Comment on: Initial Invasive or Conservative Strategy for Stable Coronary Disease (ISCHEMIA) clinical trial

Comentário para: *Initial Invasive or Conservative Strategy for Stable Coronary Disease (ISCHEMIA)*

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Much has been researched on the treatment of chronic coronary artery disease (CAD).¹⁻³ The ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches)⁴ trial had been long awaited, in the hope that it would answer many remaining questions. Our purpose is to prepare a critical analysis of this document, analyzing its methodology, its results and how it may impact the cardiologist's clinical practice.

Initially, when examining the methodology, a difference is noted between what was planned regarding sample size and what was actually accomplished. The sample size was initially calculated to detect an 18% difference in the event rate, when comparing the Invasive Strategy (INV Group) and the Conservative (CON Group) groups over a 4-year period, assuming an event rate of 20% in the second group. In other words, with an event rate of 16.4% in the INV Group, considering a test power of 90% and an alpha error of 0.05, approximately 2,500 patients would be required in each group.

However, based on a data analysis performed in 2018, the rate of events was lower than previously estimated, and the researchers were forced to recalculate the sample size to achieve an 18.5% difference when comparing the CON and INV Groups, considering an aggregate event rate of 14% over a 4-year period in the CON Group, with a test power of 83% and a significance level of 0.05. Redoing these calculations in the R statistical software package, for the desired test power of the study, a total of 2,784 patients would be required in each group, totaling more than 5,500 patients. Furthermore, for the difference actually detected between the groups, i.e. 10%, the number of patients required for each group would be 7,500 patients, totaling 15,000.

With this simple calculation, it is easy to conclude that the study did not have the statistical power for which it was proposed, since it presumed something that actually did not occur.

The analysis of the differences between the two groups was estimated using Cox's proportional regression model. However, the statistical premises of this model were violated for the primary purpose of the study (due to treatment-time interaction, according to the researchers). The statistical analysis plan had specified that the presentation of the results would emphasize non-parametric estimates for cumulative event rate if the assumption of proportional risks were violated, and this actually happened. There were further problems in the study methodology, rendering it extremely complex to be analyzed.

Examining the study results, it immediately stands out that 26% of patients in the CON Group underwent coronary angiography, and 21% of patients were revascularized. This means 544 patients out of 2,591, which is not a small number, and although these patients have undergone some type of revascularization, they were analyzed as if they were in the CON Group. Furthermore, the researchers reported that, in the INV Group, a total of 5,337 revascularization procedures were performed (including repeated

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procedures), and 1,506 procedures were performed in the CON Group. In the CON Group, in which no type of revascularization should have been performed, several procedures were conducted, amounting to 30% of the number of revascularizations performed in the INV Group. In other words, this was certainly not a conservative treatment group!

Another important data, mentioned by the researchers, concerns the definition of acute myocardial infarction (MI) used. When considering periprocedural MI, the INV Group obviously presented with higher rates. However, when considering spontaneous MI, the incidence rate in the CON Group was greater than in the INV Group. It is noteworthy that these spontaneous infarctions carry greater mortality risk than periprocedural acute MI.^{5,6}

In the Discussion, the authors commented:

The results of ISCHEMIA should be interpreted in the context of certain limitations. Power was decreased by reducing the sample size from 8000 to 5179 patients, event rates were lower than expected, and the period of follow-up was modest. With a 3.2-year median follow-up, event-rate estimates past the median are subject to progressively greater uncertainty.

Following the limitations, the authors themselves affirm that such findings do not apply to patients with left main coronary artery lesion, low ejection fraction, class III or IV heart failure, and symptomatic patients despite the use of medications. This latter limitation is relatively common to find, either because patients do not fully adhere to the appropriate medication regimen, or because they really have angina, even with the use of correct medication.

The core lab found that 14% of the cases had not enough ischemia to enter the study. Although this did not change the results, it is noteworthy that the criteria for considering a patient as having severe ischemia varied greatly in the study, and even the treadmill test was accepted.

Regarding quality of life and the angina score,⁷ two important observations: the first is that 35% of patients with severe ischemia had no symptoms at the beginning of the study. This draws attention, because treating a patient with no symptoms is uncertain, especially in terms of invasive treatment. The second observation is that the study used the Seattle Angina Questionnaire⁸ to assess the severity of angina, finding the more severe the angina before treatment, the greater the benefit of the invasive strategy. In other words, invasive treatment is clearly superior to conservative treatment in terms of angina relief. Despite this being a secondary outcome in almost all studies, we cannot help but wonder: if we had chest pain and could treat it with a procedure that would bring us greater short-term relief, or otherwise had to keep taking a large amount of medication for an unknown period of time, which option would we choose? Almost certainly we would choose the treatment providing faster relief, which is exactly the option most of our patients and colleagues choose.

The ISCHEMIA trial is undoubtedly an important milestone in the research on the best treatment for stable

CAD. However, it is far from bringing forth any conclusions on the subject. Stating there were no differences between invasive treatment and conservative treatment, without pointing out the major limitations of the study, from its sample size and statistical analysis, to the final results, the type of population analyzed, the number of patients who crossed over from one group to the other, and finally the secondary objectives of the study – secondary, albeit not unimportant, such as severity of angina and quality of life – would be misleading to readers. In the discussion of the study, the authors failed to make clear many of these limitations.

We do not believe this study will impactfully change the way we treat stable CAD. It is of common knowledge that drug therapy is the main treatment regimen, and its use is indisputable. However, underestimating the value of interventional treatment on the grounds that it brings no benefit in terms of adverse events would be profoundly unjustified, especially when guided by the detection (invasive or not) of coronary ischemia.

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