

women to find their voice in the United States against strong social stigma so long ago, victory in the battle to prevent HIV will require the women at risk for infection to find “a position different from that which they have hitherto occupied” in order for them to find their VOICE.

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Potential Relief for Refractory Angina

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Physicians who practice primarily in outpatient settings are faced with a large and growing population of patients with chronic, stable, but refractory angina,^{1,2} as a consequence of an aging population and our ability to prolong the lives of patients with coronary disease. The mortality among patients with refractory angina is surprisingly low,³ but the effect of persistent, recurrent, and frequent symptoms on quality of life is substantial and emphasizes the need for alternative therapeutic options.

The newest drug in this therapeutic area, ivabradine, which is approved in Europe, has been shown to reduce angina and improve exercise time in patients with chronic coronary disease. However, its role has been called into question on the basis of the results of the Study Assessing the Morbidity–Mortality Benefits of the I_f Inhibitor Ivabradine in Patients with Coronary Artery Disease (SIGNIFY) trial.⁴ SIGNIFY showed that ivabradine may be harmful for patients with activity-limiting angina with regard to cardiovascular death and myocardial infarction. This finding raises the question of whether and when new treatments for relieving angina

should be evaluated in clinical trials with hard outcomes.

Although coronary-artery bypass grafting and percutaneous coronary intervention have been well established as therapies for patients with angina, there is also a long history of studies of other interventional procedures for such patients, including internal mammary-artery implants (Vineberg operation), intrapericardial talcum powder or asbestos, internal mammary-artery ligation, omentopexy, transmyocardial laser revascularization, gene therapy, and more recently, cell therapy.¹ For each of these, initial promising findings have not been confirmed in larger randomized, controlled trials. Another approach, manipulation of coronary venous return to improve perfusion of ischemic myocardium, has been studied with a variety of methods including partial or complete occlusion of the coronary sinus, in a fixed or dynamic fashion, with or without retroperfusion, and in a variety of preclinical and clinical settings. Although there is some experimental evidence to suggest that obstructing the coronary sinus may protect against myocardial ischemia,⁵ this approach

has not been established as a clinically useful strategy.

The Coronary Sinus Reducer for Treatment of Refractory Angina (COSIRA) trial, the results of which are now published in the *Journal*,⁶ was a double-blind, sham-controlled trial of a coronary-sinus reducing device in patients with refractory angina. The primary end point was the proportion of patients with an improvement of at least two Canadian Cardiovascular Society functional classes at 6 months. A total of 26 patients had this degree of improvement: 18 of 52 in the treatment group, and 8 of 52 in the control group ($P=0.02$). The trial was powered for an increase of 2.7 times in the proportion of patients with this degree of improvement, as compared with control, which was both ambitious and successfully achieved. It is important to note that this total number of 26 patients with this positive outcome is not sufficient for a reliable estimation of modest treatment effects,⁷ which underscores the limitation of small trials like this one to provide definitive information. Quality of life, as assessed with the use of the Seattle Angina Questionnaire, was significantly improved. Exercise time and stress wall motion did not improve significantly, nor was the trial powered to show improvement in these outcomes, although there were favorable trends.

This high-quality trial had a well-defined population, a sham control, attempts to keep the patient and treating physicians unaware of the study assignment, and a complete follow-up. The time needed to complete enrollment was longer than expected. This slow enrollment reflects the selective approach of rigorous determination of lack of suitability for revascularization, refractory nature of symptoms, ability to exercise, and substantial inducible ischemia in the left coronary distribution — criteria that are justified but that may make the results less generalizable to the broader population of patients with refractory angina.

The major limitations, however, are the small sample size, which limits confidence about the effectiveness of the intervention, and uncertainty over the effectiveness of maintaining the double-blind nature of the trial, which is particularly important given the subjective nature of the outcome. Even when the control group has been

effectively kept unaware of the study assignment, patients may believe that they have received the active treatment, which may explain why 15% of the patients in the control group had substantial improvement in their angina. SYMPLICITY HTN 3, a blinded trial that failed to replicate earlier open-label trials showing blood-pressure control with renal-artery denervation, provides a cautionary tale with regard to the hazards of the lack of effective blinding in the control group when cardiovascular procedures are evaluated.⁸ Should trials such as the COSIRA trial, to be more convincing, include an assessment of whether the blinding procedure was effective, since the interpretation depends on that assumption?

What do we conclude from the COSIRA trial? The study, although small and thus inconclusive, was well performed and showed significant improvements in reducing angina and improving quality of life. If confirmed in subsequent trials, coronary-sinus reducing therapy may be a welcome and needed addition to the options to improve the quality of life of patients with refractory angina.

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