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Letters to the Editor

The ORBITA trial: Why is it not the last nail for coronary angioplasty in stable angina patients?

In November 2017, the online version of the randomized ORBITA trial (Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty) [1,2] in stable angina patients, which was the first study which included a sham arm in comparison to percutaneous coronary intervention (PCI), was published ahead of print.

The study compared PCI with implantation of drug-eluting stents (DES) plus optimal medical treatment (OMT) to OMT alone but with a "sham procedure". All selected patients and reference physicians were blind to patient treatment allocation. In all patients, fractional flow reserve (FFR) was done and either FFR or iFR was measured.

Patients eligible for the trial were ages 18–85 with angina or equivalent symptoms and at least one angiographically significantly lesion in a single vessel that was clinically appropriate for PCI.

Severe stenosis was defined by protocol as ≥70% obstruction by visual estimation.

The study was investigator-driven and of course was well-conducted as usually is observed when centers in Great Britain are involved; therefore, I don't have any complaints about the quality control of the study. However, like most investigator-driven studies, ORBITA has potential advantages (no industry bias) but also limitations (sample size).

In spite of this, almost immediately after the trial, hundreds of tweets and other social media comments against PCI and PCI practitioners were released, but only few said that all of their conclusions were based on results found in 200 patients.

In summary, I have few but deep concerns about the trial's main conclusions and, subsequently, how they can be misinterpreted by the media as well as the general population, including patients.

First, taking in account that 5 centers in Great Britain were involved, and presuming that each of them performed per year in a "conservative" estimation 1200 PCIs per year, during the recruitment period of January 6, 2014, to August 11, 2017, then 21,532 PCIs could have been performed in those centers. This suggests that only 1.7% (368) of patients were initially assessed for eligibility. From these, 138 were excluded; therefore, 230 were entered into the optimal medical phase of the trial (1%). Later on, 30 additional patients left the study, and finally, 200 were randomized and are the study group (0.9% of the entire group).

I want to emphasize that this small percentage is derived from a conservative estimate of the total number of PCIs performed in these 5 centers in Great Britain. It is likely that these centers actually perform more PCIs, which would make the percentage ultimately included in ORBITA even smaller than my estimate.

This relevant information should be released together with trial results in all social media communication of ORBITA trial findings.

My second concern regards the degree of stenosis and vessel size of lesions included in the study.

Remarkably, authors released in the supplementary material of the study, mandatory to read in all randomized trials, angiographies from the 200 patients [2]. In all cases target severe stenosis was marked with an asterisk.

Of course, angiographies are seen without movement; they showed only one view. That's a major limitation to assessment by visual estimation of either the degree of obstruction or vessel size. However, we can assume that the authors selected for the publication the most relevant view.

I reviewed all the angiographies and I found that 82 of them (41%) were either intermediate stenosis (<70%, which was an exclusion criteria of the study) in a main epicardial vessel, or a severe stenosis in a secondary branch of a main vessel or a severe stenosis in a distal portion of a main epicardial vessel or a severe stenosis in a small non-dominant right coronary artery (RCA). As an example of this, if we look at the angiographies from left to right and number them, in view No. 8, the patient had an intermediate stenosis in the proximal left anterior descending (LAD) artery, marked with an asterisk; view No. 13 shows another intermediate lesion in the proximal LAD, marked with an asterisk; view No. 23 shows a critical tight stenosis in a non-dominant RCA, marked with an asterisk; view No. 25 shows an intermediate proximal stenosis in the LAD, marked with an asterisk; view No. 36 shows critical stenosis in a small distal posterior ventricular branch of circumflex (CX), marked with an asterisk; view No. 43 shows an intermediate mid-LAD stenosis and critical stenosis in a small diagonal branch (<1.5 mm) marked with an asterisk; view Nos. 46 and 48 show intermediate ostial lesions in the intermedia branch and LAD, respectively, marked with asterisks; view No. 51 shows an intermediate mid LAD lesion marked with an asterisk; and view No. 53 shows an intermediate lesion in the proximal RCA, marked with an asterisk, and so on. If we review the inclusion criteria of the study, the authors stated, "*Patients with stable angina or equivalent symptoms, with a diagnostic angiography showing at least 1 lesion with angiographic stenosis ≥70% in a single vessel that is suitable for PCI*." Therefore, 41% of the lesions included in the study may not have fulfilled the inclusion criteria of the trial, unless we considered lesions >50% as an inclusion criteria or a small non-dominant RCA or small circumflex distal branch or small diagonal as target vessels.

