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Cost-Effectiveness of Mitral-Valve Repair versus Replacement for Severe Ischemic Mitral Regurgitation::

A Randomized Clinical Trial from the Cardiothoracic Surgical Trials Network

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Cardiothoracic Surgical Trials Network (CTSN) Investigators

Abstract

Background—The Cardiothoracic Surgical Trials Network (CTSN) recently reported no difference in left ventricular end-systolic volume index or in survival at 2-years between patients with severe ischemic mitral regurgitation (MR) randomized to mitral-valve repair or replacement. However, replacement provided more durable correction of MR and fewer cardiovascular readmissions. Yet, cost-effectiveness outcomes have not been addressed.

Methods and Results—We conducted a cost-effectiveness analysis of the surgical treatment of ischemic MR based on the CTSN trial (n=126 for repair; n=125 for replacement). Patient-level data on readmissions, survival, quality-of-life, and U.S. hospital costs were used to estimate costs and quality-adjusted life years (QALYs) per patient over the trial duration and a 10-year time horizon. We performed microsimulation for extrapolation of outcomes beyond the 2-years of trial data. Bootstrap and deterministic sensitivity analyses were done to address parameter uncertainty. In-hospital cost estimates were \$78,216 for replacement vs \$72,761 for repair (difference: \$5,455; 95% uncertainty interval (UI): –7,784–21,193), while 2-year costs were: \$97,427 vs \$96,261 (difference: \$1,166; 95% UI: –16,253–17,172), respectively. QALYs at 2-year were 1.18 for replacement vs 1.23 for repair (difference: –0.05; 95% UI: –0.17–0.07). Over 5- and 10-years, the benefits of reduction in cardiovascular readmission rates with replacement increased, and survival minimally improved compared to repair. At 5-years, cumulative costs and QALYs showed no difference on average, but by 10-year there was a small, uncertain benefit for replacement: \$118,023 vs \$119,837 (difference: –\$1,814; 95% UI: –27,144–22,602) and QALYs: 4.06 vs 3.97 (difference: 0.09; 95% UI: –0.87–1.08). After 10 years, the incremental cost-effectiveness of replacement continued to improve.

Conclusions—Our cost-effectiveness analysis predicts potential savings in cost and gains in quality-adjusted survival at 10 years when mitral-valve replacement is compared to repair for severe ischemic MR. These projected benefits, however, were small and subject to variability. Efforts to further delineate predictors of long-term outcomes in patients with severe ischemic MR are needed to optimize surgical decisions for individual patients, which should yield more cost-effective care.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00807040.

Introduction

Ischemic mitral regurgitation (MR) affects up to 60% of patients with myocardial infarction.^{1–6} This disorder is typically caused by a change in the geometry of the left ventricle related to myocardial injury, while the valve leaflets and chordae themselves are unaffected.^{7, 8} Patients who develop severe ischemic MR have a significantly higher incidence of heart failure and mortality.^{1–4, 6, 9} While both mitral-valve repair and replacement may improve outcomes, repair has been associated with better short-term outcomes and replacement with a more durable correction of the MR.¹⁰

The Cardiothoracic Surgical Trials Network (CTSN) has recently published the results of a trial that compared mitral-valve repair to replacement in patients with chronic, severe ischemic MR.^{11, 12} Two hundred fifty one patients were randomized and followed for two years and the primary endpoint was left ventricular end-systolic volume index (LVESVI). Secondary end points included mortality, major adverse cardiovascular events, hospitalization, recurrent MR, and quality-of-life. No difference between treatment groups was observed in the change of LVESVI at 1 and 2 years compared to baseline. Thirty-day mortality was 1.6% in the repair group and 4.0% in the replacement group ($P = 0.26$), and no significant differences between treatment arms were observed at 1 and 2 years. While quality-of-life scores also did not differ, the 2-year risk of recurrent MR was significantly higher following repair (58.8% vs 3.8%; $P < 0.001$). Moreover, repair led to a higher risk of serious adverse events related to heart failure ($P = 0.05$) and higher risk of cardiovascular readmissions ($P = 0.01$).

A less durable correction of MR with repair is likely to give rise to higher long-term costs due to greater risk of readmissions and repeat surgery as well as reduction in long-term survival. On the other hand, replacement may be more costly to perform and associated with worse short-term outcomes.¹⁰ Therefore, in the present study, a comprehensive cost-effectiveness analysis (CEA) comparing mitral-valve repair and replacement, accounting for the full spectrum of benefits, harms and costs, was performed to determine the economic and health outcomes of the two strategies.

