpoints included time to death or MI, the individual MACE events, and quality of life [4].

1. Main results of the ISCHEMIA trial

(https://professional.heart.org/professional/ScienceNews/UCM_505226_ISCHEMIA-Clinical-Trial-Details.jsp). Overall, 5179 patients were randomized, including 2588 to the invasive strategy and 2591 to the conservative strategy. The two arms were well balanced in terms of baseline characteristics and coronary anatomy by CT angiography.

The median follow-up was 3.3 years (IQR 2.2 to 4.3 years) and the primary endpoint occurred in 13.3% of the patients in the invasive strategy arm vs. 15.5% of those in the conservative arm (adjusted hazard ratio = 0.93 (0.80, 1.08); *p*-value = 0.34). The major secondary endpoint of cardiovascular death or myocardial infarction occurred in 11.7% of the patients in the invasive strategy arm vs. 13.9% of those in

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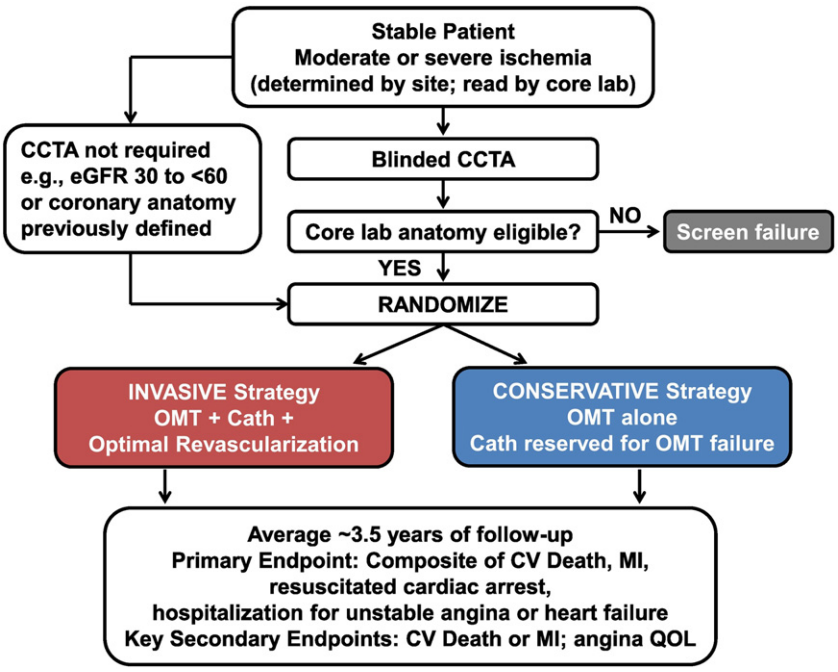

Fig. 1. Study design. Patients who underwent stress testing for clinical indications at enrolling sites were screened for eligibility if the site determined that moderate or severe ischemia was present on a stress imaging test, or severe ischemia was present on a non-imaging exercise tolerance test. Consenting participants were enrolled and most underwent blinded CCTA. (CCTA was usually performed in participants with normal renal function and not performed in participants with eGFR b60 mL/min). Participants with left main stenosis N50% or no obstructive disease were excluded. If prior CCTA or cardiac catheterization demonstrated the absence of significant left main stenosis and the presence of significant obstructive disease in other coronary arteries, a study CCTA was not required. Eligible participants were randomized to invasive or conservative management strategies. The primary endpoint is a composite of cardiovascular death, nonfatal myocardial infarction, resuscitated cardiac arrest, hospitalization for unstable angina, and hospitalization for heart failure. The composite of cardiovascular death or nonfatal myocardial infarction is a key secondary endpoint. Patients with advanced chronic kidney disease and moderate or severe ischemia on stress testing were considered for the ISCHEMIA-CKD ancillary trial. Participants with no obstructive disease who qualified for enrollment with stress echocardiography were considered for the CIAO-ISCHEMIA ancillary study. Lab, laboratory; CCTA, coronary computed tomography angiography; cath, cardiac catheterization; CV, cardiovascular; MI, myocardial infarction; QOL, quality of life (From Maron et al. Ref. [4], with permission).

the conservative arm (adjusted hazard ratio = 0.90 (0.77, 1.06); p-value = 0.21). In summary, the results of the ISCHEMIA trial, the largest trial of an invasive vs. conservative strategy for patients with stable ischemic heart disease, demonstrate that an initial invasive strategy as compared with an initial conservative strategy did not confer a reduced risk over a median of 3.3 years for the primary endpoint of cardiovascular death, myocardial infarction, hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest or for the secondary endpoint of cardiovascular death or myocardial infarction.

Angina symptoms and quality of life, however, were improved in the invasive management group compared with the conservative management group and this difference was relatively long lasting (https://www.abstractsonline.com/pp8/#!/7891/presentation/35080).

