

# World Journal of *Cardiology*

*World J Cardiol* 2021 August 26; 13(8): 237-380



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**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Lin-YuTong Wang; Production Department Director: Xiang Li; Editorial Office Director: Ya-Juan Ma.

**NAME OF JOURNAL**

*World Journal of Cardiology*

**ISSN**

ISSN 1949-8462 (online)

**LAUNCH DATE**

December 31, 2009

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Ramdas G Pai, Dimitrios Tousoulis, Marco Matteo Ciccone

**EDITORIAL BOARD MEMBERS**

<https://www.wjnet.com/1949-8462/editorialboard.htm>

**PUBLICATION DATE**

August 26, 2021

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## ISCHEMIA trial: How to apply the results to clinical practice

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**Author contributions:** Vidal-Perez R contributed to conception and design of the editorial and edited and wrote the paper; Bouzas-Mosquera A, Peteiro J, and Vazquez-Rodriguez JM contributed to the critical revision and editing of the paper.

**Conflict-of-interest statement:** The authors declare that there are no conflicts of interest.

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**Manuscript source:** Invited manuscript

**Specialty type:** Cardiac and

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### Abstract

During the last years two questions have been continuously asked in chronic coronary syndromes: (1) Do revascularization procedures (coronary artery bypass grafting or percutaneous coronary intervention) really improve symptoms of angina? and (2) Do these techniques improve outcomes, *i.e.* do they prevent new myocardial infarction events and cardiovascular death? Therefore, there was a need for a large definitive trial. This study was the ISCHEMIA trial, a large, multicentric trial sponsored by the National Heart, Lung, and Blood Institute. The main trial compared coronary revascularization and optimal medical treatment (OMT) *vs* OMT alone in 5179 patients enrolled after a stress test. During a median 3.2-year follow-up, 318 primary outcome events occurred; the adjusted hazard ratio for the invasive strategy as compared with the conservative strategy was 0.93 (95% confidence interval 0.80-1.08,  $P = 0.34$ ). The ISCHEMIA trial deeply disrupted many of our prior attitudes regarding management strategies for patients with stable coronary artery disease. The findings underscore the benefits of disease-modifying OMT for stable coronary artery disease patients. The main purposes of ischemia assessment before this trial were: Diagnostic purposes, assessment of outcome, and adding to decision-making processes. Obviously, this changed after the trial results. The results of ISCHEMIA might challenge the current diagnostic approach for stable angina patients recommended in the last European Society of Cardiology guidelines on chronic coronary disease that were based on studies published before the ISCHEMIA trial. In this editorial we propose our approach based on the ISCHEMIA study and the pretest probability for a positive test in patients with chronic coronary syndromes.

**Key Words:** Stable angina; Chronic coronary syndrome; ISCHEMIA; Stress testing; Therapy; Diagnosis

cardiovascular systems

**Country/Territory of origin:** Spain**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
 Grade B (Very good): B  
 Grade C (Good): C  
 Grade D (Fair): 0  
 Grade E (Poor): 0

**Received:** April 15, 2021**Peer-review started:** April 15, 2021**First decision:** May 13, 2021**Revised:** May 27, 2021**Accepted:** July 9, 2021**Article in press:** July 9, 2021**Published online:** August 26, 2021**P-Reviewer:** Kharlamov AN, Ueda H**S-Editor:** Ma YJ**L-Editor:** Filipodia**P-Editor:** Li X

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**Core Tip:** During the last years two questions have been continuously asked in chronic coronary syndromes: Do revascularization procedures (coronary artery bypass grafting or percutaneous coronary intervention) really improve symptoms of angina? Do these techniques improve outcomes, *i.e.* do they prevent new myocardial infarction events and cardiovascular death? The results of ISCHEMIA might challenge the current diagnostic approach for stable angina patients recommended in the last European Society of Cardiology guidelines on chronic coronary disease that were based on studies published before the ISCHEMIA trial. In this editorial we propose our approach based on the ISCHEMIA study and the pretest probability for a positive test in patients with chronic coronary syndromes.