Methods

Trial Design and Population

The severe ischemic MR trial^{11, 12} was conducted by the CTSN and funded by the National Institutes of Health (NIH) and the Canadian Institutes of Health Research (CIHR). In summary, 251 patients, admitted to 22 clinical centers for severe ischemic MR between December 2008 and April 2012, were randomized to undergo either mitral-valve repair ($n=126$) or replacement ($n=125$). Patients were eligible for enrollment, regardless of whether they required concomitant revascularization of underlying coronary disease. In agreement with guidelines,^{13–15} mitral-valve replacement was performed using a complete chordal-sparing approach and either a biological or mechanical valve was implanted at the surgeon's

discretion. Mitral-valve repair was performed using an undersized complete annuloplasty ring. Conversion to mitral-valve replacement was used when MR was not adequately corrected at the surgeon's discretion. When indicated, coronary artery bypass grafting (CABG) was performed according to standard procedures. Causes of death and adverse events were adjudicated by an independent committee of experts. An NIH-appointed data and safety monitoring board oversaw trial progress. The institutional review board at each study center approved the trial. All trial participants provided written informed consent. The trial data used in the analyses are available at BioLINCC.¹⁶

Cost and Quality-of-Life Data

We estimated costs from a U.S. healthcare perspective using uniform billing (UB) medical claims associated with index hospitalizations (N=172) and readmissions (N=101) at U.S. study sites and obtained this data from Vizient, a healthcare improvement company,¹⁷ or directly from study sites themselves. Costs were calculated per hospitalization, by converting charges using departmental cost-to-charge ratios matching reported revenue codes. Departmental cost-to-charge ratios were derived from corresponding Centers for Medicare & Medicaid Services annual hospital cost reports. All costs were expressed into 2015 U.S. dollars using the Personal Health Care index for hospital care.¹⁸ Generic health status was converted into utility scores using the SF-6D health utility index (0=death, 1=optimal quality-of-life),¹⁹ which was derived from patient-level Short Form (SF)-12 questionnaire trial data collected at baseline, 30 days, 6, 12 and 24 months. We performed multiple imputation for missing costs and SF-6D utility scores (for details see Supplemental Methods). All analyses were done using the intention-to-treat principle.

Within-Trial CEA

We initially performed a within-trial CEA. Cumulative costs were calculated by totaling hospitalization costs for each patient during the trial follow-up period. Quality-adjusted life years (QALYs) were calculated from longitudinal SF-6D utility scores assuming a linear pattern between visits. For the reference case, when an interval death occurred, we assumed that the SF-6D utility score would follow a sudden drop to zero at the moment of death.²⁰ Year 2 costs and QALYs were discounted using a rate of 3%.²¹ We then calculated the difference in the average costs and QALYs between treatment groups. An incremental cost-effectiveness ratio (ICER) was calculated when the more expensive strategy would also provide more effectiveness. For details see Supplemental Methods.

Long-Term CEA

For predicting costs and QALYs over a 5 and 10-year time horizon we developed an individual-level state-transition ('microsimulation') model with a fixed one-month cycle length (Supplemental Figure I). We designed the model to make patient-specific forecasts of mortality and readmissions (for heart failure, other CVD, non-CVD, and reoperations), in addition to tracking the expected costs and loss of quality-of-life related to these adverse events. To increase the precision of event rates, we combined CTSN severe and moderate ischemic MR trial data^{11, 12, 22, 23} and included an interaction term for trial and treatment assignment to model the trial-specific treatment effect. We individualized event rates by baseline age and gender, and included time-dependent covariates to allow for an increase in

subsequent readmission and mortality event rates following a first readmission. Hazard ratios of these covariates were estimated by Andersen-Gill models (Supplemental Table I).²⁴ For the reference case, we modeled baseline readmission rates using cubic spline functions assuming a Weibull distribution for extrapolations beyond the trial follow-up period. Competing mortality rates were assumed to follow an exponential survival distribution in concordance with survival curves from several studies that included ischemic MR patients with a complete follow-up for death.^{25–32} Parametric baseline hazard rate functions for extrapolation were estimated based on data from 9 months through 2-years post-randomization to account for hazard rates that leveled off over time and to ensure a sufficient amount of failure times (Supplemental Figure II). Model validity was assessed by comparing model-based predictions with empirically calculated 2-year event rates, cumulative costs and QALYs. SF-6D utility scores were assumed to remain stable beyond trial duration.^{33–35} Cost and quality-of-life penalties were conditioned on readmissions and estimated by prediction models that included age at admission, gender, study arm, and reason for admission. Bleeding events were assumed to occur during hospitalizations. The vast majority of bleeding events observed in the trial occurred during the index hospitalization (17 out of 18) and the one bleeding event that occurred post-discharge happened during a non-CVD readmission. Additional late bleeding events were not modeled, as the use of oral anticoagulation and antiplatelet medication was similar for both treatment arms throughout the trial (Supplemental Table II). We discounted costs and QALYs with a 3% annual rate.²¹ For details see the Supplemental Methods.

