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The ISCHEMIA trial: optimal medical therapy against PTCA in the stable patient: the endless story

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In patients with acute coronary syndrome, an aggressive approach with coronary angiography and revascularization leads to important benefits compared to medical therapy alone. On the contrary, the prognostic impact of coronary revascularization in patients suffering from stable coronary artery disease has long been the subject of debate. The pivotal study in this area is COURAGE, published in 2007, in which coronary revascularization showed no benefit about the combined endpoint of death from all causes and acute myocardial infarction (AMI), compared to medical therapy. The ISCHEMIA study, published in 2020, compared selective coronary angiography and revascularization vs. a non-invasive approach. By protocol, the patients were initially evaluated with coronary computed axial tomography angiography: in case of coronary stenosis >50%, they were then randomized to the two strategies. While in the invasive arm patients were revascularized, in the non-invasive arm revascularization was used only in case of patient destabilization. As in COURAGE, the results of ISCHEMIA did not demonstrate superiority of revascularization over medical therapy alone for a combined endpoint of cardiovascular death, AMI, or hospitalization for unstable angina, heart failure, or cardiac arrest. Based on recent evidence from ISCHEMIA, it is therefore confirmed that coronary revascularization in stable patients does not seem to improve the prognosis compared to medical therapy alone.

Introduction

Coronary heart disease (CAD) is a leading cause of death in the developed world. This disease causes angina pectoris, myocardial infarction (MI), sudden death, and heart failure.[1] Most patients with CAD can be considered to have stable ischaemic heart disease, a condition that has recently been revised in the definition taking the name of chronic coronary syndrome (CCS): it is present when there is a diagnosis or suspicion of CAD in the absence of recent acute or changes in symptoms.[1] The cornerstones of CCS treatment are three, not mutually exclusive: optimal medical therapy (OMT), percutaneous coronary intervention (PCI) revascularization, and surgical revascularization [coronary artery bypass grafting (CABG)]. The use of drugs aims to reduce the progression of atherosclerosis, while revascularization strategies aim to restore normal flow in the vessels affected by significant stenosis. It follows that, ideally, both PCI and CABG should always be associated with an OMT. The focus of this work will be to expose the literature evidence comparing OMT and PCI in patients with CCS, with particular attention to the data from the recent trial: International Study of Comparative Effectiveness with Medical and Invasive Approaches (ISCHEMIA).

Medical therapy vs. percutaneous angioplasty

Percutaneous coronary intervention has undergone significant advances in the last two decades, which have seen the evolution of both materials (from bare metal stents to the latest generation of medicated stents) and treatment techniques. Percutaneous coronary intervention has been

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demonstrated to significantly improve the prognosis in patients with acute coronary syndrome (ACS) and is also widely used in patients with multiple vessels and with complex, acute or stable coronary artery disease.[2]

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) study, published in 2007, enrolled 2287 stable patients comparing PCI with bare metal stents to OMT. In the trial, there was no difference in the risk of total mortality or MI (primary endpoint) between the two groups at a median follow-up of 4.6 years and this result was confirmed in the 12-year extended follow-up, conducted in about half of the patients in the initial cohort.[3,4] It is noteworthy that patients undergoing PCI initially demonstrated better angina control; however, the magnitude of this benefit compared to OMT was minimal and symptom relief declined over the last 3 years of follow-up.[5] In the Randomized Trial of Therapies for Type 2 Diabetes and Coronary Artery Disease (BARI-2D), revascularization (stratified by surgical or percutaneous) was compared with OMT in stable patients with diabetes mellitus (DM).[6] The analysis of the PCI subgroup vs. OMT showed no benefit of the former over the latter in terms of mortality and major adverse cardiovascular events (MACE). As also noted in the COURAGE, PCI allowed an improvement in symptoms in the medium term, without however maintaining the benefit at 5 years.

A patient-level meta-analysis on the COURAGE, BARI-2D and Strategies of Multivessel Revascularization in Patients with Diabetes (FREEDOM) trials confirmed overlapping mortality and MACE between PCI and OMT.[7]

The fractional flow reserve (FFR) invasive study method has been established in recent years as the recommended tool to guide percutaneous revascularization in stable patients.[2] Fractional flow reserve-guided PCI was compared with OMT in the Fractional Flow Reserve trial vs. Angiography for Multivessel Evaluation-2 (FAME-2).[8] In the 888 randomized patients, the composite primary endpoint (mortality, MI, or urgent revascularization) was significantly higher in the OMT group (27% vs. 14%, respectively; $P < 0.01$). This broad treatment effect led to early discontinuation of the study due to excess events in the OMT arm. It should be emphasized that only 24% of FAME-2 patients had multivessel disease, compared to 69% of COURAGE and that the increase in events in the OMT arm was related exclusively to urgent revascularization, while no significant difference was observed for mortality and MI. Finally, the enrolled population had a low-risk profile, as reflected by the very low absolute number of cardiac deaths (three patients in each group).