**Citation:** Vidal-Perez R, Bouzas-Mosquera A, Peteiro J, Vazquez-Rodriguez JM. ISCHEMIA trial: How to apply the results to clinical practice. *World J Cardiol* 2021; 13(8): 237-242

**URL:** <https://www.wjgnet.com/1949-8462/full/v13/i8/237.htm>

**DOI:** <https://dx.doi.org/10.4330/wjc.v13.i8.237>

## INTRODUCTION

Since the first definition of angina by the English physician William Heberden in 1772 [1] many aspects have been discussed about this entity. Heberden described with a lot of detail a symptom, but he did not comprehend the disease. Later, in 1793, Edward Jenner detected thickened coronary arteries at an autopsy of his colleague John Hunter after sudden cardiac death due to an angina attack [2]. It took decades to get a first treatment (amyl nitrite) [3] for angina pectoris, and it was an even greater time for a valid understanding of the underlying disorder.

In 1967, Favaloro [4] used a saphenous vein and sewed it to the narrowing diseased coronary artery, making this the first coronary artery bypass grafting (CABG). Certainly, CABG showed a marked improvement of symptoms in patients with coronary artery disease (CAD). In 1979, Andreas Grüntzig performed the first percutaneous transluminal coronary angioplasty [5]; later this technique has been known as percutaneous coronary intervention (PCI) with the use of stents.

During the last years two questions have been continuously asked: (1) Do revascularization procedures (CABG or PCI) really improve symptoms of angina? and (2) Do these techniques improve outcomes, *i.e.* do they prevent new myocardial infarction events and cardiovascular death?

The initial enthusiasm for PCI was diminished after COURAGE trial [6], which showed no benefit of revascularization over optimal medical treatment (OMT). Nevertheless, the study was criticized due to a small proportion of the recruited patients treated in the participating centers and the use of bare metal stents. Then came the ORBITA trial [7] comparing OMT with PCI, this time using drug-eluting stents in a sham-controlled design, and the final result again was neutral. Once more, the same criticisms about small sample size were raised, and while symptoms and exercise tolerance only showed a tendency, regional wall motion was improved substantially in the stress echocardiograms [8].

Therefore, because of this uncertainty, there was a need for a large definitive trial. This study was the ISCHEMIA trial, which was presented at the American Heart Association Scientific Sessions in November 2019, and some months later it was published in the New England Journal of Medicine [9].

## ISCHEMIA TRIAL

ISCHEMIA trial is a large, multicentric trial sponsored by the National Heart, Lung, and Blood Institute. The main trial compared coronary revascularization and OMT *vs* OMT alone in 5179 patients enrolled after a stress test [9]. Related to this trial was the ISCHEMIA-CKD in patients with chronic kidney disease (CKD), which had a similar design to the ISCHEMIA trial except that the use of a computed tomography (CT) scan

was not necessary[10], and the CIAO-ISCHEMIA (Changes in Ischaemia and Angina over One year), which was a registry of patients excluded from the ISCHEMIA trial because of a negative CT scan. These latter patients represented around 14% of those initially considered for the ISCHEMIA trial and ultimately considered as ischemia with normal coronary arteries (INOCA)[11]. Moreover there was a quality of life study in the main ISCHEMIA trial, which included 4617 patients[12] that brought interesting results.

The rationale of the trial was clearly stated by the authors in the study abstract, “among patients with stable coronary disease and moderate or severe ischemia, whether clinical outcomes are better in those who receive an invasive intervention plus medical therapy than in those who receive medical therapy alone is uncertain”[9].

One key element of the trial was the performance of a blinded coronary computed tomography angiography (CCTA) prior to enrolment to exclude the presence of left main CAD and the absence of obstructive CAD.

We could consider this trial as the largest comparative effectiveness trial of an invasive *vs* conservative strategy in patients with stable coronary disease. It is important to highlight a recent terminology change; these stable patients are now known as patients with chronic coronary syndromes due to a new definition of the European Society of Cardiology[13].

The ISCHEMIA study has tried to address the key limitations of previous trials, namely: Recruiting high-risk patients with at least moderate inducible ischemia at baseline, randomizing patients prior to the diagnostic coronary angiogram to reduce both selection and referral bias, incorporating the current state-of-the-art revascularization techniques that include the fractional flow reserve-guided PCI and the last generation drug-eluting stents at high-volume interventional sites who were selected for their proficiency and skill in revascularization, and employing an algorithm-based OMT and guidance for intensifying therapies in both arms of the trial.

The primary outcome of the trial was a five-component composite endpoint comprising cardiovascular death, non-fatal myocardial infarction (MI), hospitalization for unstable angina, hospitalization for heart failure, and resuscitated cardiac arrest, whereas the major secondary endpoints were time to cardiovascular death or non-fatal MI, anginal symptoms, and quality of life.