Sensitivity Analyses

We performed probabilistic sensitivity analysis by bootstrapping the trial dataset 1,000 times. Analysis steps performed for both the within-trial and long-term CEA were repeated in each bootstrap replicate to account for correlation among model parameters. Results were summarized as: 1) 95% uncertainty intervals (UIs) using a bias-corrected and accelerated method; 2) as a scatter plot of the 1,000 pairs of difference in average costs and QALYs; and 3) as cost-effectiveness acceptability curves. In the latter, the percentage of bootstraps in which replacement was deemed to be cost-effective was plotted according to a range of different time horizons and cost-effectiveness thresholds including commonly used thresholds from \$50K/QALY to 200K/QALY.²¹

To further evaluate robustness and heterogeneity of our findings, we conducted a number of deterministic sensitivity and scenario analyses. For the within-trial CEA, we assumed that patients who died would have a gradual decline in quality-of-life from the last value measured until death. For the long-term CEA, we varied the annual discount rate from 0 to 5% and used different distribution assumptions for extrapolating readmission and mortality rates. We used the same reoperation risk for the period beyond the 2-year follow-up for the two treatment arms and³⁶ and based this value on a more recently published trial.³⁷ Because mortality rates are high, the likelihood of reoperations is expected to be low for the severe ischemic MR patient population.³⁸ Nevertheless, we evaluated the potential impact of reoperations for late failure of replacement valves in patients with a long life expectancy using a 20-year time horizon. Based on a recent cohort study,³⁹ we assumed that the increase in reoperation risk occurred after 5-year³⁹ and that the maximum 20-year cumulative

incidence would be 15%. While in the reference case we assumed that hazard ratios estimated based on the intention-to-treat principle, reflect treatment cross-over effects, here we accounted for changes in hazard ratios that occurred when patients in the mitral-valve repair arm underwent late reoperation to receive a replacement. Thus, when such cross-overs occurred, we effectively reassigned the patient from repair to replacement and reset the time clock to zero for both the hazard functions of readmissions and death to account for higher hazards in the early post-surgical phase. Moreover, for mortality and readmission rates, we varied the treatment assignment hazard ratio, as well as the hazard ratio associated with previous readmission, over the 95% UI interval. Lastly, to explore heterogeneity in cost-effectiveness, we varied the baseline age of the entire trial cohort from 50 to 85. For details see Supplemental Methods.

Results

Study Population

The mean age was 68 ± 10 years and most patients (62%) were male. The mean baseline LVESVI was 63.4 ± 26.8 . The vast majority of patients had a prior history of myocardial infarction and revascularization. Nearly a quarter had a history of heart failure and a third had atrial fibrillation. Concomitant CABG was performed in 75% of patients (Supplemental Table III). Eleven of the 126 patients assigned to repair received replacement before leaving the operating room, one patient in the replacement group underwent repair. One patient who underwent repair had a reoperation with replacement before hospital discharge and three had a reoperation with replacement later on. One patient in the replacement group who initially received a bioprosthesis had a late reoperation and received a mechanical valve.

Within-Trial CEA

During the index hospitalization, there were small differences in resource use between repair and replacement (Supplemental Table IV). For example, cardiopulmonary bypass time and ICU stay were longer in replacement: 151 vs 139 mins ($P = 0.04$) and 6.5 vs 5.7 days ($P = 0.06$), respectively. Index hospitalization costs were on average higher in replacement than in repair: \$78,216 vs \$72,761 (difference: \$5,455; 95% UI: $-7,784$ to $21,193$). Yet, this difference decreased over time (Figure 1) and cumulative costs at the 2-year follow-up were: \$97,427 vs \$96,261 (difference: \$1,166; 95% UI: $-16,253$ to $17,172$). A breakdown of resource use and costs by admission type is included in Supplemental Table V. There were no relevant differences in SF-6D utility scores during the trial follow-up period (Figure 2). However, reflecting the marginally lower survival rate, cumulative QALYs were on average slightly lower in the replacement arm. At 2-year, QALYs were 1.18 for replacement vs 1.23 for repair (difference: -0.05 ; 95% UI: -0.17 to 0.07) (Table 1 and Figure 3).

