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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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BACKGROUND: The COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) demonstrated that edge-to-edge transcatheter mitral valve repair (TMVr) with the MitraClip resulted in reduced mortality and heart failure hospitalizations and improved quality of life compared with maximally tolerated guideline-directed medical therapy (GDMT) in patients with heart failure and 3 to 4+ secondary mitral regurgitation. Whether TMVr is cost-effective compared with GDMT in this population is unknown.

METHODS: We used data from the COAPT trial to perform a formal patient-level economic analysis of TMVr+GDMT versus GDMT alone for patients with heart failure and 3 to 4+ secondary mitral regurgitation from the perspective of the US healthcare system. Costs for the index TMVr hospitalization were assessed using a combination of resource-based accounting and hospital billing data (when available). Follow-up medical care costs were estimated on the basis of medical resource use collected during the COAPT trial. Health utilities were estimated for all patients at baseline and 1, 6, 12, and 24 months with the Short Form Six-Dimension Health Survey.

RESULTS: Initial costs for the TMVr procedure and index hospitalization were $35 755 and $48 198, respectively. Although follow-up costs were significantly lower with TMVr compared with GDMT ($26 654 versus $38 345; P=0.018), cumulative 2-year costs remained higher with TMVr because of the upfront cost of the index procedure ($73 416 versus $38 345; P<0.001). When in-trial survival, health utilities, and costs were modeled over a lifetime horizon, TMVr was projected to increase life expectancy by 1.13 years and quality-adjusted life-years by 0.82 years at a cost of $45 648, yielding a lifetime incremental cost-effectiveness ratio of $40 361 per life-year gained and $55 600 per quality-adjusted life-year gained.

CONCLUSIONS: For symptomatic patients with heart failure and 3 to 4+ secondary mitral regurgitation, TMVr increases life expectancy and quality-adjusted life expectancy compared with GDMT at an incremental cost per quality-adjusted life-year gained that represents acceptable economic value according to current US thresholds.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01626079.

Key Words: congestive heart failure ■ cost-benefit analysis ■ heart failure ■ mitral valve ■ mitral valve insufficiency ■ randomized controlled trial

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Clinical Perspective

What Is New?

- Although the COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) demonstrated that transcatheter mitral valve repair (TMVr) with the MitraClip resulted in reduced mortality and heart failure hospitalizations compared with guideline-directed medical therapy in patients with heart failure and 3 to 4+ secondary mitral regurgitation (SMR), whether TMVr is cost-effective compared with guideline-directed medical therapy in this population was unknown.
- Although follow-up costs were significantly lower with TMVr compared with guideline-directed medical therapy, cumulative 2-year costs remained higher with TMVr because of the upfront cost of the index procedure.
- Compared with guideline-directed medical therapy, TMVr was projected to increase quality-adjusted life expectancy by 0.82 years at a cost of $45 648, yielding a lifetime incremental cost-effectiveness ratio of $55 600 per quality-adjusted life-year gained.

What Are the Clinical Implications?

- For symptomatic patients with heart failure and 3 to 4+ secondary mitral regurgitation, TMVr increases quality-adjusted life expectancy compared with GDMT at a cost that represents acceptable economic value according to currently accepted US thresholds.
- Together with the improved clinical outcomes seen with TMVr compared with GDMT alone in the COAPT trial, these findings suggest that TMVr is a reasonable treatment strategy for this patient population on the basis of both clinical and economic considerations.

Although guideline-directed medical therapy (GDMT) and cardiac resynchronization therapy have been shown to improve symptoms and left ventricular function in patients with secondary (or functional) mitral regurgitation,[1,2] surgical intervention on the mitral valve has not been shown to decrease mortality or to reduce recurrent heart failure events in these patients.[3] Therefore, current American College of Cardiology/American Heart Association guidelines offer only a Class IIb recommendation for mitral valve surgery for the treatment of patients with severe, symptomatic secondary mitral regurgitation (SMR),[4] and the majority of these patients are treated with medical therapy alone. Recently, the COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) demonstrated that percutaneous edge-to-edge transcatheter mitral valve repair (TMVr) with the MitraClip device resulted in improved survival and lower rates of hospitalization for heart failure compared with maximally tolerated GDMT in patients with symptomatic heart failure and 3 to 4+ SMR.[5] Therefore, TMVr may offer an effective therapy for a population at high risk for poor functional status, recurrent hospitalizations for heart failure, and impaired long-term survival.[6]

Given the rising cost of health care, it is essential to understand the cost-effectiveness of new therapies, especially when the technology involved is costly and the target population is large and characterized by significant comorbidities. Because patients with severe SMR often experience poor clinical outcomes and high rates of healthcare resource use, whether TMVr can provide meaningful health benefits to this population at an acceptable cost is particularly important. To further understand the economic impact of TMVr in patients with heart failure and 3 to 4+ SMR, we conducted a formal patient-level economic analysis alongside the COAPT trial. This study aimed to evaluate the long-term costs and cost-effectiveness of TMVr with the MitraClip device compared with GDMT in this population.

METHODS

Study Design and Patient Population

As previously described, the COAPT trial (URL: https://www.clinicaltrials.gov. Unique identifier: NCT01626079) enrolled patients with symptomatic heart failure, left ventricular ejection fraction between 20% and 50%, and 3 to 4+ SMR.[5] Before randomization, patients were assessed by a heart team, including a heart failure specialist, an interventional cardiologist, and a cardiothoracic surgeon, to ensure that the patient was receiving maximally tolerated GDMT, was eligible for a MitraClip device, and was not appropriate for mitral valve surgery. Patients were then randomized in a 1:1 fashion to receive either TMVr with the MitraClip device in addition to GDMT (hereafter referred to as *TMVr*) or GDMT alone (hereafter referred to as *GDMT*). The COAPT trial was approved by the institutional review board at each site, and written informed consent was obtained from all patients. The data, analytical methods, and study materials for this analysis will not be made available to other researchers.