Additionally, most of these lesions were not included in the revascularization strategy in two recent observational prospective registries, ERACI IV [3,4] and WALTZ [5], where the penalty of not treating those lesions in the context of multiple vessel or multiple lesion coronary rtery disease (CAD) was the need for new revascularization in 3.9% [3] and 1% [6] at 3 years and 1 year, respectively, meaning that the policy of not including either intermediate lesions or small vessels in the PCI/DES strategy was right. In fact, the ERACI score did not include many

of those lesions in the stent deployment strategy and did not score ither at baseline or as residual risk score after PCI. In other words, our PCI strategy in those angiographic scenarios left them with OMT alone [7]. The SYNTAX II study also demonstrated that functional lesion ssessment allowing fewer stents per patient with similar risk score achieved better results compared with previous SYNTAX I data [8].

Almost 30% of normal instantaneous wave-free ratio (iFR) found in ORBITA patients are in agreement with our comments mentioned above [1].

Now if from the 200 study group patients, we discard these 82 patients, now we are saying that only around 0.5% of the population aving severe CAD in the centers involved in the study should be included and randomized in ORBITA trial. However, this does not end here, and we recently noticed, from unpublished data, that 85% of atients not initially treated with PCI were ultimately treated with PCI for unknown reasons [9].

After >25 years of having seen first randomized studies published between coronary artery bypass surgery, OMT or PCI [10–13]in patients with severe CAD and stable angina, it is very difficult for those who participate in these experiences to understand the behavior of those who try to minimize the benefits of PCI in certain groups of patients, including relief of angina and improved functional class as was demonstrated by other randomized studies [10–13] with appropriate long-term follow-up data.

In summary, I don't want to dismiss how the investigators conducted and performed the ORBITA trial, although I would like to emphasize that 40 years after the first coronary angioplasty performed by Gruentzig, a right lecture of coronary angiogram including lesion severity together with the amount of myocardium at risk and jeopardized score remains the “gold standard” to selected the right treatment option for our patients with severe CAD [14,15].

I would like to see ORBITA authors performing a new sham-controlled randomized clinical trial, ORBIT 2, including a “true” all severe (≥70%) stenosis in the proximal/mid portion of large epicardial vessels to replicate findings recently reported in Lancet paper [1].

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The “new” syndrome of delayed coronary obstruction after transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR) is now the treatment of choice for patients with severe aortic stenosis with increased surgical risk [1,2]. Outcomes have continually improved, but due to the nature of the procedure, by displacing an old valve with a new valve, complications such as coronary obstruction persist, especially in patients with high risk features. It is generally recognised to occur acutely; however, recently data were reported from a large international registry regarding the new phenomenon of delayed coronary obstruction (DCO), in which the coronary obstruction occurs after the index procedure [3,4]. We collected data from 18 centres on 17,092 TAVI procedures over an 11-year period (2005–2016) and the reported incidence was lower than acute coronary obstruction (n = 38, 0.22% versus approximately 1% with acute obstruction) [3]. However, more cases may occur than we realise. For example, DCO could present with sudden cardiac death and therefore go undiagnosed if out of hospital and no autopsy is performed. Additionally, patients could be relatively asymptomatic if DCO develops in the context of a patient with prior CABG and therefore not seek medical attention [5]. Whilst we found that in 2 out of every 3 patients, one well known risk factor associated with acute coronary obstruction was present, we also found that in contrast to acute obstruction that DCO occurred more commonly with self-expandable valves (0.36% vs. 0.11% balloon expanding; $p < 0.01$). DCO broadly fell into two categories: early (≤7 days; n = 24, 63.2%) and late (≥60 days; n = 14, 36.8%). Early DCO presented more with acute presentations including cardiac arrest and STEMI, in contrast to late that presented with stable angina. This is probably related to two different mechanisms, for example, early DCO may be related to the displacement of native/surgical valve leaflet due to continuing expansion of the new valve, in contrast to late whereby valve stent endothelization, fibrosis or thrombus embolization may be responsible (Fig. 1). Whilst PCI was the management of choice and successful in 68.8%, the mortality associated with the condition was high at 50% [5]. Therefore, although thankfully the incidence is rare, clinicians should be aware since it is often a deadly condition, and since one third of patients did not have a classical risk factor for acute coronary obstruction; thus future studies are needed to define new risk factors. For example, calcium distribution, leaflet length and morphology are possible risk factors that