Long-Term CEA

Predictions beyond trial follow-up demonstrated that mortality would slightly improve with replacement as compared to repair, with an uncertain decrease of 2.4% (95% UI -18.3 to 23.2) in 10-year mortality favoring replacement (Figure 4). Rates of reoperation and cardiovascular readmissions were, however, more substantially reduced in the replacement arm over time, with differences in the 10-year total event counts of -4 (95% UI -13 to 2)

and -79 (95% UI -200 to 13) respectively (Figure 5). Predictions of cumulative costs and QALYs were commensurate with these findings. At 5-years, cumulative costs and QALYs were similar between the study arms, although on average repair was still cost-effective with an ICER of \$48,270/QALY. However, by 10-years, replacement became the dominant strategy when considering average outcomes: \$118,023 vs \$119,837 (difference: -\$1,814; 95% UI: -27,144 to 22,602) and 4.06 vs 3.97 QALYs (difference: 0.09; 95% UI: -0.87 to 1.08) for replacement and repair, respectively (Supplemental Table I and Figure VI).

Outcome Uncertainty and Variation

Results of the within-trial CEA did not change when quality-of-life was assumed to decline gradually prior to death (Supplemental Figure VII). The likelihood that replacement is cost-effective compared to repair increased as the duration of follow-up increased: 25% at 2-year to 53% at 10-year and this trend was seen over a range of cost-effectiveness thresholds from \$50K/QALY to 200K/QALY (Table 1). Extending the follow-up time to 20 years further increased the likelihood that replacement is more cost-effective than repair to 56% (Figure 6). Reducing the cost of heart failure readmissions and hazard ratios of repair vs replacement for heart failure, other and non-cardiovascular readmissions favored repair where the 10-year costs were lower. However, replacement remained the more cost effective strategy even when these parameter inputs were set to their lower 95% UI limits (ICERs of replacement fell well below \$50,000/QALY). Furthermore, conclusions about cost-effectiveness were stable across different discount rates and distribution types for extrapolating readmission and survival rates, and also did not change when explicitly modeling treatment cross-over effects following reoperation in the repair arm. Increasing the long-term reoperation rate following repair, further increased the cost reduction with replacement to approximately \$3,800 (Table 2). When using a longer time horizon of 20 years and modeling higher rates of reoperations for late failures of replacement valves, replacement remained the more cost-effective option (Supplemental Table VI). Only when a significant improvement in late mortality rates with repair was assumed, i.e., a hazard ratio of repair vs replacement = 0.92, would repair become the more effective strategy at 10 years (QALYs = 4.07) and potentially more cost-effective; when assuming a hazard ratio at the lower 95% UI limit its ICER was \$16,618/QALY. Cost-effectiveness varied with the age of the patient at the time of surgery: cost savings and health benefits following replacement diminished as age increased (Table 2).

Discussion

Our analysis, when restricted to empirical data from the CTSN trial, demonstrated that at 2-years, differences in costs and quality-adjusted survival were small and uncertain for mitral-valve repair and replacement, despite the fact that initially costs for replacement are higher. Yet the real benefit of replacement is in reducing the rate of MR recurrence, which was even apparent by the 2-year mark in the trial. Given that this benefit is expected to continue over time, it is very plausible that the time horizon for the trial itself was not long enough to fully realize the expected down-stream health and cost benefits of the more durable correction of the mitral insufficiency.¹² After extrapolating outcomes it appeared that on average, the upfront costs and risks of replacement were offset by the downstream reductions in cardiovascular readmission and reoperation rates. By 10-years, the post-trial reduction in

hospitalizations associated with replacement seemed to translate into marginal net cost savings and QALY gains, although these benefits remained uncertain. Yet, conclusions about cost-effectiveness did not change using a range of potential readmission costs and rates for reoperation, survival and readmissions, as well as when varying the treatment effect of repair vs replacement on readmissions and reoperations and varying the impact of a hospital readmission on subsequent mortality. Beyond 10 years, the cost reductions and QALY gains with replacement became more certain.

An important driver of replacement being slightly more effective than repair on average, and, therefore, the dominant strategy, was the absence of a mortality benefit for repair as reflected in the mortality hazard ratio point estimate. In our microsimulation model, long-term survival was further influenced in favor of replacement by the lower likelihood of hospital readmissions. These readmissions lead to a nearly fourfold higher subsequent mortality rate (see the hazard ratio in Supplemental Table I). Conclusions about the cost-effectiveness of replacement, however, were not sensitive to varying this hazard ratio. Reasons are that a) when this hazard ratio increases, the beneficial effect of averting cardiovascular readmissions in replacement patients decreases, because life expectancy and thus time to avoid these readmissions also decreases, and b) when this hazard ratio decreases, life expectancy improves overall, but the difference in survival between replacement and repair patients decreases.

