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The argument of the ORBITA study: angioplasty is useless

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The goal of treatment in stable coronary artery disease is to improve prognosis and quality of life of the patients. International Guidelines support revascularization procedures for symptomatic patients unresponsive to optimal medical treatment. Previous studies demonstrated, in fact, the therapeutic efficacy of coronary angioplasty in reducing angina and improving the functional capacity of these patients. The ORBITA study, recently published, challenged these assertions by demonstrating the lack of benefit of angioplasty over placebo in terms of effort tolerance in a population of patients with single-vessel coronary artery disease. What lesson could we learn from the ORBITA study?

Introduction

Indications for revascularization for patients with stable coronary artery disease (SCAD) are traditionally represented by persistence of symptoms despite optimal medical treatment and improvement of prognosis.[1] In fact, although coronary angioplasty has been used for over 40 years in patients with SCAD, its superiority to medical treatment in reducing mortality and the incidence of myocardial infarction has never been clearly demonstrated. At the base of the conflicting results obtained in numerous studies and meta-analyses, there are problems related both to the external validity of these studies (on average only 3% of patients evaluated for enrolment were then considered eligible, heterogeneous populations) and internal (40% of cross-over with angioplasty in follow-up, failure to demonstrate myocardial ischaemia, exclusion of high-risk patients). Furthermore, in many studies the most modern revascularization techniques have not been used. A network meta-analysis of 100 studies comprising 93 553 patients and 262 090 patients/year of follow-up documented an improvement in survival using angioplasty with the latest generation drug release stents [everolimus: rate ratio 0.75, 95% confidence interval (CI) 0.59–0.96; zotarolimus: rate ratio 0.65, 95% CI 0.42–1.00] compared to medical treatment alone.[2] However, if the effects of angioplasty on mortality and incidence of myocardial infarction are questionable, numerous studies have clearly demonstrated its superiority in reducing angina, the use of antianginа drugs and in improving functional abilities and quality of life compared to medical treatment.[3,4] On the other hand, these endpoints are rather subjective and susceptible to the placebo and nocebo effect. Furthermore, the placebo effect appears to be particularly relevant for invasive treatments compared to non-invasive treatments.[5] Although these implications were well known to the scientific community, it was only 40 years after the introduction of coronary angioplasty that a placebo-controlled study on the effects of angioplasty on reducing angina symptoms was performed for the first time in the world.[6]

The ORBITA study

The study compared angioplasty with a drug release stent implant in combination with optimal medical treatment. Patients eligible for enrolment were between the ages of 18 and 85, had angina or equivalent symptoms and an atherosclerotic coronary artery disease with stenosis of at least 70% considered susceptible to angioplasty treatment. The fractional flow reserve (FFR) was measured in all patients. The placebo arm was represented by a ‘simulated procedure’. In fact, not only patients, referring physicians

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and the entire staff present at the procedure were not aware of the treatment arm to which the patient was allocated, but, moreover, in patients enrolled in the placebo arm the procedure with cannulation of the coronary artery was simulated with a guide catheter and engagement of the lesion with a guidewire for functional evaluation. Patients were sedated and wore headphones to ensure the study was blinded. Of the 368 patients assessed for eligibility, 230 were enrolled and started a 6-week phase of medical treatment optimization. At the end of this period the patients took on average 3 anti-angina drugs; 30 patients withdrew consent to the study so that 200 (195 in Canadian Class II or III) were actually enrolled. The primary endpoint was the exercise time. There were numerous secondary endpoints: changes in oxygen uptake at the cardiopulmonary test, time of onset of ST elevation of at least 1 mm, severity of angina assessed by questionnaire (Seattle Angina Questionnaire), quality of life (EQ-5D-SL), Duke treadmill score, and changes in the wall motion score to dobutamine echo-stress. No significant differences were observed for the primary endpoint, as well as for the secondary ones, except for the wall motion score at the peak of the dobutamine echo-stress test which was favourably influenced by angioplasty.

The publication of the ORBITA study generated reactions, even violent ones, especially from opinion leaders, exceeding every foreseeable expectation. Only on social media thousands of tweets quickly appeared, far exceeding the number of patients enrolled in the trial. For the detractors of coronary angioplasty, the study was considered the last word to deny any role in a wide spectrum of patients with SCAD; for angioplasty supporters, the study was summarily underestimated. Beyond the controversies and the radicalization of the debate, it is necessary to note the exceptional work carried out by the investigators: the hypothesis of the study and the endpoints were appropriate, the simulation procedure was rigorously performed, the study was independent of the industry, and the dissemination of the results took place transparently. However, as with any trial, this study also raises important questions about the methodology and practical implications of the results achieved which we will try to summarize in a balanced way.

