Is it possible that angioplasty does not improve the quality of life in patients with stable angina?

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The scientific evidence in favour of percutaneous transcatheter coronary angioplasty (PTCA) in chronic ischaemic heart disease in terms of reduction of myocardial infarction and mortality is very scarce and controversial. However, for many years, the cardiology community has believed in the dogma that PTCA in chronic ischaemic heart disease could improve symptoms, especially when combined with effective medical therapy. A recent randomized controlled trial (ORBIT) has completely overturned this dogma, questioning much of what we have been taught about revascularization procedures in patients with stable coronary artery disease. In this article, the ORBITA study is discussed in depth, highlighting the lights and shadows of the study itself.

KEYWORDS
Coronary angioplasty; Chronic ischaemic heart disease; Effective medical therapy

Clinical context

Coronary heart disease is the leading cause of death in Italy and around the world. It can occur acutely (myocardial infarction, unstable angina) or in chronic stable form. In the case of acute forms, urgent coronary revascularization by the percutaneous intervention (PTCA) significantly reduces mortality.

The chronic form of coronary heart disease is recognized as a completely different clinical entity. Generally, these patients require medical attention on an outpatient basis. Observational data have suggested that the amount of ischaemic myocardium and the severity of coronary artery disease are associated with mortality; similarly, the prognosis of patients who underwent coronary artery bypass grafting or PTCA was better than that seen in apparently similar patients who had not undergone revascularization.

For a long time, this belief has been a dogma for the entire cardiology community. However, the observational studies on which this dogma was based do not in any way replace the rigorous controlled and randomized clinical studies: while the effect of ‘confounding’ factors such as age and comorbidities can be corrected with several statistical methods, considerations that lead to the decision to revascularize or not—the so-called selection bias—are much more difficult to measure and therefore to weigh their effects on the final outcome.

More than 500 000 PTCA s are performed each year worldwide for the treatment of stable coronary artery disease (SCAD). However, unlike acute coronary syndromes, the evidence supporting a reduction in myocardial infarction and mortality in SCAD is lacking,1 especially in those patients with the low ischaemic burden.2 Nonetheless, there is ample evidence that coronary revascularization is capable of relieving anginal symptoms, and it is on this basis that current guidelines recommend it.3 Unfortunately, all of these studies were not conducted in a double-blind manner, and therefore, a ‘placebo’ effect in the groups of patients undergoing PTCA cannot be ruled out.

The ORBITA study (Objective Randomized Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina), published in the prestigious journal The Lancet in January 20184 more than 40 years after Andreas Grünzig’s first PTCA was performed, was specifically designed to fill this gap, as it is the first double-blind, placebo-controlled study on the effects of PTCA on medical therapy in SCAD in terms of reducing angina.

Anatomy of the ORBIT study

Patients included in the study were required to have angina or equivalent symptoms (Canadian Class angina 2–3)
and at least one angiographically significant (≥70%) lesion in a single vessel eligible for PTCA as inclusion criteria. The exclusion criteria were acute coronary syndrome, left main disease, multivessel disease, and other conditions that could obscure the symptoms and hence the study results. Eligible patients were selected after diagnostic coronary angiography. All patients underwent clinical and instrumental evaluation before and after 6 weeks of optimization of antianginal therapy according to current guidelines. Prior to randomization, all patients underwent cardiopulmonary testing and stress echocardiography with dobutamine.

Two hundred patients were randomized 1:1 to PTCA with DES + optimal medical therapy (n = 105) or 'sham' PTCA + optimal medical therapy (n = 95). Coronary physiology was assessed in all patients by 'fractional flow reserve' (FFR) or 'instantaneous wave-free ratio' (iFR). To avoid placebo-like confounding effects in the PTCA group, the study was conducted completely in a double-blind fashion, i.e. both the researchers involved in the study and the patients ignored the allocation to the treatment arm. In particular, in the catheterization laboratory, patients were sedated, wore earphones during the procedure to isolate them from the surrounding environment, and therefore, were not aware if they had been subjected to PTCA or not.

Interventional cardiologists were not involved in the study in any way. After 6 weeks, the patients were again subjected to clinical evaluation, again in a double-blind fashion, including cardiopulmonary test and echo-stress. The primary endpoint was the difference between the PTCA + OMT and sham PTCA + OMT groups in the change in exercise time on the treadmill. Statistical analysis was based on the intention to treat.4

Results of the ORBIT study

The randomization process was very effective as the two groups were homogeneous as regards demographics and clinical characteristics; at follow-up, there was no statistically significant difference between the groups in the increase in exercise time, in the time to develop 1 mm of ST segment depression, in VO₂ max or in angina severity. Specifically, exercise time increased by 28.4 s in the PTCA group and 11.8 s in the placebo group (comparison between groups, P = NS). In contrast, the wall motion score index at echo-stress significantly improved in the PTCA group compared with placebo (P < 0.0001).3

Comment

ORBIT was a commendable study in many aspects. The ORBIT investigators performed an elegant randomized controlled trial of a therapy widely accepted as effective, despite the considerable funding difficulties an investigator-driven study can suffer. The study design was exemplary, especially in terms of the optimization of medical therapy suggested by current guidelines and the double-blind design throughout the study. The inclusion of a ‘sham’ (simulated) PTCA was innovative and rigorous as it eliminated any possible placebo effect attributable to PTCA.

