Clinical Trial Perspective: Cost-effectiveness of Transcatheter Mitral Valve Repair Versus Medical Therapy in Patients with Heart Failure and Secondary Mitral Regurgitation. Results From the COAPT Trial

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Abstract

Treatment of secondary (or functional) mitral regurgitation had traditionally been limited to optimal medical therapy because studies have failed to show a survival benefit with mitral valve surgery for this condition. However, recently the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial demonstrated a significant decrease in heart failure hospitalizations and mortality in patients with severe secondary mitral regurgitation treated with percutaneous edge-to-edge mitral valve repair (TMVr) using the MitraClip device compared with medical therapy. Based on the results of the COAPT trial, the Food and Drug Administration granted approval for MitraClip treatment of patients with severe secondary mitral regurgitation in March 2019. In an attempt to understand the economic impact of treating this patient population with TMVr using the MitraClip device, a formal cost-effectiveness analysis was performed alongside the COAPT trial. This review summarizes the methods and results of the economic substudy of the COAPT trial and discusses the value of the MitraClip device from the perspective of the US healthcare system in the treatment of patients with symptomatic heart failure and secondary mitral regurgitation.

Keywords

Transcatheter mitral valve repair, secondary mitral regurgitation, cost-effectiveness, heart failure, mitral valve insufficiency, heart valve prosthesis implantation, percutaneous coronary intervention

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In the wake of transcatheter aortic valve replacement revolutionizing the treatment of aortic stenosis, sizeable interest has arisen in the development of percutaneous technologies to treat patients with mitral valve disease. Thus, when a percutaneous method of edge-to-edge mitral valve repair (TMVr) using the MitraClip device (Abbott Vascular) was introduced, this device was met with considerable enthusiasm. TMVr was first studied in the Endovascular Valve Edge-to-edge REpair STudy (EVEREST II), which randomized patients with severe mitral regurgitation to treatment with conventional mitral valve surgery or TMVr.[1] However, the results of the EVEREST II trial were mixed: TMVr demonstrated a good safety profile, but proved to be less effective than surgery in reducing mitral regurgitation.[1] Nevertheless, subgroup analyses suggested that TMVr may be more effective than surgery in the subset of patients with secondary (or functional) mitral regurgitation (SMR).[1]

Hence, the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial was designed to evaluate the effectiveness of TMVr using the MitraClip in the treatment of patients with symptomatic heart failure, reduced left ventricular ejection fraction (LVEF; 20–50%), and severe SMR.[2] Just over 600 patients were randomized 1:1 to either guideline-directed medical therapy (GDMT) or GDMT in addition to TMVr. At 2 years, treatment with TMVr led to a significant decrease in the primary endpoint of hospitalizations for heart failure (35.8% versus 67.9% per patient-year, p<0.001).[2] Furthermore, although rates of all-cause mortality were high in both groups (thereby reflecting the significant comorbidity of this patient population), patients treated with TMVr had substantially lower rates of death from any cause (29.1% versus 46.1%, p<0.001), as well as significantly better health status at 2 years (mean between-group difference in Kansas City Cardiomyopathy Questionnaire-Overall Summary Score 12.8 points, 95% CI [7.5–18.2 points]), than patients treated with GDMT only.[2,3] Reassuringly, the efficacy of TMVr appeared to be largely sustained at the 3-year follow-up in the intention-to-treat population (all-cause death 42.8% versus 55.5%, p=0.001; heart failure hospitalizations 46.5% versus 81.5%, p<0.001).[4] Given the rising cost of healthcare and the large patient population affected by severe

SMR and heart failure, a formal economic analysis was conducted alongside the COAPT trial to assess the potential effect on the US healthcare system of TMVr treatment in this population.

Clinical Trial Summary

The COAPT economic analysis included all randomized patients and was performed from the perspective of the US healthcare system. In-trial medical costs were assessed using a combination of resource-based accounting for procedural costs and hospital billing data for non-procedural costs. As the long-term efficacy and associated costs of TMVr beyond the 2-year trial period were unknown, observed in-trial data were used to project healthcare costs as well as patient-level quality-adjusted survival over a lifetime perspective. Lifetime survival was estimated using US life tables, which were recalibrated based on observed trial data so as to reflect the COAPT population. Future inpatient and outpatient healthcare costs were estimated using a regression model, which was derived from observed in-trial costs accrued 1 year after randomization. Incremental cost-effectiveness ratios (ICERs) were then calculated as the difference in mean lifetime healthcare costs divided by the difference in mean quality-adjusted life-years (QALYs) gained between the two treatment groups. Consistent with current American College of Cardiology and American Heart Association guidelines, ICERs of <$50,000, $50,000–150,000, and >$150,000 per QALY gained were considered to represent high, intermediate, and low economic value, respectively, within the US healthcare system.[5]