Age of the patient at the time of the procedure had a major impact on the variation in cost-effectiveness outcome. The average age of patients in the CTSN severe ischemic MR trial was approximately 68 years and the median life expectancy for these patients was expected to exceed 7 years (see follow-up time at 50% survival probability in Figure 2). When considering average outcomes only, this was a sufficient period of time for the long-term benefits of replacement to accrue and offset its upfront incremental risks and costs. However, as Table 2 demonstrates, in older ages, this benefit is no longer the case. Thus, in octogenarians and in younger patients with comorbidities that substantially reduce their life expectancy, repair may be the more cost-effective surgical approach.⁴⁰

Two recently published meta-analyses comparing repair to replacement for ischemic MR showed results consistent with the CTSN trial findings that repair offers a less durable correction of MR.^{36, 38} Moreover, long-term survival rates of replacement vs repair predicted by our model, seem consistent with the summary hazard ratio of 0.95 (95% CI: 0.84 to 1.09) from propensity-score adjusted studies.³⁸ However, these meta-analyses included studies involving both moderate and severe ischemic MR patients, studies in which chordal sparing and non-chordal sparing mitral-valve replacement approaches were used and studies that did not report on readmission rates. It is therefore difficult to draw inferences about cost-effectiveness from the existing literature. The model reported here conditioned cost and quality-of-life outcomes on survival and readmission rates, which were fully based on detailed patient-level trial data. This enabled us to individualize cumulative costs and QALYs, while taking into account the correlation among these outcomes when analyzing uncertainty by the bootstrap procedure and increases in mortality rates with higher incidence of readmissions. These important elements are difficult to include in a CEA based on

aggregated data from the literature, which may subsequently lead to biased outcomes and conclusions about cost-effectiveness.

Our results should be viewed in the context of a number of limitations. First, the microsimulation model used in our long-term CEA was based on two trials,^{11, 12, 22, 23} which were not designed to primarily evaluate long-term mortality rates. Nonetheless, 5 and 10 year survival, predicted by our model, was generally consistent with publications that were largely based on the experience of patients with severe ischemic MR.^{25, 27, 29, 30} A recently published trial conducted in Italy showed more favorable 5-year overall survival for repair (71.8%) than was predicted by our model, although this was a small trial with younger patients.³⁷ However, the use of alternative distributions to extrapolate mortality resulted in a similar 5-year survival and, importantly, conclusions about long-term cost-effectiveness did not change. A second limitation to consider is that we did not include costs associated with outpatient services, rehabilitation programs, nursing facilities, medications, productivity loss, and informal care.²¹ Yet, because differences in long-term survival were small between repair and replacement, the importance of these additional costs would be minimal when assuming no major differences per unit of time across study arms. Third, hospitalization costs showed substantial variation, which led to considerable uncertainty in the cumulative cost estimates. Given these limitations, our findings may be perceived by some as being too uncertain for making recommendations about which procedure is best. However, when policymakers need to make a decision about which intervention should be selected for a given budget, and this decision cannot be deferred, the decision making should be done based on cost-effectiveness point estimates, irrespective of statistical significance.^{41, 42} Moreover, the sensitivity analyses showed that conclusions based on the point estimates did not change for most of the uncertain parameter inputs with the exception of assuming significantly lower long-term mortality rates with repair. Unfortunately, larger trials are not expected for severe ischemic MR and observational studies have their limitations for extracting unbiased effect estimates.

Recently, the American College of Cardiology/American Heart Association and American Association for Thoracic Surgery updated their guidelines and now recommend it is reasonable to choose mitral-valve replacement over repair in severe ischemic MR (level IIa evidence).^{13, 15} Our results bring an economic dimension to the choice between repair and replacement and indicate that replacement is potentially a marginally more cost-effective strategy. However, as shown by the sensitivity analysis that varies patient age, the group-level predictions from our CEA should be interpreted with caution when making decisions for patients with clinical and demographic characteristics that are far from the trial norm. Moreover, for an individual patient with severe ischemic MR, it can be expected that the optimal decision regarding repair or replacement depends on the patient's risk of MR recurrence. In the repair arm of the CTSN severe ischemic MR trial, approximately 40% of the patients remained free from MR recurrence after two years of follow-up, and these patients had on average a greater degree of reverse remodeling than those with recurrence after repair and patients who underwent replacement.¹² Clinical decision making must include perioperative findings that are associated with MR recurrence including expected LV-mitral-valve ring mismatch,⁴³ as well as findings of basal aneurysm/dyskinesis, significant leaflet tethering, and severe LV enlargement.⁴⁴ An evaluation of the cost-

effectiveness of an approach using perioperative information was however beyond the scope of this study. The value of a more personalized approach integrating individualized predictions of MR recurrence, adverse outcomes, and life expectancy, together with patient preferences and costs should be evaluated in further research.

Conclusions

Our cost-effectiveness analysis predicts potential savings in cost and gains in quality-adjusted survival at 10 years when mitral-valve replacement is compared to repair for severe ischemic MR. The projected benefits following replacement, however, were small and subject to variability, with cost savings being mediated by expected improvements in long-term cardiovascular readmission and reoperation rates following replacement, and QALY gains being dependent on the absence of a significant long-term survival benefit with repair. Efforts to further delineate predictors of long-term outcomes in patients with severe ischemic MR are needed to potentially optimize surgical decisions for individual patients, which should yield more cost-effective care. Acknowledgements

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The views expressed in this article are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; National Institutes of Health; or the United States Department of Health and Human Services.