In a parallel study in patients with end-stage renal disease on dialysis or estimated glomerular filtration rate <30 mL/min/1.73 m^2, ISCHEMIA-CKD, patients in the invasive arm fared worse because stroke, and death or new dialysis, were increased in the invasive group, compared to OMT alone.

2. What are the strengths and limitations of this trial?

Strengths of this trial include: 1. The large number of patients included - it is the largest trial of invasive vs. non-invasive management carried out to date; 2. The trial was publicly funded and the investigators had no evident commercial associations; 3. It was appropriately powered to answer the primary research question: 4. the design was relatively straightforward and robust. The requirement of an initial assessment for left main and coronary artery disease using CT coronary angiography helped to control the confounding effects of obstructive left main disease and the absence of epicardial coronary artery disease. A further key strength is the rigorous approach to data management, use of independent core laboratories and oversight of the trial procedures by the trial steering committee, data and safety monitoring committee and clinical event committee. Remarkably, only 1% of the randomized participants were lost to follow-up. The trial was truly international and the top enrolling sites were in India. Achievement of guideline-directed medical management targets was similar in both of the randomized groups. There was a proportion of participants in the conservative group who progressed to invasive management (28% over 4 years). Because the initial non-invasive strategy was implemented, this progression should not necessarily be viewed as a cross-over, rather an expected outcome of the strategy. The symptoms and quality of life study was adequately powered for the pre-specified primary and secondary outcomes. However, importantly, 34.3% and 36.6% of invasive and conservative patients, respectively, had no angina at baseline and only 44.1% and 44.5% had angina several times per month. Thus, to a great extent, ISCHEMIA reflected a population with no or only minimal symptoms.

The open-label real-world design and the lack of a sham procedure, however, are major limitations of the trial. Because the participants and clinicians were aware of the treatment allocation, the conduct of the trial was susceptible to overt and unmeasured bias. This risk is not fully mitigated by the blinded evaluation of the primary and secondary outcomes. In an open trial, if patients assigned to an interventional procedure have an expectation that the intervention is beneficial, this might affect their reporting (and their physician's interpretation) of symptoms, artificially increasing the rate and magnitude of beneficial responses. Furthermore, placebo effects are known to be larger for invasive than for non-invasive treatments. This bias could have been mitigated by adding a "sham" group as in ORBITA, which documented that this approach is feasible and informative in angina patients [3]. Only 25% of the trial participants were female. This may reflect several factors including the lower prevalence of obstructive coronary disease and higher prevalence of coronary microvascular dysfunction in women,

as well as site selection bias. Although guideline-directed medical therapy and achievement of blood pressure/lipid lowering goals was balanced between the two groups, the percentages of participants achieving all these goals were low (only 41%). This finding may come as no surprise but, nonetheless, points to behavioral limitations in adherence to clinical strategies based on pharmacological and lifestyle interventions and suggests that advances in this area might demonstrate OMT superiority to revascularization. The completeness of revascularization and adoption of functional testing with fractional flow reserve are not yet known. The rates of cardiovascular events in both arms illustrate the persisting unmet health burden of cardiovascular disease.

3. Implications

The ISCHEMIA trial was challenging to implement and enrollment fell behind initial milestones. The reasons for these issues were not, by and large, due to lack of funding, but, arguably, had more to do with reluctance to enroll patients into the conservative arm. The ISCHEMIA trial asked a fundamental question about the practice of cardiology, challenging clinicians and patients about their preferences for invasive management and revascularization, or not. The study population was therefore susceptible to selection bias. The results could differ if lower or higher risk populations had been enrolled, such as patients with non-obstructive coronary disease or left main stenosis, respectively. When considering future studies, this experience should remind clinicians to put professional and personal preferences aside in the presence of clinical equipoise.

Several key groups of patients were not included in ISCHEMIA, notably patients with a recent acute coronary syndrome and those with a reduced LVEF. The trial results do not apply to these groups, but nonetheless, questions arise about whether invasive management should be routinely performed or whether an initial non-invasive imaging-guided strategy might be beneficial. Patients with mild ischemia <10% were not included in this trial. We believe the lack of a prognostic benefit from routine invasive management would be transferable to this group, but whether or not invasive management would improve persistent or refractory symptoms in this population is less certain. These points might be considered in new research studies in the future.