Although follow-up costs over the 2-year in-trial period were significantly lower in the TMVr than GDMT group ($26,654 versus $38,345, p=0.018), overall 2-year costs were substantially higher by approximately $35,000 with TMVr due to the high cost of the TMVr index hospitalization ($48,198).[6] Due to the higher initial costs of the TMVr procedure, in addition to a projected increase in quality-adjusted life expectancy of 0.82 years with TMVr, overall lifetime costs were estimated to be $45,648 higher with TMVr.[6] Accordingly, the ICER for TMVr versus GDMT was $55,600/QALY gained, consistent with TMVr therapy providing intermediate to high economic value. Further analyses did not reveal any patient subgroups (including advanced age, moderate to severe baseline tricuspid regurgitation, or severely depressed LVEF) in whom TMVr would be considered poor economic value. In addition, the ICER for TMVr remained below a threshold of $100,000/QALY gained over a range of sensitivity analyses, in which the durability of survival, quality of life, and cost benefits associated with TMVr were varied.

Discussion of Results

The results of the COAPT economic analysis demonstrated that TMVr using the MitraClip device is a cost-effective strategy by current US standards for the treatment of patients with heart failure and severe, symptomatic SMR. Although this treatment strategy is clearly not inexpensive, it is important to note that these findings are comparable to the results of cost-effectiveness analyses of other cardiovascular therapies used for the treatment of heart failure and/or valvular heart disease. For example, when transcatheter aortic valve replacement (TAVR) was compared to medical therapy in patients at extreme surgical risk in the Placement of AoRTic TraNscathetER Valve Trial (PARTNER) 1B trial, the ICER for TAVR versus medical therapy was $61,899/QALY gained.[7] Similarly, in the Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy (MADIT-CRT) trial, cardiac resynchronization therapy in addition to implantable cardiac defibrillators was associated with an ICER of $58,330/QALY gained compared with implantable cardiac defibrillators alone in patients with wide QRS complexes and reduced LVEF.[8]

Although it may seem counterintuitive that TMVr (or other cardiac device therapies) would not be cost saving in the long run, given the reduction in heart failure hospitalizations seen in follow-up, the higher long-term costs are due to a combination of factors. Certainly, the price of the MitraClip technology (estimated at $30,000 per procedure in the analysis) contributes substantially to the upfront cost of the therapy. That said, even if the device cost was assumed to be $0, TMVr would be cheaper, but still not cost saving, as demonstrated in sensitivity analyses (ICER = $20,754/QALY gained when MitraClip cost is assumed to be $0). In addition to the cost of the device, the persistently elevated long-term cost is also likely due to the substantial mortality benefit associated with TMVr and the high healthcare expenditures associated with improved survival. Indeed, researchers have estimated that the average adult over 70 years of age who reports a limitation in an activity of daily living spends approximately $22,000/year in 2018 for healthcare.[9] Thus, as long as treatment with TMVr results in prolonged survival, it is unlikely that this treatment strategy would ever result in cost savings in this complex population of patients with heart failure and other comorbidities.

There is also no guarantee that TMVr will be cost-effective in every patient with severe mitral regurgitation. The Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR) trial failed to show any mortality benefit or reduction in heart failure hospitalizations in another population of patients with severe SMR.[10] Consequently, it follows that TMVr would not have been found to be cost-effective in an economic analysis based on MITRA-FR trial data given the lack of efficacy and the known costs of the MitraClip procedure. Despite both trials enrolling patients with severe SMR, examination of the COAPT and MITRA-FR trials side by side has suggested that the populations of patients differed in important ways, with COAPT patients having more severe SMR relative to their left ventricular dysfunction and receiving more aggressive medical therapy, whereas MITRA-FR patients had more severe left ventricular dysfunction relative to their SMR and received less robust medical therapy prior to trial enrollment.[11,12] As these subtle differences in patient characteristics and treatment regimens may have led to opposing and dissimilar clinical results, which, in turn, would have different economic implications for TMVr, it follows that the acceptable economic value of TMVr can only be assumed in patients with SMR who closely mimic those enrolled in the COAPT trial.

In addition, the findings of the COAPT trial cannot necessarily be extrapolated to patients with primary mitral regurgitation or when TMVr is compared to treatments other than GDMT. In a 12-month cost-effectiveness analysis of EVEREST II (which included patients with both primary mitral regurgitation and SMR who were treated with either surgery or TMVr), researchers estimated that TMVr was decidedly not cost-effective (ICER >$400,000/QALY gained) compared to surgery in a modified intention-to-treat population.[13] Interestingly though, when the analysis was limited only to patients with acute procedural success, the cost-effectiveness of TMVr was found to be of good economic value, with

an ICER estimated at approximately $54,000/QALY gained compared with surgery.[13] As such, this further suggests that the economic value of TMVr in the treatment of mitral regurgitation is exceptionally reliant on its use in a highly selected patient population.

