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EDITOR'S PAGE

COAPTing Heart Failure Physicians, Interventional Cardiologists, and CardioThoracic Surgeons

A New Opportunity for Patients

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I recently attended a national meeting where I had the opportunity to hear the long awaited late-breaking trials presentation of the COAPT study. The trial was overwhelmingly positive on the primary and secondary endpoints (1). Dr. Gregg Stone received a great reception and applause from the crowd. It reminded me of the many great cardiovascular meetings in the past and late-breaking trials of acute coronary syndromes and heart failure that have been presented in these sessions. It has been a long time since the late-breaking trials was received with surprise and remarkable findings. What are the lessons learned from the COAPT trial that we can apply to our understanding of heart failure and the care of our patients, and why was this so different from the MITRA-FR study? (2)

COAPT was a trial that struggled with enrollment, requiring 89 centers over a 5-year period and screening over 1,500 patients to find 614 eligible for randomization. Many would have thought that an enrollment of <2 patients per site per year would not have survived trial conduct futility, and yet the investigators and leaders pushed on and met their anticipated sample size and event rates. Surprisingly, the primary endpoint of all hospitalizations for heart failure within the first 24 months was reduced by 47% and was highly statistically significant. The findings went even more robust in that over 443 events occurred in this study, making the stability of the findings sound with a relatively high magnitude of benefit. The hierarchical ordered secondary endpoints were all statistically significant, including a 38% reduction in all-cause mortality with the Mitra-Clip strategy versus guideline-directed medical therapy alone.

What would be potential reasons that this trial was so positive while MITRA-FR, a trial of 304 patients in France studying a similar patient population showed no significant difference on the primary endpoint, or any of the secondary endpoints?

Several important differences must be noted. First, the mitral regurgitation criteria were different, more severe in the COAPT study with smaller left ventricular dimensions. Acute suboptimal results occurred twice as often in the MITRA-FR patients in contrast to the COAPT patients. There was a 50% higher procedure complication rate in the MITRA-FR study. Perhaps the most important difference was the vigorous conduct of guideline-directed medical therapy by the heart failure co-principal investigators in COAPT. The study required that patients failed maximally tolerated guideline-directed medical therapy at baseline, and, therefore no major changes were made during follow-up, in contrast to the MITRA-FR study. While MITRA-FR patients achieved good baseline medication use, there were variable adjustments in each group during the follow-up phase reflecting a real-world practice pattern. This indeed may constitute part of the explanation, but when looking at the baseline medications of each group, there was high use of ACE-ARB/ARNI, beta-blockers, and MRAs, and, therefore, the adjustments in the doses may explain some of the differences at baseline and throughout the trial. Interestingly, there was significant dose adjustment in beta-blockers in the Mitra-Clip arm of COAPT versus the control group. There was also a trend towards more

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MRA adjustments. There were also statistically significant interactions in the MITRA-FR study favoring patients with less abnormal renal function. Despite this, the magnitude of the difference between the trials was large. A combination of these aspects explains some differences in outcomes, but the differences are still not fully explained.

How should we reconcile these findings in our subsequent guidelines? First, it is unlikely that there will be another trial in this patient population given the robust findings of COAPT and difficulty in maintaining equipoise. Second, the number of events and the magnitude of effect suggest that this is more than just a borderline finding, but a finding that is equivalent to two trials reaching a modest statistical significance at 0.05. Thus, given the strength of the COAPT findings in this narrow patient population of advanced heart failure, I believe that the evidence would warrant a Level 1B-R recommendation for this severely symptomatic and ill patient population. As we continue to digest the divergent findings from these two trials, we cannot underestimate the geographic variation and all potential factors that may be playing a role. Indeed, it was a day to celebrate for patients, a therapy that has profound effect on morbidity, mortality, and functional status, but should be limited, for now, to the patients with this subset of advanced heart failure after coapting with heart team.

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