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Response to Letters re: The COAPT Trial

The COAPT trial was a landmark study that demonstrated for the first time that correction of secondary or functional mitral regurgitation (MR) results in significant clinical benefits in patients with heart failure [1]. The addition of the MitraClip to maximally tolerated guideline-directed medical therapy (GDMT) resulted in a 47% reduction in hospitalization for heart failure, the primary endpoint at two years. In addition, there were significant 2-year improvements in survival, quality-of-life and exercise performance.

We appreciate the great interest generated by the COAPT outcomes as reflected by the letters to the editor in this issue. They raise some salient points that we would like to address. Khan et al. note that in COAPT, there was significant up-titration of both beta-blockers and mineralocorticoid receptor antagonists (MRA) during follow-up in the device arm [2]. The protocol intent was to maintain GDMT in both arms, and as reported, there were few major increases or reductions in medical therapy in both groups. However, MR reduction by the MitraClip increases cardiac output and blood pressure, enabling up-titration of medical therapy in some patients. These medication changes, which might be expected in real-world practice, may have contributed in small part to the therapeutic benefit in the device arm. However, we do not agree with the authors that a double-blinded sham-controlled study is required to mitigate this potential "bias" (which is actually a response to improved hemodynamics, not bias). The beta-blocker increase was transient (1-year timepoint only), and the MRA difference was small and not significant. Nitrate use at 1 and 2 years was actually more common in the control arm. These modest changes in medications cannot explain the marked absolute benefits of MR reduction observed in COAPT (number needed-to-treat 3 and 6 patients, respectively, to prevent one hospitalization and save one life within 2 years). Given these outcomes, it would be both unfeasible and unethical to conduct a sham-controlled study in which a group of patients meeting COAPT-eligibility criteria were not offered active treatment.

Goldberg raises a number of important issues [3]. First, he asks the question of whether MitraClip should now be a Class I indication for the treatment of secondary MR. This decision, of course, is made by guideline-writing committees based upon the robustness and the totality of the evidence. He rightly points out that more than one randomized trial is usually necessary for a Level of Evidence A. However, this does not preclude a Class I indication if the writing committee deems that the evidence from a single trial is conclusive. The guidelines are replete with such occurrences. It should be noted that the US Food and Drug Administration has recently approved MitraClip for the treatment of patients with secondary MR based on the COAPT trial without the need to convene an expert advisory panel, indicating its use for patients meeting strict COAPT eligibility criteria. And, as discussed above, it is unlikely that a randomized controlled trial as robust as COAPT will be repeated given the marked improvements in survival and quality of life by MitraClip treatment.

Goldberg also points out that while COAPT was strongly positive, the MITRA-FR trial, of similar design at first glance, did not show a mortality or heart failure benefit [4]. In addition to COAPT being twice as large and with 2-year rather than 1-year follow-up compared with MITRA-FR, closer inspection reveals that the patient populations enrolled in these two studies were different, as were the procedural performance and outcomes. Maximally tolerated GDMT was required and carefully monitored in COAPT, but not in MITRA-FR. Because of the differences in US and European definitions of the severity of secondary MR, patients in the French trial had less severe MR (mean effective regurgitant orifice area (EROA) 0.31 vs. 0.41 cm^2). The degree of left ventricular dilation was also substantially greater in MITRA-FR (mean LV end-diastolic volume index (LVEDVi) 135 mL/m^2 vs. 101 mL/m^2), further reducing the hemodynamic impact of the regurgitant volume. Grayburn and Packer have proposed that there was a greater responder population with "disproportionate" (very severe) MR in the COAPT trial than with MITRA-FR, in which most patients had "proportionate" or non-severe MR [5]. Finally, most of the US and Canadian interventionalists in COAPT were experienced MitraClip operators. The MitraClip acute success rates were higher and complications less frequent in COAPT than in MITRA-FR. Moreover, fewer clips were used and there was less durability of the repair in MITRA-FR, with greater recurrence of severe MR at one year than in COAPT.

The third point Goldberg raises is that patients may have been harmed by the aggressive medical therapy employed in COAPT. We find this comment baffling. All of the GDMT agents and their dosing regimens required in COAPT are Class I in the US and European Union heart failure guidelines and have been shown in large-scale randomized trials to reduce mortality and heart failure hospitalizations. GDMT usage in COAPT was reviewed and adjudicated in each patient by independent heart failure experts through central eligibility committee calls with the investigators. Many screened patients became asymptomatic and/or their MR substantially reduced once their medical regimen was optimized based on these expert recommendations. We feel strongly that the requirement for maximally tolerated GDMT was a key reason why there was such a compelling therapeutic benefit to the MitraClip: all appropriate alternative therapeutic options had been exhausted in the enrolled patients, identifying a population that could truly benefit by a mechanical intervention to reduce severe MR. Whether patients with lesser degrees of secondary MR might have benefitted is unknown, although treatment of moderate ischemic MR with a downsized annuloplasty ring was not beneficial in a large randomized trial [6].

We believe that adherence to the patient eligibility requirements and therapies utilized in the COAPT trial will maximize the chance of practitioners to replicate the trial results and avoid treatment of patients less likely to benefit. In this regard, the MITRA-FR trial was extremely helpful in helping define the responder and non-responder populations. Specifically, eligible heart failure patients should be symptomatic despite optimization on maximally tolerated doses of GDMT with prior cardiac resynchronization therapy and revascularization if indicated. Moderate-to-severe or severe MR should be present as assessed by a

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skilled echocardiographer, typically with an EROA of ≥0.3, LVESD ≤70 mm and left ventricular ejection fraction 20% to 50%. MitraClip implantation by experienced operators with as complete correction of MR as possible will likely lead to the best results. As the MitraClip addresses the secondary MR but not the underlying left ventricular dysfunction, it is important after the procedure to maintain and, if possible, up-titrate GDMT if hemodynamics improve.

Whether the beneficial effects of correcting secondary MR with the MitraClip are device-specific remains to be determined. We do not view the MitraClip as the final answer to the treatment of secondary MR but, rather, the first step in establishing the complementary roles of device therapy and GDMT. There likely will be MitraClip-ineligible patient cohorts who benefit from other types of repair therapy as well as surgical and transcatheter mitral valve replacement. Some of these approaches may also have utility in COAPT-eligible patients, but these approaches should be demonstrated to have a comparable or superior risk-benefit profile to the MitraClip in randomized trials. And, yes, there may be synergies in the combined use of different transcatheter devices with distinct mechanisms of MR reduction. We envision the COAPT trial as a rising tide that floats all boats and look forward to further developments in this exciting field.

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