Study Limitations

The findings of the COAPT economic analysis should be considered in the context of several limitations. First, because billing data were not collected for follow-up costs, various costing methodologies were used to assign follow-up costs. As such, it is likely that these methods resulted in some underestimation of the total costs for both the GDMT and TMVr groups. In addition, the projections of lifetime costs and quality-adjusted survival were uncertain and were based on data through 2 years. As the COAPT trial allowed patients treated with GDMT to crossover to TMVr after 2 years, the accuracy of the lifetime assumptions in this analysis cannot be ascertained in future analyses. That said, sensitivity analyses, in which the duration of clinical and economic benefits associated with TMVr were varied, did demonstrate that TMVr provided at least intermediate economic value even under the most conservative of assumptions. Finally, as discussed above, these economic results only apply to patients who fit the inclusion and exclusion criteria for the COAPT trial because the same benefit of TMVr treatment versus GDMT was not observed in the MITRA-FR trial, which included patients with very poor left ventricular function, non-optimized medical therapy, and lesser degrees of mitral regurgitation.[10]

Clinical Practice Implications

For symptomatic heart failure patients with severe SMR despite optimal GDMT, TMVr using the MitraClip device increases quality-adjusted life expectancy at a cost that represents intermediate to high economic value in the US healthcare system. As such, TMVr represents a reasonable treatment strategy from both from a clinical and economic perspective in patients with severe SMR, similar to those enrolled in the COAPT trial. ■

1. Feldman T, Foster E, Glower DD, et al. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med* 2011;364:1395–406. https://doi.org/10.1056/NEJMoa1009355; PMID: 21463154.
2. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018;379:2307–18. https://doi.org/10.1056/NEJMoa1806640; PMID: 30280640.
3. Arnold SV, Chinnakondepalli KM, Spertus JA, et al. Health status after transcatheter mitral-valve repair in heart failure and secondary mitral regurgitation: COAPT trial. *J Am Coll Cardiol* 2019;73:2123–32. https://doi.org/10.1016/j.jacc.2019.02.010; PMID: 30894288.
4. Mack MJ. COAPT: three-year outcomes from a randomized trial of the MitraClip in patients with heart failure and severe secondary mitral regurgitation. Presented at TCT 2019, San Francisco, US, September 28, 2019.
5. Anderson JL, Heidenreich PA, Barnett PG, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:2304–22. https://doi.org/10.1016/j.jacc.2014.03.016; PMID: 24681044.
6. Baron SJ, Wang K, Arnold SV, et al. Cost-effectiveness of transcatheter mitral valve repair versus medical therapy in patients with heart failure and secondary mitral regurgitation: results from the COAPT trial. *Circulation* 2019;140:1881–91. https://doi.org/10.1161/CIRCULATIONAHA.119.043275; PMID: 31564137.
7. Reynolds MR, Magnuson EA, Wang K, et al. Cost-effectiveness of transcatheter aortic valve replacement compared with standard care among inoperable patients with severe aortic stenosis: results from the placement of aortic transcatheter valves (PARTNER) trial (cohort B). *Circulation* 2012;125:1102–9. https://doi.org/10.1161/CIRCULATIONAHA.111.054072; PMID: 22308299.
8. Noyes K, Veazie P, Hall WJ, et al. Cost-effectiveness of cardiac resynchronization therapy in the MADIT-CRT trial. *J Cardiovasc Electrophysiol* 2013;24:66–74. https://doi.org/10.1111/j.1540-8167.2012.02413.x; PMID: 22913474.
9. Lubitz J, Cai L, Kramarow E, Lentzner H. Health, life expectancy, and health care spending among the elderly. *N Engl J Med* 2003;349:1048–55. https://doi.org/10.1056/NEJMsa020614; PMID: 12968089.
10. Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med* 2018;379:2297–306. https://doi.org/10.1056/NEJMoa1805374; PMID: 30145927.
11. Nishimura RA, Bonow RO. Percutaneous repair of secondary mitral regurgitation – a tale of two trials. *N Engl J Med* 2018;379:2374–6. https://doi.org/10.1056/NEJMe1812279; PMID: 30575469.
12. Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT trials. *JACC Cardiovasc Imaging* 2019;12:353–62. https://doi.org/10.1016/j.jcmg.2018.11.006; PMID: 30553663.
13. Reynolds M, Galper B, Apruzzese P, et al. Cost effectiveness of the MitraClip compared with mitral valve surgery: 12-month results from the EVEREST II randomized controlled trial. *J Am Coll Cardiol* 2012;60(17 Suppl):B229. https://doi.org/10.1016/j.jacc.2012.08.831