Analytic Overview

The economic analysis was performed from the perspective of the US healthcare system and included all randomized patients analyzed from the time of randomization according to intention to treat. Hospital charges for the index MitraClip procedure and data on survival, quality of life, and healthcare resource use were collected through a minimum of 1 year on all patients and up to 2 years of follow-up. Observed in-trial data were used to project patient-level survival, health utilities, and costs over a lifetime perspective; and uncertainty was assessed with bootstrap resampling. Lifetime cost-effectiveness at the treatment group level was calculated in terms

of cost per life-year and cost per quality-adjusted life-year (QALY) gained. By combining patient-level data from the in-trial period with patient-level projections of lifetime survival, utilities, and cost projections, this blended analytical approach remains faithful to the observed trial outcomes while still capturing the full range of stochastic variability in the clinical and economic effects of TMVr.

Assessment of In-Trial Medical Costs

Medical costs were assessed using a combination of resource-based accounting and hospital billing data, as described previously,[7,8] and are reported in 2018 US dollars. Costs from years before 2018 were converted to 2018 dollars using the medical care component of the Consumer Price Index.

Index MitraClip Hospitalization Costs

For the initial procedure, resources used during a standard MitraClip procedure, including sheaths, guidewires, transseptal needles, and closure devices, were identified. Resource costs were estimated by multiplying item counts by the average acquisition cost per unit at Saint Luke's Mid America Heart Institute in Kansas City, Missouri. According to data from the manufacturer, the acquisition cost for the MitraClip device is currently $30 000 per procedure and does not vary with the number of MitraClips used or implanted (Abbott internal data; personal communication with Abbott representative, August 28, 2019). This fixed price per procedure (rather than per device) was designed to ensure that operators would not be tempted to accept suboptimal procedural results to limit procedural costs. Ancillary procedural costs (including catheterization laboratory overhead, nonphysician personnel, and general supplies) were derived from the average cost per procedure at Saint Luke's Mid America Heart Institute and adjusted for measured procedural room time. Because it was assumed that an echocardiography technologist would be present for every procedure in addition to standard catheterization laboratory staff, this cost was also included in the procedural cost and was based on the hourly wage of an echocardiography technologist.

The remaining nonprocedural costs for each index admission for patients who underwent an attempted MitraClip were calculated from hospital bills when available (n=96) by multiplying nonprocedural charges by cost center–specific cost-to-charge ratios obtained from the Medicare cost report for each hospital. When bills were not available (n=197), nonprocedural costs were estimated using a linear regression model derived from patients with billing data. Covariates considered for the model included age, sex, intensive care unit (ICU) and non-ICU length of stay, days on mechanical ventilation, transfusion, intra-aortic balloon pump use, mitral valve surgery, repeat MitraClip procedure, and renal replacement therapy. Because of the infrequency of complications, only age, sex, and length of stay (ICU and non-ICU) were retained in the final model (R^2=0.36).

In-Trial Follow-Up Costs

During the trial period, details (including primary diagnosis, major procedures, and length of stay) for all follow-up hospitalizations were recorded on case report forms. From these data, each admission was assigned a Medicare Severity-Adjusted Diagnosis-Related Group by a study investigator who was blinded to treatment assignment. Costs for these admissions were calculated by assigning the mean national reimbursement for each respective Medicare Severity-Adjusted Diagnosis-Related Group to the admission.[9]

Data on emergency room visits and medication use also were collected on case report forms. The primary diagnoses for emergency room visits were identified, and each visit was assigned a diagnosis-based cost, which was derived from the average cost of an emergency room visit at Saint Luke's Mid America Heart Institute for a similar diagnosis. Outpatient cardiac medication use was assessed at each follow-up visit, and costs were assigned with the use of average wholesale prices from the Micromedex Red Book.[10] Costs associated with short-term skilled nursing facility stays, in-patient rehabilitation stays, and outpatient rehabilitation services were estimated on the basis of average Medicare reimbursement for these services in the 30-day period after hospitalization for the specific Medicare Severity-Adjusted Diagnosis-Related Group using data derived from the IBM MarketScan research database.[11]

Physician Fees

Physician fees for the MitraClip procedure were derived from the Medicare fee schedule and included fees for a primary operator (adjusted for the number of MitraClips implanted) and an assisting implanter, fees for a cardiac anesthesiologist (based on measured duration of anesthesia), and fees for intraoperative transesophageal echocardiography. Fees for nonprocedural daily care for the index hospitalization were derived from the Medicare fee schedule on the basis of measured ICU and non-ICU length of stay. For follow-up hospitalizations, physician fees were assumed to be 20% of the hospital costs for each admission.[7,8] For heart failure–related office visits, physician fees were estimated from the Medicare fee schedule.

Estimation of Life-Expectancy, Quality-Adjusted Life Expectancy, and Long-Term Costs

Projected survival beyond the trial was estimated separately for the TMVr and GDMT groups. For the GDMT group, survival between time of randomization and last observed follow-up within 2 years was compared with expected age- and sex-adjusted mortality using US life tables[12] to calculate a calibration factor (relative mortality hazard). For each surviving patient, life expectancy beyond the last observed follow-up was then estimated from recalibrated life tables. Survival for the TMVr group was estimated in an analogous fashion after application of the hazard ratio for mortality after TMVr versus GDMT derived from a landmark analysis of trial data between 30 days and the last observed follow-up within 2 years. This landmark analysis was chosen to minimize the effect of periprocedural complications on the long-term hazard ratios.

