To the Editor,

We have read with great interest the results of the ISCHEMIA trial\(^1\) of 5179 patients with moderate or severe ischemia who were randomized to receive an early invasive strategy of angiography plus revascularization, when necessary, or a conservative strategy of early optimal medical therapy and angiography if the medical therapy failed. As already known, the conclusion is that an early invasive strategy does not reduce the risk of cardiovascular ischemic events or all-cause mortality at the follow-up. However, it had beneficial effects because it reduced the occurrence of myocardial infarction at the expense of a number of peri-PCI myocardial infarctions. Currently, this observation is under discussion probably because a different result was expected by researchers.

In an interesting article\(^2\) it has been argued that the ISCHEMIA trial did not compare the benefits of coronary revascularization vs medical therapy, but assessed an early strategy of medical therapy vs early invasive treatment with angiography. In this sense, 79.4% of the patients from the invasive group were percutaneous or surgically revascularized vs 21.0% of the patients from the conservative group. A careful review of the supplementary data of the original publication\(^1\) reveals interesting additional data that we wish to share. A total of 667 patients from the early conservative group were referred to undergo a coronary angiography at the follow-up for different reasons including failed medical therapy unable to control the angina (15%) or the appearance of a confirmed adverse event (unstable angina, myocardial infarction, heart failure or reversed cardiac arrest) in 27%. Therefore, in a significant percentage of these patients (\(n = 387, 14.9\%\) of the overall conservative group) the decision to request the angiography was based on criteria different from the aforementioned including adverse events categorized as «unconfirmed» (\(n = 177\)) or less obvious reasons like «noncompliance» to the medication or «other reasons» (\(n = 210\)). In other words, overall, in 58% of the patients initially randomized to conservative treatment later referred to undergo an angiography there was not refractory angina or confirmation of the appearance of adverse events that justified such a decision. These patients underwent 477 PCIs, 198 surgical revascularizations and 955 were referred to the cath lab.\(^1\)

A second relevant aspect here is follow-up, which is unusually strange regarding clinical trials. Authors say that the median follow-up was 3.2 years, but interquartile range was 2.1/2.2 years to 4.3 years. This peculiarity of the study, associated with low recruitment rate in most centers,\(^3\) elevates significantly the degree of uncertainty on the comparative analysis of the benefits derived from the 2 strategies and runs parallel to the higher percentage of patients who were censored, that is, as the comparison is conducted beyond the median. However, the article includes comparative data between the different strategies of treatment at the 5-year follow-up when the percentage of individuals «censored» or «not at risk» at that time is already > 75%. Therefore, it is incomprehensible that a more homogeneous follow-up was not available, despite reaching the number of events anticipated, to conduct a more consistent analysis due to the clinical implications of such a relevant trial.

Finally, we wish to emphasize that the population included in the ISCHEMIA trial\(^1\) was a highly selected one as the strict inclusion and exclusion criteria suggest and the fact that only 5179 out of 8518 patients (61% of those potentially recruitable) were included. On this regard, out of the 5 criteria specifically established by the Guidelines on Myocardial Revascularization of the European Society of Cardiology\(^4\) to improve prognosis in this context, only 2 improve prognosis in this context (left main coronary artery disease > 50% and left ventricular systolic function < 35%) and they became exclusion criteria. The pressure guidewire (also considered by the guidelines as a tool to detect patients who may benefit from revascularization) was used in 481 patients only (20.3%). We should remember that the exclusion of patients with chronic kidney disease and an estimated renal clearance rate < 30 mL/min/1.73 m\(^2\), also categorized as patients of «very high cardiovascular risks» by the Clinical Practice Guidelines of the European Society of Cardiology,\(^5\) may have limited the potential prognostic benefit of the early invasive strategy and the corresponding revascularization.

We conclude that, in light of the controversial methodological aspects mentioned above and some others,\(^6\) maybe the practical implications of the ISCHEMIA trial should be «limited» to some selected patients (without serious left ventricular dysfunction or end-stage renal disease) with chronic coronary syndrome and...
moderate ischemia, and only after left main coronary artery disease has been discarded, in whom the early optimal medical therapy may have a chance. If the patient «prefers» greater symptom relief or wishes to take less medication, the invasive strategy can still be the favorite option.

REFERENCES


