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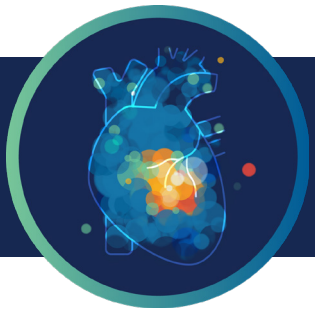
EXPERT INSIGHTS: Q&A WITH DR. DANIEL JONES



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How would you sum up the key points from the ORBITA-2 trial in plain language to a patient in your clinic?

In a well designed study of 300 patients, angioplasty improves angina compared to a sham (fake) procedure in the absence of medical (anti-anginal) therapy. There was a 3 fold reduction in anginal frequency and no safety signal was seen. The benefits of percutaneous coronary intervention (PCI) occurred immediately, and were sustained over 12 weeks. This provides evidence that PCI reduces angina as a safe alternative to pills for the treatment of angina although at the cost of the need for long term dual antiplatelet therapy.

ORBITA-2 studied a predominantly male white Caucasian cohort with physiologically significant single vessel coronary artery disease. Can or should the results of the trial be extrapolated to encompass an all comers stable angina population with single or multivessel coronary artery disease given this demographic and anatomical context?

The generalisability of a trial outcomes always depends on the eligibility criteria and the patients included, the trial team tried to keep this as broad as possible i.e expanding on the single vessel disease inclusion criteria used in ORBITA-1 to try and enrol a greater degree of multi-vessel disease. However as stated the majority of patients (80%) still had single vessel disease and were predominantly male and Caucasian. This is understandable with treatments such as coronary artery bypass graft surgery considered for patients with multi-vessel disease and a male predominance in patients presenting with coronary artery disease. Therefore I think we need to be wary of this when counselling patients however there is currently no evidence to suggest a different effect.

On a more general note, how can we improve and optimally enrich the gender and ethnic diversity of cardiovascular clinical trials?

This is an ongoing and important issue. The majority of key or landmark trials of coronary artery disease often predominantly enrol white male populations and how generalisable these results are to a more diverse cohort is difficult to ascertain. It isn't a new problem and more needs to be done to change this. Locally we are trying to utilise language specific study materials alongside animation assisted consent videos to try and improve this clear gap but this is just the start.

It is unclear why a 12-week blinded follow-up phase was specifically chosen for the study design. Would there have been any added value in extending follow-up to 6 months or 1 year?

Its always a balance in clinical trials with endpoints to ensure clinical relevance but to maximise follow-up and protocol adherence. The ORBITA-1 trial used a 6 week endpoint so 12 weeks is already longer and addresses one of the criticisms labelled at the first study. We do have to remember that patients were removed from all antianginals in the placebo arm, and therefore I think longer than 12 weeks may have been considered unethical.

Subjects may have deliberately (or subconsciously) reduced the frequency and/or intensity of their daily activities in response to complete cessation of their pre-existing anti-anginal therapy. This information is not recorded by the Seattle Angina Questionnaire nor was it recorded by the smartphone angina symptom score during the trial. This is speculative of course, but could this have affected the study outcomes?

I agree this is a potential effect of stopping medical therapy however this was a necessary step required to prove the effect of PCI. You would expect the effect to be similar in the 2 treatment arms however and therefore if anything this may have reduced the benefit of PCI if individuals reduced their activity. The beauty of the trial design means that although logical that this may have happened a negligible effect would have been seen on the outcomes.

Do you think the introduction of a smartphone-based angina symptom score inadvertently introduced a volunteer or self-selection bias to the trial?

A large number of trials now use smartphone or digital solutions to capture endpoints and encourage adherence. I think this is a strength of the trial with a minimal introduction of bias with most individuals now able to utilise technology very effectively. This meant that the trial wasn't just reliant on more historic measures of angina such as the Seattle angina questionnaire which I feel gives the trial an extra dimension.

Will ORBITA-2 change your clinical practice?

It will provide me with a greater evidence base to tell patients that on the basis of a placebo-controlled trial that PCI certainly does have a favourable impact on symptoms in patients with documented angina, severe coronary stenosis, and demonstrated ischemia. Personally I would still be managing patients with stable angina on medical therapy and reserving PCI for those with ongoing symptoms due to the risks of the procedure and residual Long-term event rates (stent thrombosis etc). However, for patients intolerant of or reluctant to take medication this proves that PCI is a safe and effective first line alternative and allows for a more nuanced discussion with patients about the pros and cons of each option.