Quality of life was assessed at baseline and at 1, 6, 12, and 24 months with the Medical Outcomes Study Short-Form 36 health status instrument, and responses were converted to utility weights using a published algorithm.[13] During the

in-trial period, quality-adjusted life expectancy was calculated for each patient as a time-weighted average of his or her utility values, with the midpoint between assessments used as the transition between health states. Missing utility values were estimated from fully conditional multiple imputation, with baseline patient characteristics and previous utility values informing the imputation. Utilities for lifetime projections were estimated from a regression model on the basis of available data through 2 years and adjusted for age, sex, baseline utility, treatment group, stroke before the last observed utility assessment, and left ventricular assist device or transplantation before the last observed utility assessment. Quality-adjusted life expectancy beyond the in-trial period was then calculated by multiplying estimated survival in 30-day intervals by predicted utilities.

Future healthcare costs (including costs associated with hospitalizations, rehabilitation, physician services, medications, and outpatient services) beyond the trial period were estimated on the basis of a regression model (which included age, sex, and treatment group as covariates) that was derived from observed costs from 1 year after randomization to the end of the in-trial observation period (up to 2 years).

Statistical Analysis

Categorical data are reported as frequencies and were compared by use of the Fisher exact test. Continuous data are reported as mean±SD and were compared by 2-sample Student *t* tests for normally distributed variables or Wilcoxon rank-sum tests for nonnormally distributed variables. Cost data are reported as both mean and median values, and costs between groups were compared by nonparametric bootstrapping. Because not all patients had complete 2-year follow-up data, methods for the analysis of censored data were used to estimate costs, resource use, and utilities at each follow-up time point,[14] and the bootstrap method was used to calculate confidence limits associated with these calculations.[15] Treatment group means and between-group differences (with associated 95% CIs) for projected life expectancy, quality-adjusted life expectancy, and lifetime costs were generated with bootstrap resampling with 1000 replicates. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). A value of $P<0.05$ was considered statistically significant with no adjustment for multiple comparisons.

Cost-Effectiveness Analyses

For the purpose of cost-effectiveness analyses, all future costs and benefits were discounted at 3%/y, consistent with US guidelines.[16] Incremental cost-effectiveness ratios were calculated as the difference in mean discounted lifetime costs divided by the difference in mean discounted life expectancy or quality-adjusted life expectancy. Uncertainty in the joint distribution of lifetime cost and survival differences was estimated using bootstrap resampling (1000 replicates).

Because the duration of the survival, quality of life, and follow-up cost benefits of TMVr versus GDMT beyond the 2-year trial period are unknown, 3 sets of analyses were performed on the basis of different assumptions regarding the length of TMVr benefit. The base case analysis assumed that the benefits of TMVr decreased in a linear fashion from years 2 to 5, such that there was no benefit of TMVr beyond year 5 (ie, difference in utility=0; cost difference=0; mortality hazard ratio for TMVr versus GDMT=1 beyond year 5). Two separate sensitivity analyses were also performed with the assumptions that the benefits of TMVr observed at the end of the trial period remained constant through a patient's lifetime (ie, mortality hazard ratio, utility benefits, and cost differences sustained without attenuation; best case scenario) and that the in-trial benefits of TMVr did not extend beyond 2 years (ie, difference in utility=0; cost difference=0; mortality hazard ratio for TMVr versus GDMT=1 after year 2; worst case scenario).

In addition to evaluating the effects of varying the duration of benefit seen with TMVr, further sensitivity analyses were performed to evaluate the effect of variation in the discount rate, MitraClip device cost, and index procedural costs (excluding the cost of the MitraClip device). Lifetime cost-effectiveness results were also estimated for subgroups according to sex, age (dichotomized at 75 years), Society of Thoracic Surgeons Mortality Risk Score (dichotomized at 8%), degree of tricuspid regurgitation at baseline (dichotomized at 3+), baseline left ventricular ejection fraction (dichotomized at 30%), type of cardiomyopathy (ischemic versus nonischemic), baseline mitral regurgitation (3+ versus 4+), and severity of symptoms at baseline (New York Heart Association class I/II versus III/IV).

RESULTS

Study Population

Between December 2012 and June 2017, 614 patients were enrolled in the COAPT trial at 78 centers and randomized to treatment with either TMVr in addition to GDMT (n=302) or GDMT alone (n=312). Of the 302 patients randomized to TMVr, 293 underwent attempted device implantation. All patients randomized to TMVr were analyzed in the TMVr cohort, including the 9 patients who did not undergo the MitraClip procedure. Baseline characteristics of the study population are summarized in Table 1. Patients had a mean age of ≈72 years, and >60% were male. Patients in both groups had frequent comorbidities, including 40% with prior coronary artery bypass graft surgery, ≈50% with prior myocardial infarction, and >50% with atrial fibrillation or flutter. The type of cardiomyopathy was ischemic in 61% of patients, and the mean left ventricular ejection fraction was 31% in both groups. There were no important differences in baseline clinical or echocardiographic characteristics between the TMVr and GDMT groups.