Obviously, the urgent revascularization endpoint can be influenced by the lack of blindness or by the placebo effect.

To investigate these two aspects, the Objective Randomized Blinded Investigation with Optimal Medical Therapy of Angioplasty in Stable Angina (ORBITA)[9] trial was designed. In this study, PCI was compared with a sham procedure, on an OMT background. The data showed no significant differences between sham procedure and PCI in exercise time, time to reach 1 mm ST depression, and peak O_2 consumption or symptoms. Although the endpoints set by this interesting trial were not 'hard', so the impact on prognosis was not assessed, the study achieved the goal of demonstrating a significant placebo effect related to PCI.

Finally, a meta-analysis by Stergiopoulos, conducted on five randomized trials of PCI vs. OMT (4064 patients), showed no benefit of PCI in reducing the incidence of acute myocardial infarction (AMI) and mortality at 5 years.[10] Also, it is worth mentioning a recent patient-level meta-analysis which collected FAME 2 data along with those of two trials of similar design, however carried out in patients with ACS: the DANAMI-3-PRIMULTI[11] and the COMPARE-ACUTE.[12] In these two studies, multivessel patients with ST-segment elevation AMI, once the culprit lesion was effectively treated by primary PCI, were randomized to FFR-guided non-culprit PCI vs.—medical therapy.

The results of this meta-analysis, which included a total of 2400 patients, showed a 28% reduction in the composite endpoint of cardiovascular (CV) death and MI in the FFR arm at the median follow-up of 35 months [hazard ratio 0.72, 95% confidence interval (CI) 0.54-0.96; $P = 0.02$].[13] This reduction was driven, in particular, by a lower incidence of AMI. However, it should be emphasized that the results must be interpreted with caution, since most patients analysed were ACS patients and, therefore, the conclusions of the work cannot be fully translated into the context of the CCS subject of this discussion.

In a nutshell, based on the literature evidence available at the time of publication of the ISCHEMIA trial results, PCI has consistently failed to demonstrate an effective prognostic benefit in patients with CCS.

The ISCHEMIA study

The ISCHEMIA[14] study was carried out with the aim of comparing, in patients with moderate or severe inducible myocardial ischaemia, an invasive strategy (angiography and revascularization when possible—INV) associated with OMT vs. an initial conservative strategy (CON) of OMT alone (coronary angiography and possible PCI or CABG only in case of failure of medical therapy or destabilization of the patient).

The primary outcome was a composite of CV death, MI, or hospitalization for unstable angina, heart failure, or rescued cardiac arrest. Secondary endpoint a composite of CV death or AMI. The trial was designed to test the possible superiority of the INV strategy over the CON one.

The study protocol provided for the execution of coronary computed axial tomography (CT) before randomization: patients were enrolled if significant disease of the left main was excluded and at the same time a stenosis of >50% of one of the main coronary vessels was found. It should be noted that 1266 patients, according to the protocol, did not perform CT before enrolment, as they suffered from renal insufficiency [estimated glomerular filtration rate (eGFR) <60 mL/min] and, therefore, at risk of contrast nephropathy; patients with an eGFR <30 mL/min were not eligible in the pivotal study but were analysed in the ancillary ISCHEMIA-CKD study.

Among the exclusion criteria there were: left ventricular ejection fraction <35%; known disease of the left main coronary artery (from previous invasive angiography or CT);

coronary anatomy known unsuitable for revascularization; intractable angina despite maximal medical therapy; ACS in the last 2 months; revascularization in the past 12 months (percutaneous or surgical).

The study enrolled 5179 patients (2588 and 2591 in the INV and CON group, respectively). To achieve statistical power, the original protocol was revised, with a consequent modification of the inclusion criteria, of the total population (8000 patients the initial target) and of the primary endpoint. In particular, the study originally aimed to enroll only patients with ischaemia assessed by imaging. Difficulties were found in achieving the expected number of patients using the original protocol; accordingly, a further 25% of patients, in whom the provocative test was represented by the exercise electrocardiogram, were included in the trial. A history of angina, although present in 90% of enrolled patients, was not a necessary condition for inclusion in the trial.

At a median follow-up of 3.2 years, 318 primary events occurred in the INV group, and 352 in the CON group. At 6 months, the cumulative event rate was 5.3% in the INV and 3.4% in the CON group (difference of 1.9%; 95% CI, 0.8-3.0); at 5 years, the cumulative event rate was 16.4% and 18.2%, respectively (difference, 1.8%; 95% CI, −4.7 to 1.0). The results were similar for the secondary endpoint of CV death and MI. All-cause mortality was similar between the two groups with 145 events in the INV arm and 144 in the CON group.

