

# ISCHEMIA trial: a win for the optimal medical therapy in the management of stable coronary artery disease?



## *Estudio ISCHEMIA: ¿una victoria del tratamiento conservador en la enfermedad coronaria estable?*

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### To the Editor,

We have read with great interest the results of the ISCHEMIA trial<sup>1</sup> 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 spontaneous 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<sup>2</sup> 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<sup>1</sup> 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.<sup>1</sup>

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,<sup>2</sup> 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<sup>1</sup> 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<sup>3</sup> 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<sup>2</sup>, also categorized as patients of «very high cardiovascular risk» by the Clinical Practice Guidelines of the European Society of Cardiology,<sup>4</sup> 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,<sup>2</sup> maybe the practical implications of the ISCHEMIA trial<sup>1</sup> should be «limited» to some selected patients (without serious left ventricular dysfunction or end-stage renal disease) with chronic coronary syndrome and

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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.

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# Temporal relation between invasively managed acute coronary syndromes and confinement during the current COVID-19 pandemic



## *Relación temporal entre ingresos por síndrome coronario agudo con tratamiento invasivo y confinamiento durante la pandemia de COVID-19*

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### To the Editor,

The infection caused by the SARS-CoV-2 virus (COVID-19) has impacted significantly the management of other conditions. In particular, the data from surveys conducted in coronary<sup>1</sup> and interventional cardiology units<sup>2</sup> show fewer admissions due to myocardial infarctions and coronary interventions, respectively.

Although these are observational and retrospective data that cannot be used to establish causal relations, they are valuable information, actually they may be the only information available to this day. Different hypotheses have been proposed to explain this 40% to 50% drop in the number of acute coronary syndromes (ACS) managed at the hospital setting. The first hypothesis is that a true reduction of new cases of ACS (health epidemic) would have been due to the population physical rest and reduction of air pollution.<sup>3</sup> The second one is that it was due to the patients' lower attendance rate on fears of acquiring COVID-19 in the hospital setting and to avoid saturating health services. The third hypothesis is that it was due to the worse quality of care of the healthcare system due to saturated ERs and diagnostic biases from ACS towards COVID-19.

We conducted a study to analyze the impact of SARS-CoV-2 on the new cases of ACS that were managed invasively. Our interventional cardiology database included prospective data until hospital

discharge and covered an area of approximately 1 million people (*Hospital Príncipe de Asturias, Hospital Severo Ochoa, Hospital de Fuenlabrada, and Hospital Clínico San Carlos de Madrid*). The data provided here go from March 1 until April 30, 2020 and include a total of 118 patients with ACS and cardiac arrest who underwent a coronary angiography. **Table 1** shows the clinical characteristics (similar) and angiographic findings (fewer culprit lesions in the group of COVID-19 positive patients).

In the first place, the new cases of ACS were examined in patients in whom a coronary angiography was performed, this number was compared to the same period from 2019, and a significant 40.4% reduction was seen (chi-square goodness of fit test,  $P < .001$ ) in the new diagnoses of ACS (**figure 1**). These data are similar to the ones obtained in the national surveys conducted in Spain and Italy.<sup>1,2</sup>

When an in-depth temporal analysis was conducted (with data only from 2020 this time), we compared the new cases of ACS that were managed invasively on a weekly basis to the new cases of COVID-19 from our regional registry (**figure 2**). A negative correlation was seen with the number of new cases of COVID-19 diagnosed in Madrid (official data from the Spanish Ministry of Health dated March 15, 2020<sup>4</sup>) as well as an obvious impact of the mandatory confinement declared in Spain back in March 15, 2020. Afterwards, the cases recovered gradually as the incidence of new cases of COVID-19 decreased. This means that, during confinement, it is

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