Internal validity of the ORBITA study

- Selection bias. The drop-outs were rare in the angioplasty arm (1/104), but more frequent in the placebo arm (8/95). In addition, four patients in the placebo group underwent angioplasty due to dissection of the vessel after the guidewire had passed and four were excluded from follow-up (two for resting chest pain, one for exacerbation of chronic obstructive pulmonary disease, and two for painful symptoms in the lower limbs), all four with a performance under stress probably worse than the average. Therefore, a potential study selection bias cannot be excluded.
- The power of the study in detecting a difference in the primary endpoint between the two groups is lower than expected. In fact, when average values of continuous variables are compared, such as running time, the standard deviation of the values is a fundamental variable in determining the sample size. In the study, the observed standard deviation was significantly higher than the one assumed (95 vs. 75 s). The sample size needed to satisfy the original assumptions of the study with a power of 90% should have been 424 patients, more than twice that used.[7]
- Despite the randomization, the average exercise time was 38 s higher in the placebo arm compared to the angioplasty arm. Furthermore, the non-significance of the primary endpoint among the two groups is mainly due to a subsequent increase in exercise time in the placebo group. From the statistical point of view, this phenomenon (increase of a variable in repeated tests with basal values not balanced between two groups) is known as 'regression of the average' and, if not recognized, frequently conditions the interpretation of the results of clinical trials. In a subsequent analysis adjusted for the differences in basal conditions the variation of the exercise time was 20.7 s greater in the angioplasty group suggesting that the trial could have been positive with an adequate sample size.[8]

External validity of the ORBITA study

- Considering that in the study five centres involved in Great Britain, and assuming (conservative estimate) a volume of procedures of $\sim$1200 per centre, during the enrolment period (from 6 January 2014 to 11 August 2017) 21 532 patients should have been treated. It follows that only 1.7% (368) of patients were initially assessed for eligibility and only 230 actually enrolled (1%). Subsequently 30 patients were excluded so only 200 (0.9%) were actually randomized.
- The optimization of medical treatment and the constant level of interaction with the referring physician make the transfer of the results to the real world difficult both in terms of adherence to treatment and in terms of acceptability on the part of the patient. In fact, at the end of the study, 85% of patients on the placebo arm had angioplasty. Furthermore, at the end of the run-in period a significant proportion of patients was asymptomatic (23% of patients in the angioplasty arm and 25% of the placebo arm were in Canadian Class 0 or I).
- About one-third of patients with an FFR $>$0.80 (the usual limit for considering a lesion as functionally non-significant) were randomized to angioplasty. Including patients with FFR $>$0.80 the results are unbalanced in favour of the placebo group by diluting the benefits of angioplasty

The practical implications of the study

What are the lessons we can learn from the ORBITA study? First of all it reminds us and strongly reaffirms that patients who do not have an appropriate indication for angioplasty (persistence of symptoms despite optimal medical treatment) should not undergo the procedure for symptom

control. Instead, it does not provide any information on the question of whether angioplasty is indicated in patients with SCAD regardless of symptom control. In this regard, large-scale randomized trials are needed such as the ISCHEMIA study that has recently completed enrolment.[9] It has been much discussed whether the ORBITA study should lead to a change in the recommendations of the Guidelines on the indications of coronary angioplasty in patients with SCAD. Considering that the patients included had a single-vessel atheromatous disease, the reduced duration of follow-up (6 weeks), and the reduced statistical power of the study, the impact on clinical practice and on the Guidelines does not appear to be significant. In fact, the newly published Guidelines of the European Society of Cardiology on Myocardial Revascularization do not specifically take into account the results of the study which, therefore, did not affect the final recommendations.[10] Certainly this study represents a stimulus for the cardiology community to reflect on the appropriateness of the indications and on the need to ponder and share the risks and benefits of the procedure with the patient. A better understanding of the pathophysiology of the disease and an adequate interpretation of the available scientific evidence are fundamental elements in this process.

Conflict of interest: none declared.

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