Appendix: Cardiothoracic Surgical Trials Network (CTSN)

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Echocardiography Core Lab:Judy Hung (PI), Xin Zeng, Niamh Kilcullen, David Hung;

Cardiopulmonary Testing Core Lab:Steve Keteyian (PI), Heather Aldred, Clinton Brawner;

Neurocognitive Core Lab:Joseph Mathew (PI), Jeffrey Browndyke, Yanne Toulgoat-Dubois.

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What is known

- A recently reported RCT by the Cardiothoracic Surgical Trials Network, which compared mitral valve repair and replacement for severe ischemic mitral regurgitation, reported no difference in left ventricular end-systolic volume index or in survival at 2-years.
- Mitral-valve replacement was found to provide a more durable correction of MR and fewer cardiovascular readmissions.

What the Study Adds

- Based on CTSN trial results alone, 2-year costs and quality-adjusted survival were similar for repair and replacement, although replacement was associated with higher index hospitalization costs.
- Extrapolating outcomes beyond 2 years of the CTSN empirical data using microsimulation, the high upfront costs of replacement were found to be further offset by downstream reductions in cardiovascular readmission rates, potentially resulting in cost savings and gains in quality-adjusted survival with replacement at 10 years.
- Utilization of predictors of long-term clinical and economic outcomes could potentially optimize surgical decisions for more cost-effective care in patients with severe ischemic MR.

