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VIEWPOINT

ORBITA revisited: what it really means and what it does not?

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> *The significant problems we face cannot be solved at the same level of thinking we were when we created them*
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> Albert Einstein

Ever since William Heberden's seminal description of angina pectoris in 1772,[1] attempts have been made to find an effective treatment of this condition. Thomas Lauder Brunton was the first to describe the effectiveness of amyl nitrate for angina pectoris in the *Lancet* in 1867,[2] followed by William Murrell who 12 years later, in the same journal, reported on the benefits of nitroglycerin in this condition.[3] Thereafter, not much progress occurred for many decades until the discovery of propranolol in 1964 by Sir James Black.[4] Three years later René Favoloro performed the first successful coronary bypass operation using the saphenous vein.[5] Finally, in 1977 Andreas Grüntzig performed the first percutaneous coronary angioplasty in a patient with angina pectoris and a stenosis of the left anterior coronary artery.[6] Ever since, the spectrum of antianginal strategies has been widened by the introduction of newer drugs such as calcium antagonists, inhibitors of the I_F-channel, late inward sodium channel current inhibitors, and modulators of myocardial metabolism. Also the results of bypass surgery were improved by the use of arterial grafts[7] and percutaneous coronary interventions (PCI) have been made more effective through the introduction of stents, particularly drug-eluting stents.[8] Nevertheless, the best way to treat angina pectoris remained a point of discussion.

In the *Lancet*, Francis and his ORBITA co-workers attempted to reassess the value of PCI compared to medical therapy and concluded based on the results of their sham-controlled trial that 'patients with medically treated angina and severe coronary stenosis, PCI did not increase exercise time by more than the effect of a placebo procedure'.[9] The accompanying editorial by Brown and Redberg[10] stated that 'all cardiology revascularization guidelines should be revised'. Moreover, the editorial also concluded 'since the procedure carries some risks, including death, stents should be used only for people who are having heart attacks'.[10] Dr Al-Lamee, went on to say 'surprisingly even though the stents improved the blood supply (in patients who were getting pain only on exertion caused by narrow but not blocked arteries) they didn't provide more relief of symptoms compared to drug treatments'[9] and the New York Times heralded these findings '"Unbelievable": Heart stents fail to ease chest pain'.[11]

In ORBITA, 230 patients with single vessel disease were enrolled and entered a 6 week medical optimization phase and were then randomized to angioplasty (105 patients) or a sham procedure (95 patients). Treadmill exercise testing using a modified Bruce protocol was performed pre-randomization and 6 weeks later. After the initial 6 weeks of escalating antianginal therapy pre-randomization, 24% (i.e. 48 out of 200) of the population were Canadian Angina Class 1 or 0 consistent with the overall pre-randomization exercise times of approximately 7 METS or completion of standard Bruce Stage 2. The primary endpoint was the change in exercise duration from pre-randomization to 6 weeks.

When dropouts are imbalanced between two treatment groups in such trials and when selection of subjects to be included in the analysis is related to both the exposure/treatment group and to outcome measures, a selection bias is introduced that may potentially lead to a biased treatment comparison. Of note, drop-outs were rare in the PCI group (1 of 104 patients did not have PCI), whereas they were more frequent in the placebo group (8 of 95). Four patients of the placebo group had a dissection requiring PCI and four were withdrawn during follow-up, two because of a chest pain admission, one for a COPD exacerbation with right sided heart failure, and one for bilateral leg pain, all four of whom would likely have had worse exercise performance than average. Thus, there is reason to be concerned that the ORBITA trial results have a potential selection bias.

Randomization achieved overall balance in baseline characteristics, except for coronary anatomy. Of note, of 170 patients with either isolated LAD or RCA disease, 53% of patients had proximal or ostial

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disease—known to cause more pronounced ischaemia—in the PCI group compared to only 36% of the placebo group.

The study was designed as a 'superiority' trial powered to detect an intergroup difference in exercise time of 30 s using a beta of 0.8 and alpha of 0.05 assuming a normally distributed distribution of exercise time and an estimated standard deviation of 75 s. It is critical to recognize that the failure to prove superiority does not imply equivalence. In order to conclude that the assigned treatments in a well-conducted trial have 'similar' results, we must be convinced that the trial was well powered to detect clinically meaningful differences. Importantly, the hypothesized standard deviation in ORBITA is considerably lower than that observed when testing for antianginal drug efficacy in patients with angina and exercise induced ST segment depression where a markedly higher standard deviation of 110–180 s is more typical. A smaller standard deviation leads to lower sample size estimates; however, it may not represent what might be expected in this population or had a broader population been studied. Indeed, based on our calculations from the published confidence intervals in the ORBITA paper, the observed standard deviation for the per-person change (or 'increment') in exercise time was ~87 s in the PCI group and ~95 s in the placebo group. Given the trial design, the study has 68% power to detect an inter-treatment group difference of 30 s with 100 patients in each group if the standard deviation were assumed to be 87 s or or 60% power if the standard deviation were assumed to be 95 s, respectively. The sample size necessary to fulfil the original assumptions in ORBITA using the observed rather than the hypothesized standard deviation would require analysing a total of 266 subjects for an assumed standard deviation of 87 s and 318 subjects for a standard deviation of 95 s (i.e. before increasing the number to account for drop-outs), respectively. If 90% power were stipulated, as is the case with more recent trials testing antianginal drug therapy, 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.[12]