The incidence of the primary endpoint was inevitably affected by the definition of AMI used; in particular, applying a more extensive definition of peri-procedural AMI than that of AMI type 4b and 4c of the universal definition[15] and based only on the increase in markers of myocardial necrosis, a clear increase in the incidence of AMI appeared in the INV group in the first months of randomization, a difference that is not significant at the end of the follow-up. On the contrary, restricting the analysis to spontaneous AMI only, the risk of AMI appears significantly reduced for the INV group and equal to 0.67 (95% CI from 0.53 to 0.83).

There were 145 deaths in the invasive strategy (INV) group and 144 deaths in the CON group (hazard ratio, 1.05; 95% CI 0.83–1.32).

Among patients in the invasive strategy group, 96% underwent angiography and of these a large part (79% of the total) underwent revascularization (PCI in 74% and CABG in 26%); in the CON group, 26% of patients underwent coronary angiography and 21% underwent revascularization; of these, 19% underwent angiography and 15% underwent revascularization before the occurrence of the primary endpoint.[14]

The subgroup analyses showed homogeneity of the results in patients at greater risk: in the case of proximal anterior descending disease, three-vessel disease, DM, or extensive area of ischaemia, no differences emerged between the two treatments regarding the primary endpoint. A meta-analysis, carried out using data from trials for 37 757 patients randomized to PCI or OMT, included the patients of ISCHEMIA[16]: in the paper, the results were stratified according to the ACS vs. stable clinical presentation: ACS patients showed a benefit of total mortality, CV mortality, and MI when undergoing PCI. On the contrary, for stable patients the effect of PCI was neutral on the events mentioned above. This therefore confirms and strengthens, what emerged from the ISCHEMIA trial.

In view of all of this, we can state that the ISCHEMIA study has several strengths: (i) the size of the sample studied (although lower than the initial objective), which makes this study the largest trial on the subject; (ii) the simple and effective design; (iii) the choice of documenting inducible myocardial ischaemia, rather than the presence of angina (not mandatory by protocol); (iv) the very low number of patients lost to follow-up (1%); (v) the 'upstream' randomization of coronary angiography; and (vi) the absence of sponsors and the transparent funding.

In ISCHEMIA, CT made it possible to accurately identify the significant pathology of the left main coronary artery, which we know to have an unfavourable prognosis. This is documented by the main null outcome and by the absolutely superimposable total mortality among the two strategies; similarly, CT made it possible to identify significant coronary stenosis with good correspondence to invasive angiography (in fact 79.4% of patients in the INV group underwent revascularization). It should also be noted that the non-invasive approach to the study of coronary anatomy could have significant cost benefits compared to an invasive angiography approach.

Similarly, some weaknesses should be emphasized: (i) PCI and CABG do not have the same impact on prognosis in patients with CCS, as CABG can improve prognosis compared to PCI in some subgroups of patients; this was not taken into account in ISCHEMIA where the revascularization strategy was, in turn, not randomized (e.g. a 2×2 factorial design could have been carried out); (ii) inevitably, patients were not always assigned to the more appropriate revascularization strategy based on the guidelines, as the decision was made by the individual Heart Teams of the participating centres; (iii) patients with the same degree of inducible ischaemia may have even profoundly different coronary anatomies (however, the subgroup analyses seem to reassure on the impact of these characteristics); (iv) (linked to the previous point) the high cross-over rate (20%) between the CON and INV arm due to poor symptom control or concerns about the risk of AMI or death have probably diluted the effect of revascularization. (v) Some groups of patients were excluded by protocol: patients with significant left main disease and patients with left ventricular dysfunction were not enrolled, as previous evidence showed the superiority of revascularization (in particular CABG) compared to OMT[17,18]; the hypothesis has not been retested in the ISCHEMIA.

Undoubtedly, the long-term follow-up data (ISCHEMIA-EXTEND) will be very interesting, when available, one in the light of the diverging curves of the events of the CON group compared to the INV group.

Conclusions

Instead of putting an end to this endless story, ISCHEMIA has provided an even more complex and difficult to interpret framework for the management of patients with CCS and inducible ischaemia. Trying to summarize, we can say

that ISCHEMIA informed us about the usefulness of coronary CT in the prognostic stratification of patients with CAD. In addition, the study further highlighted the importance of OMT in the context of CCS, which must therefore always be considered as an option and carefully evaluated within the Heart Team. Finally, the study clearly documented a favourable impact of revascularization on 'spontaneous heart attacks', at the price, however, of an increase in 'procedural' ones. The long-term prognostic equivalence between the two types of heart attacks still represents one of the most debated topics.

The study does not clarify when it is appropriate for each patient to switch from the initial conservative strategy to revascularization (percutaneous or surgical). However, in the era of tailored medicine, the challenge appears fascinating for cardiologists and perhaps this is precisely the legacy of ISCHEMIA: one size does not fit all; the trial reassured us that on large numbers an initial conservative approach appears safe and reasonable; however, it is up to the sensitivity of each physician to choose the right trade-off for every single patient between risk of acute events, bleedings, procedural risk, and quality of life.

Conflict of interest: none declared.

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