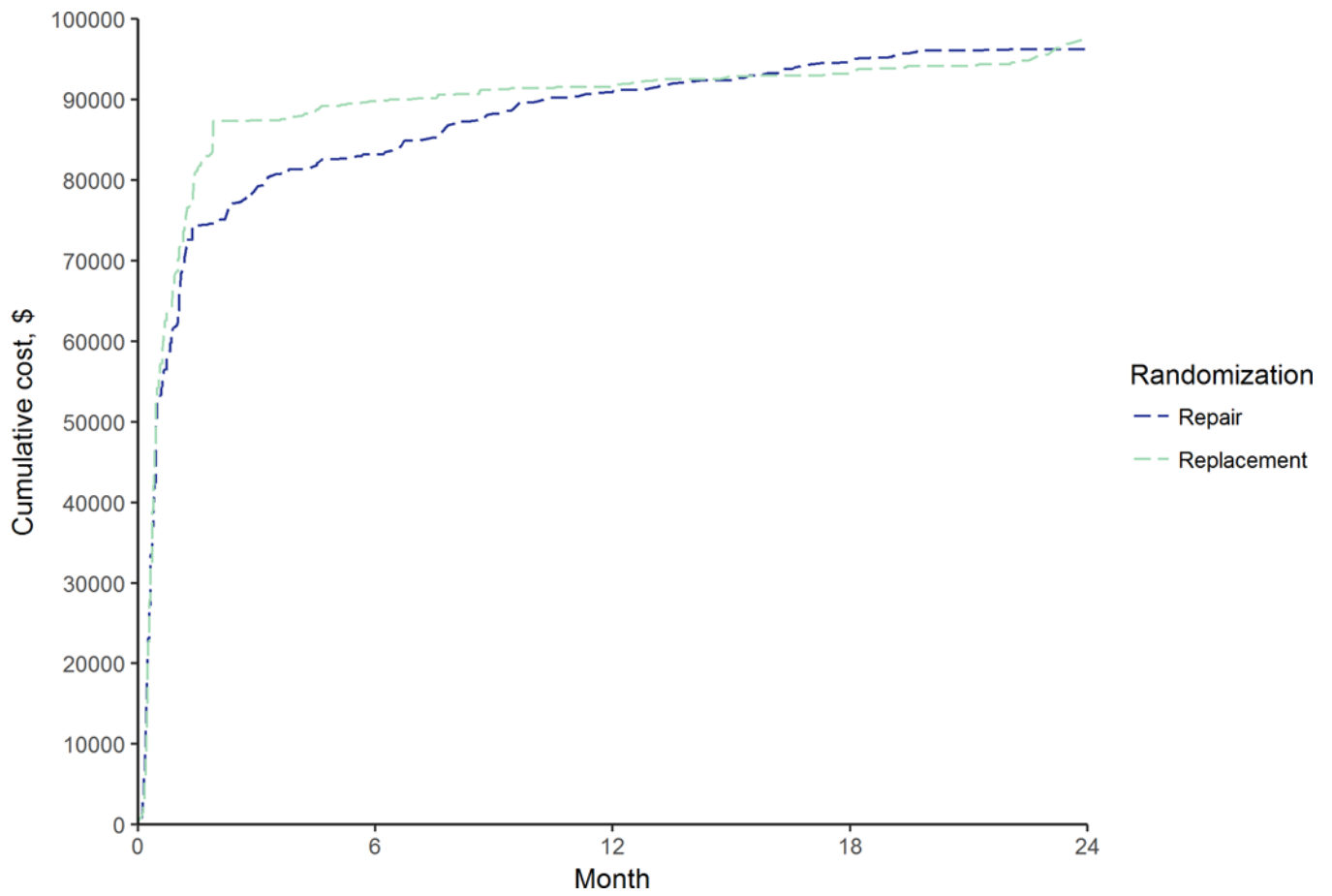


Figure 1. Within-trial cumulative average cost by study arm.
Shown are cumulative costs averaged across N=126 for repair and N=125 for replacement.

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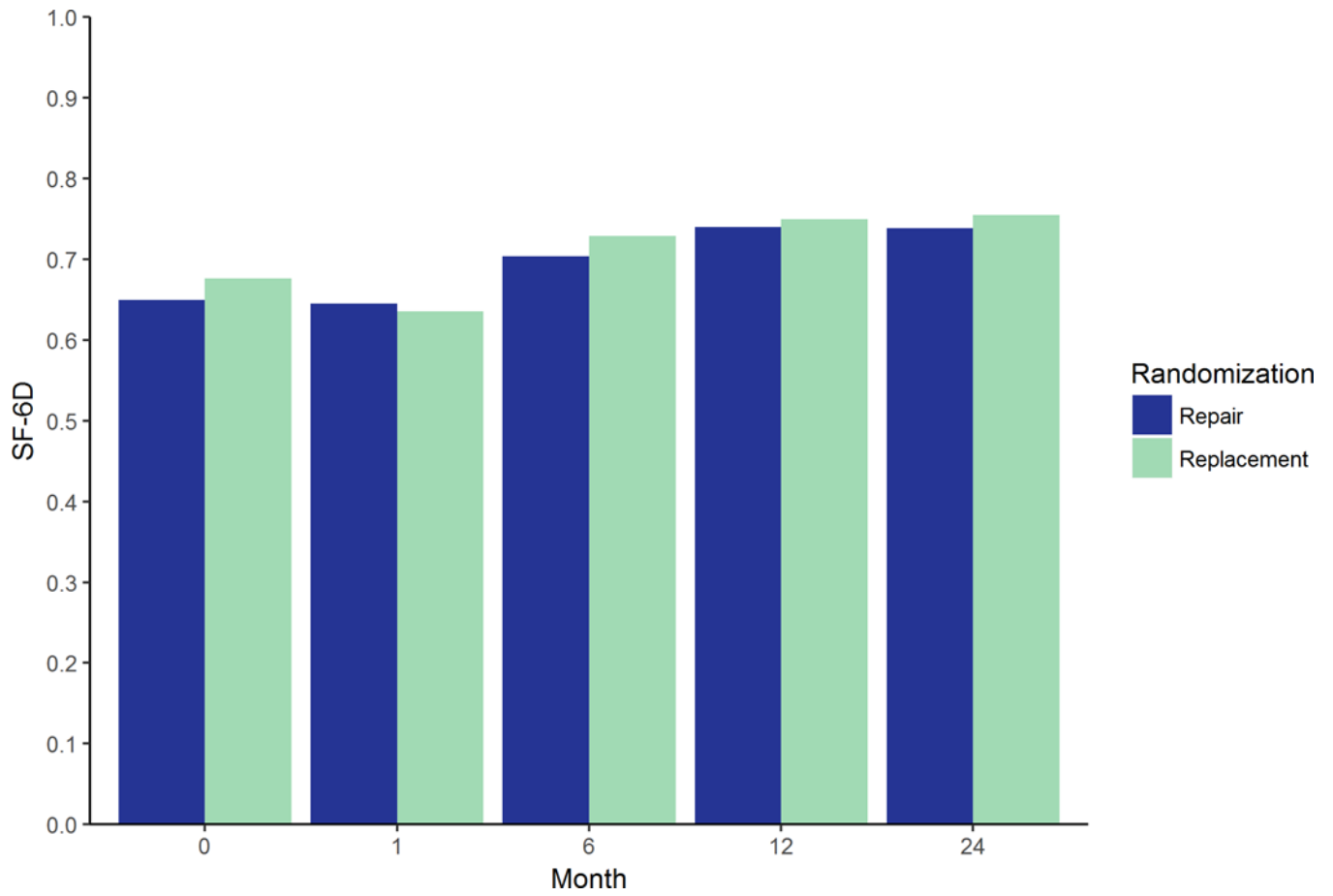


Figure 2. Average SF-6D utility index by study arm.

