# Chronic Coronary Syndrome: What to Expect from Investigation and Management After ISCHEMIA?

***Síndrome Coronariana Crônica: O que Esperar da Investigação e da Conduta após o ISCHEMIA?***

*Lucas Cronemberger Maia Mendes[1], Rafael Willain Lopes[2], Rodrigo Julio Cerci[3], Simone Cristina Soares Brandão[4]*

*[1]Hospital do Coração do Brasil / Rede D´Or - Brasília - DF Instituto Hospital de Base - Brasília – DF. [2]Hospital do Coração - HCOR, São Paulo-SP. [3]Quanta Diagnóstico por Imagem, Curitiba PR. [4]Hospital das Clínicas da Universidade Federal de Pernambuco, Recife, PE e Clínica Diagson, João Pessoa, PB.*

Several clinical trials have questioned the best approach in Chronic Coronary Syndrome (CCS). Perhaps the greatest example was the COURAGE (Optimal Medical Therapy with or without PCI for Stable Coronary Disease) study in stable patients with obstructive coronary disease documented by invasive angiography, in which optimized clinical treatment (OCT) associated with percutaneous coronary intervention (PCI) were not better than OCT alone.[1] In the same direction, the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) was presented at the American Heart Association Congress in November 2019, and has not been published yet. It was conducted on a higher risk CCS patient profile compared to COURAGE, an obstructive coronary disease and at least moderate ischemia. In the study, the comparison of OCT alone and OCT associated with coronary revascularization showed no differences in terms of major cardiovascular outcomes[2] suggesting that in CCS, investing in cardiometabolic profile improvement seems to be the treatment key point.

The focus of this editorial was to discuss the design and results presented by ISCHEMIA so far, contributing to the debate. First of all, it is necessary to remember the importance of of the accumulated knowledge, which supports guidelines and should not be ignored. Considering a patient with chronic chest pain or an equivalent condition, the traditional clinical rational has taught us for many years that we should first consider coronary artery disease (CAD) diagnosis and risk stratification before defining management. Investigation can be initiated by identifying epicardial coronary atherosclerosis (and, for moderate to severe lesions, functional methods can be used to determine whether these symptoms are actually due to the obstructions detected); or by initially investigating the presence of significant myocardial ischemia, and then determining whether there is obstructive CAD or not and, if positive, its location, atherosclerotic burden and severity. Both information are useful and support clinical rational. Based on the pretest probability of CAD, the recently CCS guideline released at the European Cardiology Congress of 2019 defined the best strategy for the initial assessment in each case — whether anatomy or ischemia.[3]

Noninvasive diagnosis of coronary atherosclerosis has improved in the past 10 years, facilitated by the great accuracy of coronary computed tomography angiography (CCTA) compared to invasive angiography. Considering its great negative predictive value, ruling out obstructive CAD has become simple and safe. Besides, the detection of mild nonobstructive atherosclerosis has shown to impact drug treatment optimization, as shown at the SCOT-HEART study.[4] Coronary stenosis between 50% and 90%, on other hand, do not necessarily have functional repercussion.[3] In addition, the problem may not only be restricted to the epicardial arteries, but also includes the large myocardial capillary bed. Often, microcirculation has been shown to be even more important than epicardial atherosclerosis to justify ischemic symptoms, because, despite the presence of significant obstructions in the epicardial arteries, a healthy microcirculation could handle the myocardium demand, and the opposite is not possible.[5]

Before examining the findings of the study, it is essential to point out that the intention of ISCHEMIA was not to investigate the best initial diagnostic strategy for CCS, whether functional methods or CCTA. This specific question has been addressed in other clinical trials in patients without known CAD and with another risk profile.[4,6] ISCHEMIA was designed to answer the following question: in the setting of a CCS patient with at least moderate myocardial ischemia and significant coronary obstruction (≥50% luminal obstruction), both documented, is there really any benefit in adding invasive angiography and coronary revascularization when possible, to current OCT? [7]

That was a randomized "non-blinded" study involving 320 centers and 37 countries around the world. It included 5,179 patients with the initial assumption that there was moderate to severe ischemia identified by a functional examination (using myocardial perfusion scintigraphy, stress echocardiography, exercise treadmill testing or cardiac magnetic resonance imaging), after which a CCTA was performed to exclude patients with non-significant epicardial obstructive lesions (<50% luminal obstruction) or severe left main coronary artery disease. Patients with this inclusion profile were divided into two groups: "conservative", treated with OCT alone; and "invasive," which in addition to OCT according to current guidelines, would be submitted to an intended complete coronary revascularization with PCI or surgery, with on-site specialist decision for each case.[7,8]

Of the included patients, 90% reported angina; 75% of

## Keywords

Coronary Artery Disease; Clinical Trial; Therapeutics.