Index Procedure and Hospitalization Costs

Resource use and costs for the initial TMVr procedure and associated index hospitalization are shown in Table 2. For the 293 patients who underwent attempted TMVr implantation, mean procedural duration (defined as time the patient was in the procedure room) was 171 minutes, and mean total length of stay was 2.5 days. The mean cost for the TMVr procedure was $35 755

Table 1. Baseline Characteristics

Characteristic	Transcatheter Mitral Valve Repair (n=302)	Guideline-Directed Medical Therapy (n=312)	*P* Value
Age, y	71.1±11.8	72.8±10.5	0.217
Male sex	201 (67)	192 (62)	0.195
Society of Thoracic Surgery risk score, %	7.8±5.5	8.5±6.2	0.157
Hypertension	243 (81)	251 (80)	0.996
Hyperlipidemia	166 (55)	163 (52)	0.498
Diabetes mellitus	106 (35)	123 (39)	0.268
Coronary artery disease	218 (72)	228 (73)	0.804
Prior myocardial infarction	156 (52)	160 (51)	0.926
Prior percutaneous coronary intervention	130 (43)	153 (49)	0.136
Prior coronary artery bypass grafting	121 (40)	126 (40)	0.935
Prior stroke or transient ischemic attack	56 (19)	49 (16)	0.350
Peripheral arterial disease	52 (17)	57 (18)	0.733
Atrial fibrillation/flutter	173 (57)	166 (53)	0.309
Chronic obstructive pulmonary disease	71 (24)	72 (23)	0.899
Type of cardiomyopathy			0.929
Ischemic	184 (61)	189 (61)	
Nonischemic	118 (39)	123 (39)	
Left ventricular ejection fraction, %	31.3±9.1	31.3±9.6	0.971
New York Heart Association class III or IV	172 (57)	201 (65)	0.051
Prior cardiac resynchronization therapy	115 (38)	109 (35)	0.418

Values are n (%) or mean±SD.

(excluding physician fees), of which $30 628 was attributable to the cost of devices used in the procedure. After the inclusion of ancillary costs and physician costs, the total cost of the index hospitalization was $48 198. There were no significant differences in index hospitalization costs between patients with available billing data and patients in whom index hospitalization costs were imputed (Table I in the online-only Data Supplement).

Follow-Up Resource Use and Costs

Follow-up resource use and costs for the intention-to-treat study population are summarized in Table 3. Between discharge and the 2-year follow-up, TMVr led to a significant reduction in the number of hospitalizations compared with GDMT (1.7 versus 2.2 per patient; *P*=0.004), driven largely by a reduction in heart failure–related hospitalizations. There was a trend toward fewer hospital days per patient with TMVr versus GDMT (10.6 versus 13.8 per patient; *P*=0.06), and the use of post–acute care services was also less frequent with

Table 2. Index Hospitalization Resource Use and Costs for Patients Who Underwent Attempted Transcatheter Mitral Valve Repair

Resource Category	Transcatheter Mitral Valve Repair (n=293)
Procedure duration, min	171±110
Length of stay, d	
Intensive care unit	0.6±1.2 (0)
Non– intensive care unit	1.9±2.0 (1)
Total	2.5±2.3 (2)
Index procedural costs, $	
Devices	30 628±3888 (31 135)
Room/depreciation	4034±1250 (3978)
Nonphysician personnel	1093±353 (1047)
Total index procedural costs, $*	35 755±4080 (36 107)
Index hospitalization costs, $	
Index procedure costs	35 755±4080 (36 107)
Nonprocedural costs	8030±6283 (6214)
Physician fees	4413±667 (4519)
Total index admission costs	48 198±8107 (47 009)

Values are mean±SD (median).
*Excluding physician fees.

TMVr. As a result, follow-up medical care costs were reduced by $11 690 per patient with TMVr versus GDMT (95% CI, −$20 714 to −$3,010; *P*=0.018). However, combined with the upfront cost of the initial TMVr admission, cumulative 2-year costs remained significantly higher with TMVr ($73 416 versus $38 345; mean difference, $35 072 [95% CI, 26 370–44 085]; *P*<0.001).

In-Trial Utilities and QALYs

As reported previously, all-cause mortality within 24 months was 29.1% in the TMVr group versus 46.1% in the GDMT group (*P*<0.001).[5] As a result, mean in-trial survival duration was greater with TMVr than with GDMT (1.48 years versus 1.34 years; mean difference, 0.14 years [95% CI, 0.05–0.26]; *P*=0.006). In addition, utility scores were significantly higher at all follow-up time points in patients treated with TMVr (Table II in the online-only Data Supplement). When these utilities were combined with survival, in-trial QALYs were 1.13 and 1.00 years for TMVr and GDMT, respectively (mean difference, 0.13 QALYs [95% CI, 0.06–0.21]; *P*<0.001).

Lifetime Projections

Figure 1 displays projected survival curves for the TMVr and GDMT groups under our base case assumptions. In this scenario, life expectancy was projected to be 6.12 and 4.63 years for the TMVr and GDMT groups, respectively (mean difference, 1.49 years [95% CI, 0.60– to 2.43]). After discounting, these values decreased to 5.05 and 3.92 years (mean difference, 1.13 years [95%