Almost immediately after the study was published, hundreds of tweets and other comments appeared on social media against PTCA and interventional cardiologists; the New York Times headlined: ‘Incredible: coronary stents fail to relieve chest pain!’ In the editorial comment on the study entitled ‘Last nail in the coffin for PCI in stable angina’ appearing in the same issue of The Lancet, Brown and Redberg conclude: ‘The implications of the ORBITA study are profound and far-reaching. First, the study results unequivocally demonstrate that there are no advantages for PTCA over medical therapy for stable angina, even when it is refractory to medical therapy. Based on these data, all cardiology guidelines should be revised to downgrade the recommendation for PTCA in patients with stable angina’.

I believe, however, that these comments are excessively ‘tranchant’ and that on the contrary, great caution should be used in interpreting the results of the ORBITA study mainly because there are a few but important elements that can weaken or even not support the conclusions reached by the researchers of the ORBIT study.

In the initial phase of therapeutic optimization, patients had up to three consultations per week with a cardiologist; in fact, therapeutic optimization was so effective that 48 of 200 patients (24%) were substantially angina-free (Canadian Class angina 0–1) at the time of randomization and should therefore have been excluded from the study, as per protocol design. Thus, at least a quarter of the study population was asymptomatic; in these conditions, it is impossible to evaluate the effectiveness of any antiangiinal therapy.

A second concern is related to the degree of stenosis and the size of the vessel subjected to PTCA. Correctly, the authors included all coronary angiographies of the 200 patients included in the study in the Supplementary material of the study. Of course, these images are not in motion; however, I assume the authors have selected the most relevant images for publication. Well, looking at the angiographies, it shows that 82 of them (41%) were intermediate stenoses of <70% (which was an exclusion criterion of the study) in a major epicardial vessel, or severe stenosis in a secondary branch of a main vessel. Thus, an additional 40% of the patients included in the study should have been excluded. But that is not enough: as a consequence of this, almost one-third of randomized patients did not have coronary stenosis with physiological evidence of ischaemia (FFR or iFR > 0.80) which, according to the current guideline, one should not be treated with PTCA.

The ORBITA study failed to reach its primary endpoint: the increase in exercise time was 28.4 s in 104 patients with follow-up data available in the percutaneous coronary intervention (PCI) group [95% confidence interval (CI): 11.6-45.1] and 11.8 s in the 90 patients with available follow-up data in the sham group (95% CI: −7.8-31.3) (Figure 1).

However, the standard deviations of baseline exercise times were particularly high, and the sample size and statistical power calculations seem to suggest that the
sample size may be too small to be unequivocally able to detect the primary endpoint. The study was designed as a ‘superiority’ study capable of detecting an intergroup difference in exercise time of 30 s using a beta error of 0.8 and an alpha error of 0.05, assuming a normal distribution of exercise time and a deviation standard estimated at 75 s.

It is essential to recognize that failure to demonstrate superiority does not imply equivalence. In order to conclude that the treatments considered in a given study have ‘similar’ results, we must be sure that the study itself has sufficient statistical power (and therefore a sample size) to detect clinically significant differences in the primary endpoint. And therefore, it is important to emphasize that the standard deviations are very large, pose a serious concern about the correct calculation of the sample size (see text for details). The bars represent the mean ± standard errors.

Figure 1  Changes in exercise time at 6 weeks from baseline in patients in the PTCA + optimal medical therapy (PTCA) group and patients undergoing sham PTCA + optimal medical therapy (SHAM). No statistically significant differences were observed in the comparison between groups, while in the PTCA group, there was a significant difference from baseline values. These observations, together with the consideration that the standard deviations are very large, pose serious concern about the correct calculation of the sample size (see text for details). The bars represent the mean ± standard errors.

...of 266 subjects for an assumed standard deviation of 87 s and 318 subjects for a standard deviation of 95 s.

If 90% statistical power had been predicted, as in the case of more recent studies testing the efficacy of antianginal drugs,11 the sample size would have required 356 subjects for an assumed standard deviation of 87 s and 424 subjects for a standard deviation of 95 s.

Researchers in the ORBITA study reported an average 28.4 s increase in exercise time from baseline at 6 weeks in the PTCA group and a shorter, though not statistically significant, time of 11.8 s in the sham group. However, it is interesting to note that the difference in exercise time between the basal time and that observed after 6 weeks within the same group is statistically significant only in the PTCA group and not in the sham group (Figure 1).

Hence, the legitimate doubt that if the sample numbers had been calculated adequately, the primary endpoint of the study would have been reached. Last but not least, although PTCA did not increase exercise time, some secondary endpoints, such as freedom from angina (PTCA group 49.5%, sham group 31.5%, P = 0.006) or wall motion index at ecostress (PTCA group −0.08, sham group 0.02, P = 0.0011), strongly favoured treatment with PTCA.

Conclusions

So what should we learn from this study? What are the most important messages of the ORBITA study? First, patients who do not have an appropriate indication according to current guidelines for elective PTCA, i.e. persistent symptoms despite optimal titration of antianginal drugs, should not undergo PTCA for symptom control. The optimization of drug therapy should be implemented as an initial strategy as it can alleviate the symptoms of many patients.

Second, the ORBITA trial was limited to patients with single-vessel disease, lasted only 6 weeks after randomization, and was largely underpowered to detect a significant difference in exercise time. Hence, the suggestion that the guidelines should be rewritten based on the ORBITA study is completely unwarranted.

Third, the ORBITA study represents a wake-up call on the difficulty in comparing the therapeutic efficacy of different strategies; such studies are inherently difficult and require not only a sophisticated and rigorous protocol but also adequate statistical power. While the ORBITA researchers should be congratulated for the first aspect, the second aspect is clearly a weakness of the study that limits its implications for clinical practice.

Conflict of interest: None declared.

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