**Mailing Address: Lucas Cronemberger Maia Mendes •**
SHLS 716 Bloco F Lote 6 - Asa Sul, Brasília - DF, 70390-700
E-mail: lucascmm@yahoo.com.br

**DOI:** 10.5935/2318-8219.20200004

them were submitted to functional imaging exams and 25% to exercise treadmill testing only. In case of less than 60 mL/min creatinine clearance, CCTA was not performed to avoid contrast nephropathy, but most patients (73%) were able to do it. The groups were analyzed by intention-to-treat, with median follow-up of 3.3 years, more than 99% followed-up, and the chosen primary outcome was cardiovascular death, acute myocardial infarction (AMI), hospitalization for unstable angina or heart failure and resuscitated cardiac arrest.[2,7,8]

Still regarding the inclusion criteria in the ISCHEMIA study, patients were 21 years-old or older; moderate to severe ischemia was defined as ischemic burden greater than 10% on myocardial perfusion scintigraphy; stress echocardiogram showing at least three segments with moderate to severe hypocontractility or akinesia during the stress phase; ≥12% or ≥3 segments with severe hypocontractility or akinesia on cardiac magnetic resonance imaging; and exercise treadmill stress test demonstrating ST-segment depression on exertion ≥1.5 mm in ≥2 leads, or ≥2.0 mm in a single lead, in a low load (<7 METs), and angina. In addition to the rigorous and clear exercise test definitions, these patients needed to have a more severe lesion on CCTA (>70% luminal obstruction) to be included in order to avoid false positives as much as possible. The inclusion of exercise treadmill testing was important to bring the study closer to the reality of several places that still does not have access to more sophisticated imaging methods. [7,8]

The ISCHEMIA exclusion criteria were: NYHA functional class III–IV; unacceptable angina despite OCT; left ventricular ejection fraction (LVEF) ≤35%; acute coronary syndrome (ACS) in the last 2 months; PCI or coronary artery bypass grafting (CABG) in the last 12 months. Patients with glomerular filtration rate <30 mL/min or on dialysis were reallocated to an ancillary study (ISCHEMIA CKD); and those with ischemia detected on functional examination without significant lesions on CCTA were referred for the CIAO-ISCHEMIA study. [7,8]

It was difficult to recruit patients for the study, and the lower than expected rate of hard endpoints would decrease the statistical power to less than 60%. This led to modifications suggested by an independent panel in May 2017. The following were approved: expansion of primary outcome, initially death and AMI only; sample size reducing from 8,000 patients to about 5,000 randomized patients, and extension of follow-up. This produced a statistical power of >80% to detect a relative reduction of 18.5% in primary outcome in favor of the invasive group.[7] It is important to note that the primary outcome changing was pre-specified in the original protocol description and, therefore, did not compromise the results analysis. In another fact that may raise questions, 23% of the patients in the group initially proposed for OCT alone required coronary intervention throughout follow-up.[2] From a statistical point of view, there is no concern with this crossover, since the "intention-to-treat" analysis objective is to compare the initial strategies, and thus avoid multiple biases.

Baseline characteristics were very similar in the two study groups ("conservative" and "invasive"). It is remarkable the small proportion of women, only 23% of patients, and the high prevalence of hypertension (73%) and diabetes (42%); 33% had moderate ischemia, and 54% had severe ischemia; almost half of the patients included were triple vessel disease, with 87% affecting the anterior descending coronary artery (about 47% located at the proximal third).[2] This is, therefore, a population of greater severity than previous clinical trials.