Table 3. Follow-Up Resource Use and Costs at 2 Years

Resource Category*	Transcatheter Mitral Valve Repair (n=302)	Guideline-Directed Medical Therapy (n=312)	Difference (95% CI)	*P* Value
Hospitalizations, n	169 (145 to 191)	218 (195 to 245)	−50 (−84 to −16)	0.004
Heart failure	56 (44 to 70)	95 (81 to 111)	−38 (−60 to −18)	<0.001
Cardiovascular but not heart failure	35 (27 to 43)	35 (28 to 43)	−0.2 (−12 to 10)	0.972
Noncardiovascular	78 (64 to 92)	89 (75 to 107)	−12 (−35 to 9)	0.270
Hospital days	1060 (823 to 1323)	1383 (1163 to 1620)	−323 (−633 to 13)	0.060
Skilled nursing facility/rehabilitation days	289 (240 to 344)	375 (316 to 443)	−86 (−170 to −6)	0.040
Emergency room visits, n	49 (39 to 61)	52 (40 to 66)	−3 (−19 to 14)	0.758
Office visits related to heart failure, n	94 (62 to 131)	105 (73 to 144)	−11 (−61 to 40)	0.668
Costs, $				
Hospitalizations	18072 (13918 to 22601)	27211 (21869 to 33139)	−9149 (−16456 to −2046)	0.020
Skilled nursing facility/rehabilitation	2091 (1756 to 2444)	2694 (2330 to 3100)	−602 (−1137 to −57)	0.030
Outpatient services	301 (233 to 380)	354 (273 to 439)	−53 (−162 to 62)	0.370
Medications	2506 (2096 to 2988)	2553 (1964 to 3172)	−48 (−834 to 708)	0.954
Physician fees	3684 (2844 to 4598)	5522 (4457 to 6714)	−1838 (−3325 to −411)	0.020
Total follow-up	26654 (21415 to 32327)	38345 (31715 to 45626)	−11690 (−20714 to −3010)	0.018
Cumulative 2 y	73416 (67973 to 79494)	38345 (31715 to 45626)	35072 (26370 to 44085)	<0.001

Values are mean (95% CI) and are adjusted for censoring.
*Resource counts are per 100 patients.

CI, 0.47–1.81]). Discounted quality-adjusted life expectancy was projected to be 3.32 and 2.50 QALYs with TMVr and GDMT, respectively (mean difference, 0.82 QALYs [95% CI, 0.39–1.29]). Projected lifetime medical care costs were $121390 and $75742 for the TMVr and GDMT groups, a difference of $45648 (95% CI, 32807–59143) per patient.

Cost-Effectiveness Analyses

A plot of the joint distributions of the projected differences in lifetime costs and QALYs based on bootstrap replication is shown in Figure 2. According to these lifetime projections, the incremental cost-effectiveness ratio for TMVr versus GDMT was $55600 per QALY. The probability that TMVr would provide high economic value (ie, incremental cost-effectiveness ratio <$50000 per QALY) was 27.5%, whereas the probability that TMVr would provide at least intermediate economic value (ie, incremental cost-effectiveness ratio <$150000 per QALY) was 99.8% (Figure 3). When benefits were assessed in life-years, the incremental cost-effectiveness ratio was $40361 per life-year, and the probabilities that the ratios were <$50000 or <$150000 per life-year were 82.9% and 99.8%, respectively (Figures I and II in the online-only Data Supplement).

Sensitivity and Subgroup Analyses

Table 4 summarizes the results of key sensitivity analyses. Varying assumptions about the durability of benefits (survival, quality of life, and follow-up costs) of TMVr resulted in modest alterations in the estimated incremental cost-effectiveness ratios. Under the best case scenario, TMVr was associated with an incremental cost-effectiveness ratio of $27733 per QALY, whereas the worst-case scenario resulted in an incremental cost-effectiveness ratio of $70592 per QALY. Although lifetime costs only varied by ≈10% between the best case and worst case scenarios, differences in projected life expectancy varied >2-fold (Figure III in the online-only Data Supplement), which drove most of the variation in the incremental cost-effectiveness ratios. We estimated that TMVr would be highly cost-effective (ie, incremen-

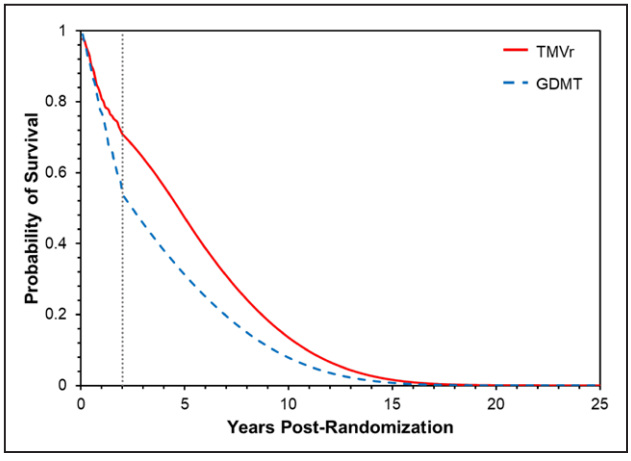

Figure 1. Survival projections for transcatheter mitral valve repair (TMVr) and guideline-directed medical therapy (GDMT).
Projected survival with TMVr (red) and GDMT (blue) based on 2-year observed data and recalibrated life tables under base case assumptions.