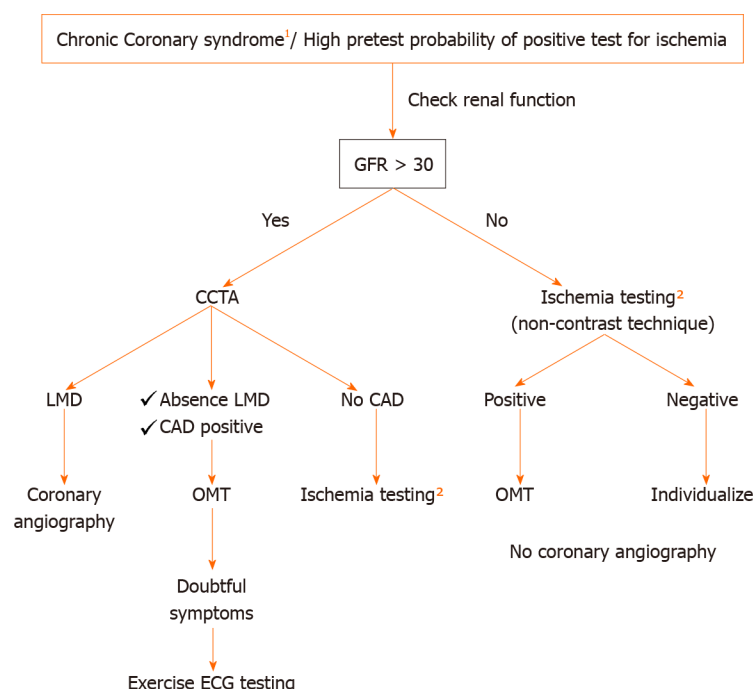
During a median 3.2-year follow-up, 318 primary outcome events occurred; the adjusted hazard ratio (HR) for the invasive strategy as compared with the conservative strategy was 0.93 [95% confidence interval (CI) 0.80-1.08,  $P = 0.34$ ]. There was no heterogeneity of treatment effect based on a broad range of pre-specified subgroups, including the presence of diabetes mellitus, high rate of OMT attainment, new or more frequent angina, degree of baseline ischemia, CAD severity based on 50% stenosis (*i.e.* one, two, or three vessel disease) or the presence of proximal left anterior descending coronary stenosis > 50%.

There was no significant difference in total death for the invasive strategy ( $n = 145$ ) group *vs* the conservative strategy ( $n = 144$ ) group (HR = 1.05, 95%CI: 0.83-1.32) or in cardiovascular death (HR = 0.87, 95%CI: 0.66-1.15). There was also no significant difference in the rate of overall MI between the two treatment strategies (adjusted HR = 0.92, 95%CI: 0.76-1.11), although there were more procedural infarctions in the invasive strategy arm in early follow-up and more spontaneous myocardial infarctions in the conservative strategy arm in the late follow-up period[9].

There were significant and lasting improvements in angina control and quality of life metrics with an invasive approach in those patients who had significant angina [consider as daily/weekly (20% of ISCHEMIA patients)], but more modest improvements in patients with monthly angina (44%), while there was no improvement in patients with less frequent or no angina (35%)[12].

In the companion ISCHEMIA trial study (ISCHEMIA-CKD) of patients with CKD (defined as estimated glomerular filtration rate < 30 mL/min/body surface area)[10], with the same entry criteria and randomized treatment strategies, there was similarly no significant difference in outcome results between invasive *vs* conservative arms for the primary or secondary endpoints, however the invasive arm was associated with a higher incidence of stroke than the conservative arm (HR = 3.76, 95%CI: 1.52-9.32,  $P = 0.004$ ) and higher incidence of death or initiation of dialysis (HR = 1.48, 95%CI: 1.04-2.11,  $P = 0.03$ ). There were no significant or sustained benefits in relation with angina-related health status between the two arms.





**Figure 1 Algorithm for chronic coronary syndrome with high pretest probability of positive test for ischemia.** <sup>1</sup>Previously known as stable angina. <sup>2</sup>Stress echocardiography (non-contrast technique), single photon emission computed tomography (non-contrast technique), or magnetic resonance imaging (contrast technique). CAD: Coronary artery disease; CCTA: Coronary computed tomography angiography; GFR: Estimated Glomerular filtration rate (mL/min/1.73 m<sup>2</sup>); LMD: Left main disease; OMT: Optimal medical therapy.