Another interesting point was the management of risk factors: at the end of the described follow-up, despite all the rigor of a controlled study, 34% were not on high potency statins; 30% did not use angiotensin converting enzyme inhibitors (ACEI); 41% did not reach the established LDL cholesterol target <70 mg/dL; 3% did not use aspirin or a substitute; and, most impressive, 59% did not meet criteria for "high-level OCT," defined by the achievement of all established clinical goals.[2] This shows how difficult it is to put the OCT into practice.

Functional imaging exams were performed at the beginning of the study, in a phase in which when only 20% of the patients were optimized for therapeutic goals for stable angina.[2] It would be interesting to obtain data from the same exams after initiation of treatment (whether the "conservative" group or the "invasive" group) to assess if there was a significant reduction in stress-induced ischemia and, moreover, if patients who attended this improvement had less outcomes than those who did not, as observed in the COURAGE nuclear substudy.[9] This analysis may never be possible, as imaging stress testing for CCS monitoring was discouraged in the description of ISCHEMIA.[8]

About the reported results, there was no statistically significant difference in the primary outcome between the groups during an average follow-up of 3.3 years: 15.5% in the "conservative" group and 13.3% in the "invasive" group (HR 0.93 — 0.80 to 1.08; p=NS). The same was true for secondary outcomes, which included separated assessment of each of the primary outcome components, and the addition of stroke in some scenarios. Both the curves of primary outcome and those of certain secondary outcomes intersect around the two-year follow-up, and there is a supposed propensity for more outcomes in the OCT-only group.[2] The secondary outcome in which a difference was found was related to angina control and quality of life, improved in the invasive strategy group significantly and longstanding.[10] Another curious observation is that when analyzing "spontaneous AMI" only, a significant difference was found, being smaller in the invasive group (HR = 0.67; 0.53 to 0.83; p<0.01). Nonetheless, perioperative infarction episodes also happen in the real world and must be taken into account. When these were included in the subanalysis (obviously larger in the invasive treatment group), the AMI outcome was the same in both groups.[2]

Thus, so far, the main message of the ISCHEMIA study is that in patients with CCS and moderate to severe ischemia, generally speaking, adding coronary revascularization to OCT was not better than OCT alone, in terms of major cardiovascular outcomes (death, AMI, hospitalization for angina or heart failure, and resuscitated cardiac arrest), and any other conclusions are speculative.[2] It is not known whether the effect of coronary revascularization may become important in a longer-term follow-up, as observed in coronary heart disease patients with reduced LVEF from the STICH

study.[11] In the ISCHEMIA protocol, follow-up time was pre-specified, the consent term included the possibility of contact for up to 20 years, and more data may be available in the future.[8]

Some final messages about the initial presentation of the ISCHEMIA study findings:

1. It was designed to confront different treatment strategies in CCS;

2. It does not only reinforce but amplify COURAGE's concept of adding value to OCT: even in patients with moderate to severe ischemia, OCT can be as powerful as the interventions, and should more often be considered as an initial option for these patients too, and not just for those with little or no ischemia;

3. Learning about the functional consequence was the starting point in the study to establish a causal relationship between symptoms and the obstructive coronary lesions later seen or not on CCTA (14% had no obstructive disease greater than 50%);

4. The coronary anatomy knowledge of patients with suspected CCS was not questioned: the presence, location of the lesions and their degree of obstruction remain as relevant information, noting that 5% of the patients were excluded from the study due to the presence of significant left main coronary artery disease;

5. The study results do not apply to patients with acute coronary syndrome;

6. The study results do not apply to patients with CCS, ischemia and LVEF <35%, or with NYHA III–IV;

7. The study results do not apply to patients with CCS, ischemia and epicardial coronary lesion <50% or with significant left main coronary artery disease;

8. The study results do not apply to patients with CCS, ischemia and limiting symptoms despite OCT;

9. It is likely to impact future guidelines, decreasing the grade of recommendation of invasive treatment in certain CCS scenarios, such as, no longer suggesting coronary revascularization solely based on information on the degree of ischemia;

10. The best approach for patients with suspected chronic coronary syndrome is bring the patient to the center of the decision, providing as many information as possible — clinical, functional and anatomical data — and then decide the best management.

## Conflict of interest

The authors declare that there is no conflict of interest regarding this manuscript.

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