The trial's results call into question a routine clinical strategy of ischemia testing in patients with stable symptoms. This is because the onward action of invasive management did not improve prognosis, as reflected by the primary outcome. There were no interactions on the primary outcome according to the severity of ischemia at baseline, as reflected by analyses across subgroups. On the other hand, ischemia testing was not randomized, therefore, strictly speaking, the impact of the results are most relevant to management downstream of ischemia testing. CTCA was undertaken to identify obstructive left main coronary artery disease. However, left main disease affects <1.0% of all-comers with chest pain and these individuals would be identified by high-risk features on ischemia testing [5]. In ISCHEMIA, the prevalence of left main disease was 5.1% but this trial population was highly selected so much less relevant for clinical translation. The trial's results support a revascularization strategy for angina quality of life, as 25% patients with daily angina before revascularization reported to be angina-free at three months after the procedure compared to 7,5% with the conservative strategy. Finally, relying on CT coronary angiography for excluding epicardial coronary artery disease will result in under diagnosis of patients with functional coronary abnormalities such as epicardial coronary spasm or coronary microvascular dysfunction [6]. The specific diagnosis of these conditions often requires invasive diagnostic procedures [7].

4. Future directions

The diagnosis and management of angina are distinct yet related. In an all-comer population of patients presenting with angina, the prevalence of obstructive coronary artery disease is relatively low (e.g. <1 in 5 patients, the majority being male [SCOTHEART]) [8], while microvascular and vasospastic angina are more common (e.g. 2 in 5 patients, the majority being female [CorMicA]) [9]. These patients may be correctly diagnosed using functional tests, but cannot be diagnosed with anatomical imaging using CT coronary angiography. For these reasons, a single-test strategy for all comers is not necessarily feasible and a variety of factors will influence the choice of test strategy.

The value of an initial anatomical test using CT coronary angiography followed by functional tests, where appropriate, would be to identify subjects with coronary atherosclerosis and stratify them for preventive medical therapy. A major limitation of a CT-guided approach relates to patients with angina but no obstructive CAD. The prevalence and clinical significance of vasomotor disorders in this setting is being assessed in the Coronary Microvascular Function and CT Coronary Angiography (CorCTCA) trial [10]. For this large subgroup (most of whom are female), a CT-approach necessitates multiple tests (anatomical first, then functional) and clinic attendances [8]. On the other hand, given the ISCHEMIA trial results, there is no rationale for routinely undertaking invasive management following CT coronary angiography, unless left main disease is identified. This is an important outcome since, perhaps surprisingly, coronary imaging non-invasively with CTCA does not reduce referrals for invasive coronary angiography [11]. This is because imaging atherosclerosis by CTCA in symptomatic patients typically lowers the threshold for invasive management. Therefore, a CTCA strategy doubles the number of angiograms and related exposure to ionizing radiation. The results from ISCHEMIA should arrest this trend. In the majority of patients with angina and no obstructive CAD, COVADIS the Coronary Artery Vasomotor Disorders International Summit [12,13] recommends functional testing to assess for inducible ischemia in order to clarify whether or not microvascular angina may be relevant for targeted therapy. In affected patients, if symptoms are not controlled by medical therapy then invasive management should be performed to assess for vasospastic angina or obstructive CAD (false negative CT coronary angiography). In the minority of patients with obstructive CAD identified by CT coronary angiography, the initial management should involve OMT with antianginal drugs and those who do not exhibit satisfactory symptom control should then undergo invasive coronary angiography and revascularization where appropriate.

There is concern that ISCHEMIA will drive angina care away from invasive coronary angiography. Consecutive case coronary angiography registry studies document that most angina patients do not have obstructive CAD. If those patients are driven away from invasive evaluation of coronary arteries, an opportunity is lost for early evaluation of the functional characteristics of the coronary macro and microcirculation during the initial angiography. The health burden of microvascular angina and vasospastic angina, including symptoms, hospitalizations and major cardiovascular events, is comparable to that experienced by patients with obstructive coronary artery disease [14,15], and a proactive approach is warranted for all patients, regardless of the endotype.

While there are not yet evidence-based guidelines for the diagnosis and treatment of vasospastic and microvascular angina, the CorMicA trial demonstrated that adjunctive tests of coronary vascular function with therapy specifically linked to disease endotypes (stratified medicine) reduces angina and improves quality of life by 6 months [8] with these benefits sustained through to one year [16]. Recognition of the beneficial effects of high intensity statin and angiotensin-renin system therapies for coronary endothelial function [17] led the design of the Women's Ischemia Trial to Reduce Events in Non-Obstructive CAD or WARRIOR clinical trial. Currently enrolling subjects, WARRIOR (NCT03417388) is a multicenter, prospective, randomized blinded outcome evaluation. This strategy trial will evaluate the influence of intensive statin and ACEI/ARB therapy (IMT) and usual care (UC) on MACE in symptomatic women with INOCA, over a 3-year follow-up period.

Results from this novel investigation should help formulate evidence-based guidelines, which can be utilized by providers to most optimally treat symptomatic coronary microvascular dysfunction patients.

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