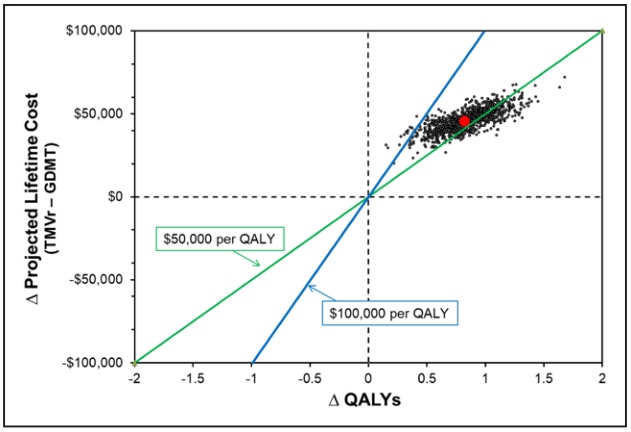

Figure 2. Joint distribution of lifetime incremental cost and quality-adjusted life-years (QALYs) for transcatheter mitral valve repair (TMVr) vs guideline-directed medical therapy (GDMT).
Incremental lifetime costs and benefits with TMVr vs GDMT plotted on the cost-effectiveness plane with benefits expressed as QALYs. Solid red circle represents base case estimates; the surrounding small circles represent individual results for 1000 replicates of the study using bootstrap resampling; the solid green line represents a willingness-to-pay threshold of $50 000 per QALY gained; and the solid blue line represents a willingness-to-pay threshold of $100 000 per QALY gained. The base case results demonstrated a gain of 0.82 QALYs at an incremental cost of $45 648 per patient (after discounting), resulting in an incremental cost-effectiveness ratio of $55 600 per QALY gained.

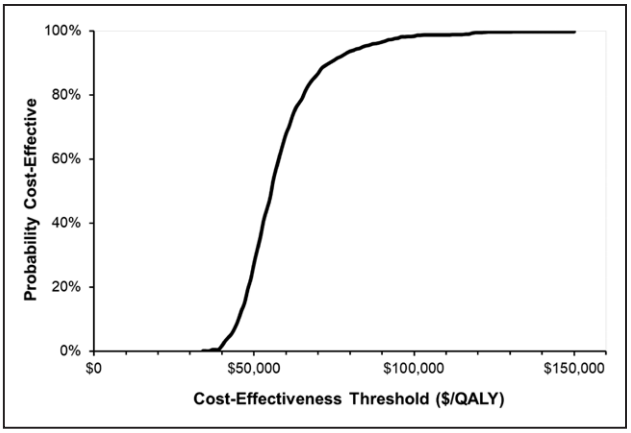

Figure 3. Cost-effectiveness acceptability curve for transcatheter mitral valve repair (TMVr) vs guideline directed medical therapy.
The probability that TMVr is cost-effective, calculated as the proportion of bootstrap iterations that fall below a given cost-effectiveness threshold, plotted across a range of possible cost-effectiveness thresholds. QALY indicates quality-adjusted life-year.

tal cost-effectiveness ratio <$50 000 per QALY) if the benefit of TMVr was sustained with gradual attenuation for ≥7 years (Figure 4).

The incremental cost-effectiveness ratio for TMVr remained below a threshold of $100 000 per QALY with plausible variations in the discount rate, index procedure costs, and MitraClip device costs (Table 4) and across all prespecified subgroups (Table 5). Of note, even if the MitraClip device cost was $0, TMVr was not projected to reduce overall healthcare costs compared with GDMT alone (Figure IV in the online-only Data Supplement). Results were similar when cost-effectiveness was expressed in terms of cost per life-year gained (Tables III and IV in the online-only Data Supplement).

DISCUSSION

This is the first study to evaluate the cost-effectiveness of TMVr versus GDMT in patients with 3 to 4+ SMR and heart failure from the perspective of the US healthcare system. Using individual patient-level survival, quality of life, and cost data from the randomized COAPT trial, we found that TMVr in addition to GDMT reduced 2-year follow-up costs by more than $11 000 per patient compared with GDMT alone. Nonetheless, cumulative 2-year costs remained substantially higher by approximately $35 000 per patient with TMVr as a result of the upfront cost of the index TMVr hospitalization. When the observed in-trial results were projected over a lifetime horizon, TMVr was associated with substantial gains in life expectancy and quality-adjusted life expectancy at an incremental cost of about $45 000 per patient. The resulting incremental cost-effectiveness ratios for TMVr compared with GDMT were $55 600 per QALY gained and $40 361 per life-year gained, values near or below the thresholds considered to represent high economic value for cardiac therapies in the United States.[17] Although results varied modestly across a range of subgroup and sensitivity analyses, there were no patient subgroups or alternative scenarios in which TMVr would be considered to be of low economic value.

To place this analysis in context, it is useful to consider these results relative to other cardiovascular therapies used to treat valvular heart disease and heart failure. Perhaps the most comparable case is the use of transcatheter aortic valve replacement for patients with severe aortic stenosis at extreme surgical risk. Using data from the PARTNER 1B trial (Placement of Aortic Transcatheter Valves), Reynolds and colleagues[7] found that the incremental cost-effectiveness ratio for transcatheter aortic valve replacement versus medical therapy was $61 889 per QALY gained, a value that is very similar to the incremental cost-effectiveness ratio for TMVr versus GDMT in the COAPT trial. The cost-effectiveness of TMVr is also comparable to that of other commonly used technologies for the treatment of heart failure, including implantable cardiac defibrillators for the prevention of sudden cardiac death[18] and biventricular pacing,[19–21] and TMVr is substantially more cost-effective than continuous-flow left ventricular assist devices used for destination therapy.[22]

Our study provides several unique insights into the value proposition for TMVr. Although we found TMVr to be reasonably cost-effective by current US standards, it does not appear to be a cost-saving strategy, even if we assumed that the cost of the MitraClip device was $0. Of note, similar findings were noted with transcatheter aortic valve replacement in patients with aortic stenosis at extreme surgical risk.[7] Although this finding