## HOW TO APPLY THE RESULTS TO CLINICAL PRACTICE

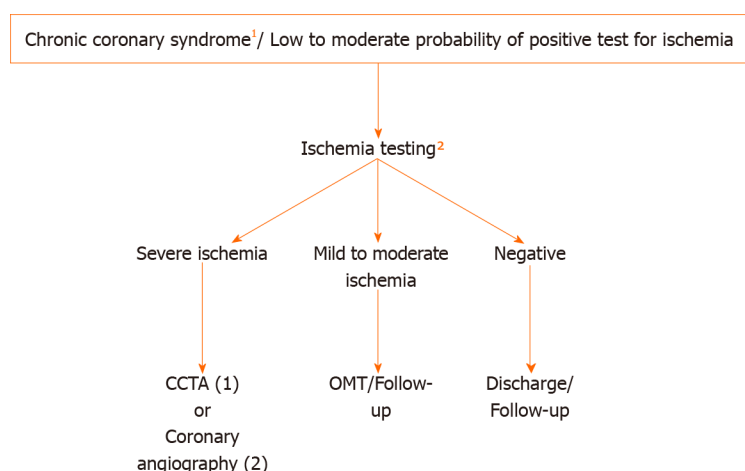
The ISCHEMIA trial deeply disrupts many of our prior attitudes regarding management strategies for patients with stable CAD. The findings underscore the benefits of disease-modifying OMT for stable CAD patients, and this must be our most important focus. While revascularization will always have a crucial role in symptom relief and improving quality of life, our primary goal should be to reduce incident cardiovascular events by utilizing proven therapies that stabilize vulnerable coronary plaques and improve event-free survival.

The main purposes of ischemia assessment before this trial were: Diagnostic purposes, assessment of outcome, and adding to the decision-making processes. Obviously, this has changed after the trial results.

The results of this study cannot be applied to patients with a known higher risk, such as those with very severe symptoms, left ventricular dysfunction (left ventricular ejection fraction < 35%), or left main disease, since these patients were excluded from the ISCHEMIA study. The authors of the study point out, however, that the selection was near to our daily practice patients; more than half of those included were patients with severe ischemia, and also almost half of them had multivessel disease and/or CAD that included the proximal left anterior descending artery, in whom before we went to invasive management without even considering another option.

The results of ISCHEMIA and ISCHEMIA CKD might challenge the current diagnostic approach for stable angina patients recommended in the last European Society of Cardiology guidelines on chronic coronary disease[13] that were based on studies published before the ISCHEMIA trial. In the next two figures we propose our approach based on the ISCHEMIA study and the pretest probability for a positive test in patients with chronic coronary syndromes. Figure 1 shows our approach for high pretest probability patients where renal function needs to be known in advance, and Figure 2 can be applied for the low to moderate pretest probability patients. It should be pointed out that starting the work-out diagnosis by CCTA in every patient would miss a considerable number of patients with INOCA according to the combined ISCHEMIA and CIAO results (data not yet published)[11]. In addition, an initial CCTA approach would significantly increase the number of further functional tests due to unconvulsive/positive CCTAs and spurious revascularizations[14]. Another important remark for a better comprehension of our approach is that according to the ISCHEMIA-CKD results, starting ischemia testing and trying to avoid coronary intervention seems desirable for patients with kidney dysfunction.





(1) Exclude LMD as main goal

(2) Perform revascularization as main goal

**Figure 2 Algorithm for chronic coronary syndrome with low to moderate pretest probability of positive test for ischemia.** <sup>1</sup>Previously known as stable angina. <sup>2</sup>Stress echocardiography [any glomerular filtration rate (GFR) (mL/min/1.73 m<sup>2</sup>)], single photon emission computed tomography (any GFR), or magnetic resonance imaging (only if GFR > 30). CCTA: Coronary computed tomography angiography; LMD: Left main disease; OMT: Optimal medical therapy.

## CONCLUSION

To summarize our view on stable coronary disease patients after the ISCHEMIA trial, the assessment of ischemia loses priority in this scenario, symptoms evaluation gains importance, and ischemia (and not anatomy) should be the focus in certain entities like CKD or INOCA[15].

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