The investigators reported an average increase of 28.4 s in exercise time from baseline to 6 weeks in the PCI group and a lower, although not statistically significant, average 11.8 s increase in the placebo group resulting in or a placebo-corrected estimated difference of 16.6 s ($P = 0.20$). The relatively small observed increase in exercise time after 6 weeks (28.4 and 11.8 s) are substantially shorter than the 60–100 s increase observed in placebo exercise times for studies testing antianginal drug efficacy. Interestingly, the within person change is significantly different from 0 in the PCI group indicating a significant improvement in exercise time while the within person change was not significantly different from 0 in the placebo group despite the fact that the appropriate between group comparisons was not significant given the large variability in the two estimates.

We therefore need to ask some questions: first of all, why were patients with CCS angina Class 0–1 enrolled into the study? Guidelines do not recommend PCI in patients with minimal or no angina.[13] It is not clear how many patients had exercise-induced ischaemia pre-randomization making it somewhat difficult to compare the patient population to that of other trials testing antianginal strategies. Although many patients were classified as having angina Class 2 or 3 pre-randomization, the average exercise time at baseline (~7 METS) and Duke treadmill score <5 indicates a population with relatively well-preserved exercise capacity. Exercise time in patients that remained CCS angina Class 2–3 pre-randomization are not presented; thus it is difficult to assess the impact of PCI compared to placebo in this group. We are given a preview from the patients themselves, since 63% of those that received PCI correctly guessed their assignment vs. 49% of the placebo group. Second, was the number of individuals enrolled in ORBITA high enough to detect any difference in exercise time between patients undergoing PCI and controls in such a patient population? The answer is, most likely not.

It is also important to understand the primary endpoint and its value in determining the efficacy of PCI in this setting. Indeed, it appears obvious that an increase in exercise time with any intervention is likely to be seen mainly in patients with more severe symptoms unless large populations are studied. For example, in the AGENT trial assessing Ad5-FGF4 in patients with stable angina,[14] improved exercise treadmill time with Ad5-FGF4 was only significant in the group of patients with reduced exercise times (i.e. in those being more symptomatic) at baseline.

Of note, in the CARISA trial testing the effectiveness of the antianginal drug ranolazine,[15] also in a parallel design as in ORBITA, the calculated sample size was 462 evaluable patients and not only 190 finally eligible patients as in ORBITA. The investigators assumed a standard deviation of 80 s to have a 90% power to detect a 30 s increase in exercise time. Although the MARISA trial of the same development program was smaller[16] as the authors point out, the trial design was completely different, since the 191 patients enrolled were assessed in a cross over design allowing each patient to be their own control. Thus, contrary to what the authors argued, ORBITA and MARISA are not comparable. In other words, one would not expect PCI to improve the physical performance due to factors outside the procedure being tested such as absent or mild baseline symptoms, an already improved exercise time in the run-in medical therapy phase, as well the fact the trial was underpowered. A 30 s increase in exercise time is therefore difficult, if not impossible to detect within such a small patient population given the large variability of this clinical test. Indeed, in the ACME Trial involving 328 patients with stable coronary disease and symptoms of angina or ischaemia on treadmill,[17] medical therapy led to an increase in exercise time of 30 s, while PCI did increase it by over 2 min.

Finally, it is sanguine to reflect that the undertaking of an angiogram procedure using a pressure wire should not be embarked on lightly; of note, in ORBITA there were 4% serious adverse events which required angioplasty in the sham procedure group. In contrast, in the large FFR trials such a high incidence of complications have not been reported[18,19] and also in registries seems to be very low.

Thus, what should we learn from this study? First, patients who do not have the appropriate guideline indication for elective PCI, i.e. persistent symptoms in spite of optimal titration of antianginal medication,[13] should not undergo PCI for symptom control. Antianginal drug therapy and management of secondary causes for angina should be addressed as the initial strategy and can alleviate symptoms in many patients. Hence, the suggestion that guidelines should be rewritten based on the ORBITA trial is completely unwarranted. Indeed, the ORBITA trial was limited to patients with single vessel disease, was only 6 weeks in duration after randomization, and was underpowered to detect a meaningful difference in exercise time.

Second, the further question whether PCI is indicated for better outcome in stable patients with coronary artery disease independent

of symptoms could not have, nor was it intended to be addressed in ORBITA. This will require much larger randomized trials using state-of-the-art technology such as the ongoing ISCHEMIA Trial.[20] Third, as an unintended consequence, the complications following the use of diagnostic invasive procedures using a pressure wire are worrying as this has not reported at such a high incidence previously. This may be accidental or due to limited experience with this particular system. Alternative non-invasive means of measuring fractional flow reserve such as with CT scans[21] or MRI[22] will become more accessible as an alternative to those who wish to use this as a diagnostic technique. Thus, ORBITA is a wake-up call that the effectiveness of therapeutic strategies are difficult to compare and require not only a sophisticated protocol but also appropriate statistical power. While for the former the ORBITA investigators should be congratulated, the latter is clearly a weak point of the trial limiting its implications for clinical practice.

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