Table 4. Projected Lifetime Costs, Quality-Adjusted Life-Years, and Incremental Cost-Effectiveness Ratio Under Base Case Assumptions and Sensitivity Analyses

	Lifetime Costs, $			Quality-Adjusted Life-Years			ICER, $/QALY	Probability <$50 000 per QALY Gained, %	Probability <$100 000 per QALY Gained, %
	TMVr	GDMT	Difference	TMVr	GDMT	Difference			
Base case	121 390	75 742	45 648	3.32	2.50	0.82	55 600	28	98
Discount rate									
0%	137 274	86 481	50 792	4.01	2.96	1.06	48 144	60	99
5%	113 943	70 532	43 411	3.00	2.28	0.71	60 800	13	97
MitraClip device cost									
$0	92 781	75 742	17 039	3.23	2.50	0.82	20 754	100	100
$20 000	111 853	75 742	36 112	3.23	2.50	0.82	43 985	78	100
$40 000	130 926	75 742	55 185	3.23	2.50	0.82	67 217	4	95
Index procedure costs*									
↓50%	117 937	75 742	42 195	3.32	2.50	0.82	51 395	43	100
↑50%	123 862	75 742	48 120	3.32	2.50	0.82	58 611	14	99
Varying benefit of TMVr									
Best-case scenario†	116 897	75 742	41 156	3.99	2.50	1.48	27 733	99	100
Worst-case scenario‡	122 333	75 742	46 591	3.16	2.50	0.66	70 592	4	90

GDMT indicates guideline-directed medical therapy; QALY, quality-adjusted life-year; and TMVr, transcatheter mitral valve repair.

*Excludes the cost of the MitraClip device.

†Best-case scenario: survival benefit, health status benefit, and cost benefit observed at 2 years remain constant throughout the patient's lifetime.

‡Worst-case scenario: no further survival benefit, health status benefit, or cost benefit after 2 years (ie, hazard ratio=1; difference in cost=0; difference in utilities=0).

may seem counterintuitive given the substantial clinical benefits and follow-up cost-savings seen with TMVr, it is a direct consequence of the high healthcare costs (estimated at about $21 770/y in 2018 dollars for an average adult >70 years of age with a reported limitation in an activity of daily living[23]) associated with prolonged survival in a complex population with heart failure and multiple other comorbidities.

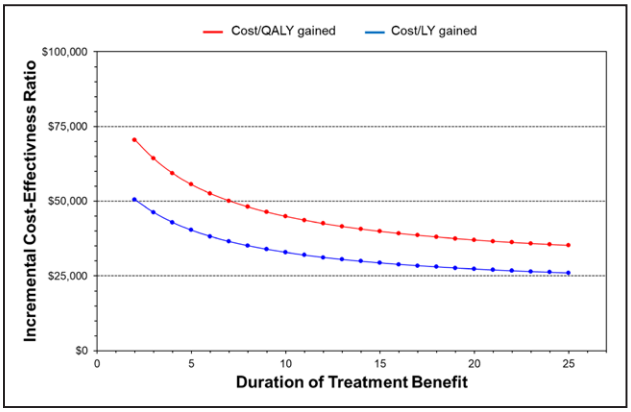

Figure 4. Sensitivity analysis: impact of alternative assumptions on the duration of benefit of transcatheter mitral valve repair (TMVr) on cost-effectiveness compared with guideline-directed medical therapy (GDMT) alone. The impact of variations in duration of clinical and economic benefit with TMVr vs GDMT shown as dollars per quality-adjusted life-year (QALY) gained (red) or dollars per life-year (LY) gained (blue). A duration of TMVr benefit of ≈7 years would result in the incremental cost-effectiveness ratios falling below a threshold of $50 000 per QALY gained. Duration of treatment benefit refers to the time at which the economic, quality of life, and survival benefits of TMVr become equal to those of GDMT.

Another important finding from our study is that the cost-effectiveness of TMVr varies according to the duration of clinical benefit provided by TMVr compared with GDMT. Our base case scenario was based on the expectation that the initial benefit of TMVr in patients with SMR would decrease over time because of the underlying cardiomyopathy; under this scenario, our model projected that TMVr would increase quality-adjusted life expectancy by 0.82 QALYs compared with GDMT alone. However, if we assumed continued accrual of benefit over a lifetime horizon (ie, our best case scenario), our model projected that TMVr would increase quality-adjusted survival by 1.48 years with an associated incremental cost-effectiveness ratio of about $27 000 per QALY. On the other hand, in our worst case scenario (ie, no further benefit beyond 2 years), the projected QALY gain was only 0.66 years with an incremental cost-effectiveness ratio of about $70 000 per QALY. Given that the observed relative survival benefit of TMVr in the COAPT trial was greater in year 2 than in the first year of follow-up, we felt that our base case assumption of gradual attenuation of benefit by 5 years was a reasonable compromise between the 2 extreme scenarios on the basis of both clinical judgement and the similar projected survival curves between the base case and worst-case scenarios (Figure III in the online-only Data Supplement). Because the COAPT trial allowed patients to cross over from GDMT to TMVr

Table 5. Subgroup Analyses (Benefit in Quality-Adjusted Life-Years)

