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EDITORIAL

Coronary sinus Reducer for the treatment of refractory angina: how much more evidence do we need?

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The coronary sinus Reducer (CSR; Shockwave Medical) is an unintuitive antianginal therapy which is currently utilised in patients with severe epicardial coronary artery disease who have no further conventional treatment options. It has been shown to improve symptoms in this patient group in two randomised placebo-controlled trials: COSIRA and ORBITA-COSMIC[1,2]. The efficacy of the CSR is far from universally accepted among cardiologists – an unusual position for a cardiac therapy with two separate placebo-controlled trials supporting its use. This may be because the mechanism of action of the device remains incompletely explained, despite recent insights[3]. Placebo-controlled trials necessarily curtail follow-up to timepoints that balance detection of device efficacy and ethical considerations for patients. There have therefore been questions raised regarding the longer-term safety and efficacy of the CSR in the "real world".

In this issue of EuroIntervention, Verheye et al report the findings of the REDUCER-I study, the largest observational study to date of patients treated with the CSR[4]. The 400 enrolled patients were broadly similar to those in the aforementioned randomised trials: a majority were male, approximately half were diabetic, a high proportion had undergone previous coronary revascularisation, and most were at the upper end of physician-assessed angina severity (72% in Canadian Cardiovascular Society [CCS] class III or IV). At 1-year follow-up, the authors reported a major adverse cardiac event rate of 7.5%, including 9 deaths. Of the 332 patients, 227 (70.5%) improved by ≥1 CCS class, and 82 (25.5%) improved by ≥2 CCS classes. Similar improvements in the Seattle Angina Questionnaire domains, 6-minute walk test distance, and hospital emergency department attendance were seen.

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The authors are to be commended for providing 1-year data for a large group of patients treated with the CSR. However, we should consider what impact this report has on the totality of our understanding in this space. Two notable limitations are evident. First, this is a single-arm study. Without a comparator group, we cannot know if the changes seen in reported symptoms were amplified by the Hawthorne effect or simply represent regression to the mean in a highly symptomatic group of patients. Second, and crucially, the study is unblinded. As such, the measured treatment effects include the placebo effect and potential bias from unblinded physician assessors.

There is a tension in trial design between the quality of the data collected and the feasibility of trial delivery. Ideally, we would have long-term placebo-controlled data on the efficacy of the CSR. However, long-term blinding of patients may not be ethically acceptable or practically deliverable. Ideally, placebo-controlled trials would have large sample sizes. Importantly, the rigorous blinding methodology necessitated by invasive placebo-controlled procedure trials and the commitment required from patients may make large-scale trials of this kind unfeasible. This raises the following question: is it reasonable to respond to these challenges by accepting the data from observational registries as a replacement for robust randomised clinical trials?

A risk with the presentation of uncontrolled, unblinded, observational data is that the reported improvement in symptoms may be conflated by the reader with the true placebo-subtracted physical efficacy of the therapy. For cardiologists seeking more evidence of the efficacy of the CSR in a larger number of patients than previously included in randomised trials, such data will be provided by the COSIRA-II trial, the largest randomised trial of the CSR to date.

But how should the long-term effects of the CSR be assessed? Perhaps, analysis of "real-world" data, such as that provided by REDUCER-I, is a reasonable solution. With longer follow-up and a larger sample size than the randomised placebo-controlled trials, REDUCER-I is able to produce estimates of long-term effect. However, these estimates must be interpreted with the knowledge that the true physical effect of the device cannot be understood because of the inclusion of the placebo component and the lack of a control group comparator. We should caution the reader against interpreting these results as an estimation of efficacy.

Perhaps, the most important results from observational data are safety endpoints, which are less susceptible to unblinded study design and reflect real-world practice. To this end, REDUCER-I reported a 99% procedural success rate and very low rates of procedural complications[5].

There are significant unaddressed questions about the CSR, a technology in its relative infancy which represents a new paradigm in the treatment of stable angina. Do we have enough data to know if it works, and should this therapy truly only be utilised for patients with no alternative? There are many patients for whom clinical factors, such as frailty, or coronary anatomy, including diffuse or complex disease, make revascularisation highly unattractive, even if it is technically possible. The focus on so called "refractory angina" comes with caveats. The definition exists in the eye of the beholder. This has perhaps delayed the description of a biological endotype in which the CSR has the greatest impact and, indeed, patients for whom it is futile. These questions speak to the greater, as-yet unanswered question that underpins persistent physician uncertainty with the CSR: how does it work? While ORBITA-COSMIC has suggested that improved subendocardial perfusion in ischaemic areas of myocardium is the underlying physiological substrate for angina benefit, how coronary sinus narrowing achieves this remains unknown.

REDUCER-I, with all its limitations, tells us that most patients treated with a CSR report feeling better than they did the year before. The effect experienced at 6 months seems to persist to 1 year, although this cannot be attributed to the CSR alone. It has provided evidence that hundreds of patients can be safely treated with the device with minimal complications and no signal of harm at 1 year. Now, we must do more to understand the therapy and determine how we can ensure it is offered to those patients with the most to gain.

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Conflict of interest statement

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