	Lifetime Costs, $			Quality-Adjusted Life-Years			Incremental Cost-Effectiveness Ratio, $/Quality-Adjusted Life-Years	Probability <$50 000/Quality-Adjusted Life-Years, %	Probability <$150 000/Quality-Adjusted Life-Years, %
	TMVr	GDMT	Difference	TMVr	GDMT	Difference			
Base case	121 390	75 742	45 648	3.32	2.5	0.82	55 600	28	100
Age, y									
<75 (n=323)	158 957	110 943	48 014	4.66	3.46	1.20	39 945	84	100
≥75 (n=291)	81 505	35 200	46 305	1.91	1.41	0.51	91 512	0	91
Sex									
Male (n=393)	109 567	64 143	45 425	2.84	2.12	0.72	63 003	12	98
Female (n=221)	145 394	94 300	51 094	4.31	3.11	1.19	42 828	72	99
Society of Thoracic Surgeons Risk Score									
<8% (n=352)	145 859	100 585	45 274	4.24	3.23	1.01	44 826	75	100
≥8% (n=262)	86 683	43 592	43 091	2.02	1.56	0.46	93 880	1	73
Type of cardiomyopathy									
Ischemic (n=373)	100 988	62 992	37 997	2.70	2.18	0.52	72 931	7	90
Nonischemic (n=241)	153 242	95 333	57 909	4.29	2.99	1.30	44 614	67	99
Baseline left ventricular ejection fraction, %									
<30 (n=274)	131 560	78 305	53 255	3.71	2.33	1.38	38 619	90	100
≥30 (n=301)	113 540	73 209	40 332	3.09	2.65	0.44	91 872	3	72
Baseline mitral regurgitation									
3+ (n=320)	118 662	79 011	39 651	3.39	2.63	0.76	52 518	42	97
4+ (n=293)	124 192	71 459	52 732	3.27	2.32	0.95	55 333	32	99
Baseline tricuspid regurgitation									
Moderate or severe (n=98)	116 484	72 762	43 722	3.31	1.67	1.64	26 692	97	100
Mild or less (n=501)	122 094	76 331	45 763	3.31	2.64	0.67	67 999	7	96
New York Heart Association class									
I or II (n=240)	129 888	85 102	44 786	3.67	2.90	0.77	58 391	29	90
III or IV (n=373)	114 963	70 389	44 574	3.06	2.28	0.78	56 855	28	98

GDMT indicates guideline-directed medical therapy; and TMVr, transcatheter mitral valve repair.

after 2 years, it is unlikely that the true durability of benefit from TMVR compared with GDMT in patients with 3 to 4+ SMR will ever be known.

Comparison With Previous Studies

Although our study is the first to use patient-level data from a randomized clinical trial to evaluate the cost-effectiveness of TMVr versus medical therapy, 2 previous studies have used decision analytic models based on observational data to evaluate the cost-effectiveness of TMVr. Mealing and colleagues[24] used data from the EVEREST II high-risk study (Endovascular Valve Edge-to-Edge Repair Study II), which included patients with both primary mitral regurgitation and SMR, to examine the cost-effectiveness of TMVr versus medical management from the UK National Health Service perspective and found that TMVr was reasonably cost-effective with an incremental cost-effectiveness ratio of £13 664 per QALY gained (approximately $20 800 in 2018 US dollars) over a 10-year horizon. A second economic analysis restricted to patients with SMR and performed from the Canadian perspective reported an incremental cost-effectiveness ratio of CAN $32 300 per QALY gained (about $35 000 in 2018 US dollars) over a 10-year horizon.[25] Although these results appear to be more favorable than the results of our study, cross-study comparisons are challenging because the earlier studies were based on small observational data sets and were performed from the perspective of different healthcare systems, whereas our study was based on a relatively large randomized trial and used a US healthcare system perspective. In addition, both prior studies assumed that the benefit of TMVr would persist over a patient's lifetime. When we analyzed the COAPT data using a similar assumption (ie, our best case scenario), we found results similar to these previous studies.

Limitations

These results should be interpreted in the context of several limitations. First, billing data were available for only about one-third of the index TMVr hospitalizations, thus necessitating the use of regression models to estimate the costs of the remaining index TMVr hospitalizations without billing data. Thus, it is possible that we underestimated the true variance of cost for the index hospitalization. Second, billing data were not collected for subsequent hospitalizations, nor were complete data collected on post–acute care resource use. Therefore, follow-up costs were assigned using a variety of external cost sources (including Medicare reimbursement rates for hospitalizations and post–acute care) based on data collected on primary diagnosis, procedures, and length of stay for follow-up hospitalizations. Because it is likely that these methods resulted in some underestimation of total costs (which were higher in the GDMT cohort), we believe that the net effect would be to bias our results against TMVr. Third, the lifetime projections of survival, quality of life, and costs beyond the in-trial period are uncertain and are unlikely to be addressed by longer-term follow-up given the design of the COAPT trial, which allowed crossover to MitraClip therapy at 2 years. Thus, our cost-effectiveness results could be inaccurate if our lifetime assumptions were incorrect. To address this uncertainty, we performed sensitivity analyses evaluating a wide range of alternative assumptions about the duration of clinical and economic benefit, which demonstrated that, even under the most conservative of assumptions, TMVr provided at least intermediate economic value. Our findings should not be generalized to patients who differ substantially from those included in the COAPT trial such as those patients with very poor left ventricular function, those with less severe degrees of mitral regurgitation, or patients in whom medical therapy has not been optimized.[26]

Conclusions

Among patients with symptomatic heart failure and 3 to 4+ SMR enrolled in the COAPT trial, TMVr with the MitraClip device improved both life expectancy and quality-adjusted life expectancy compared with GDMT alone at an incremental cost per QALY (or life-year) gained that represents acceptable economic value in the US healthcare system. Future studies are needed to examine the durability of TMVr benefit in this population and to evaluate the cost-effectiveness of TMVr compared with other available and emerging mitral valve therapies.

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