Shown are mean SF-6D utility index scores in N=126 for repair and N=125 for replacement.

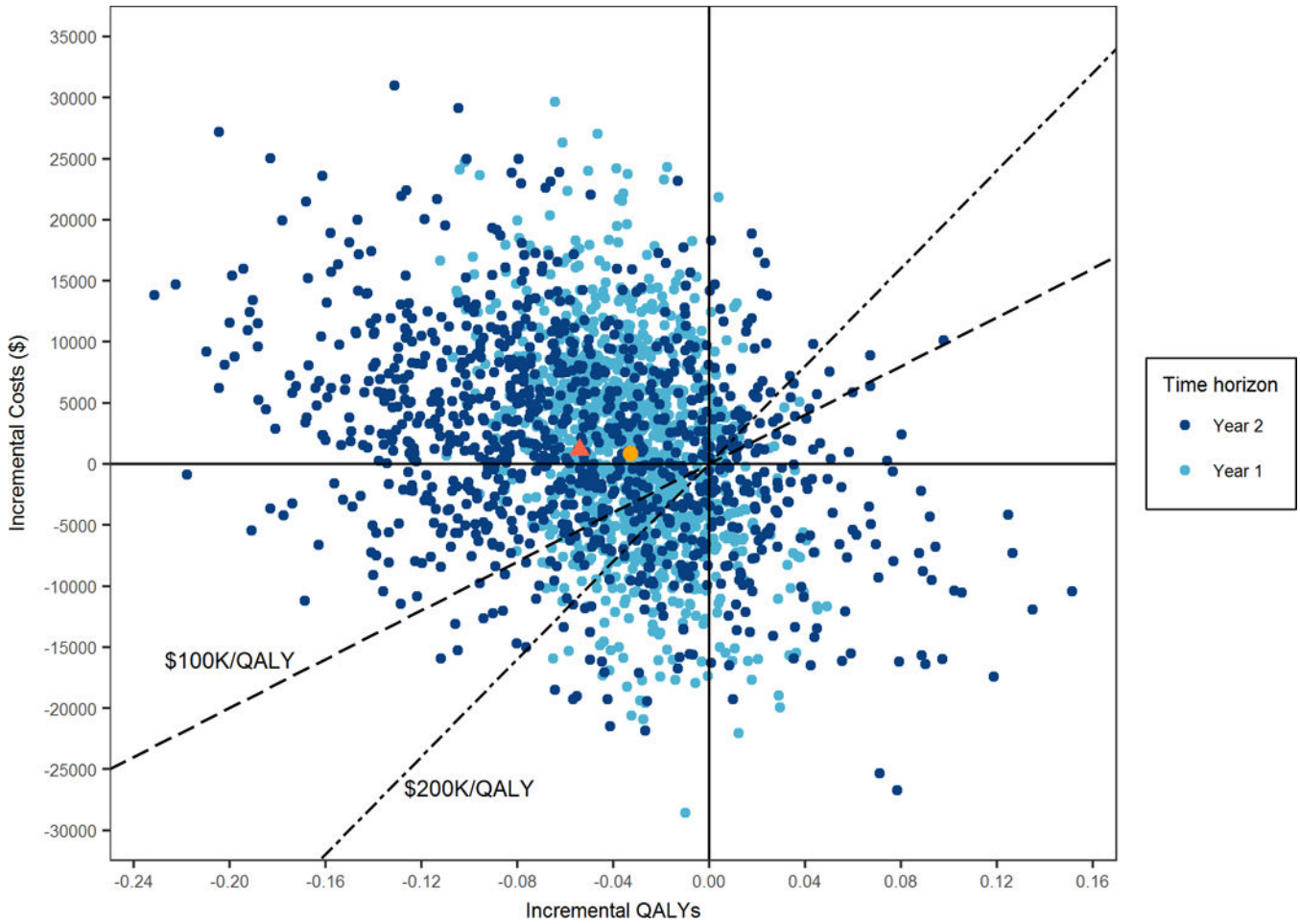


Figure 3. Within-trial cost-effectiveness analysis bootstrap results comparing replacement vs repair.
 Shown are s in average costs and average QALYs as measured in each bootstrap replicate of the trial data with repair as the reference strategy. The yellow and red figures represent the point estimates (costs, QALYs) at 1-year (\$848; -0.03) and 2-year (\$1,166; -0.05) respectively. The two diagonals represent commonly used cost-effectiveness thresholds of \$100K/QALY and \$200K/QALY. The proportion of iterations below or to the right of the selected diagonal equals the likelihood of the replacement strategy being cost-effective as compared with repair given the applicable cost-effectiveness threshold.

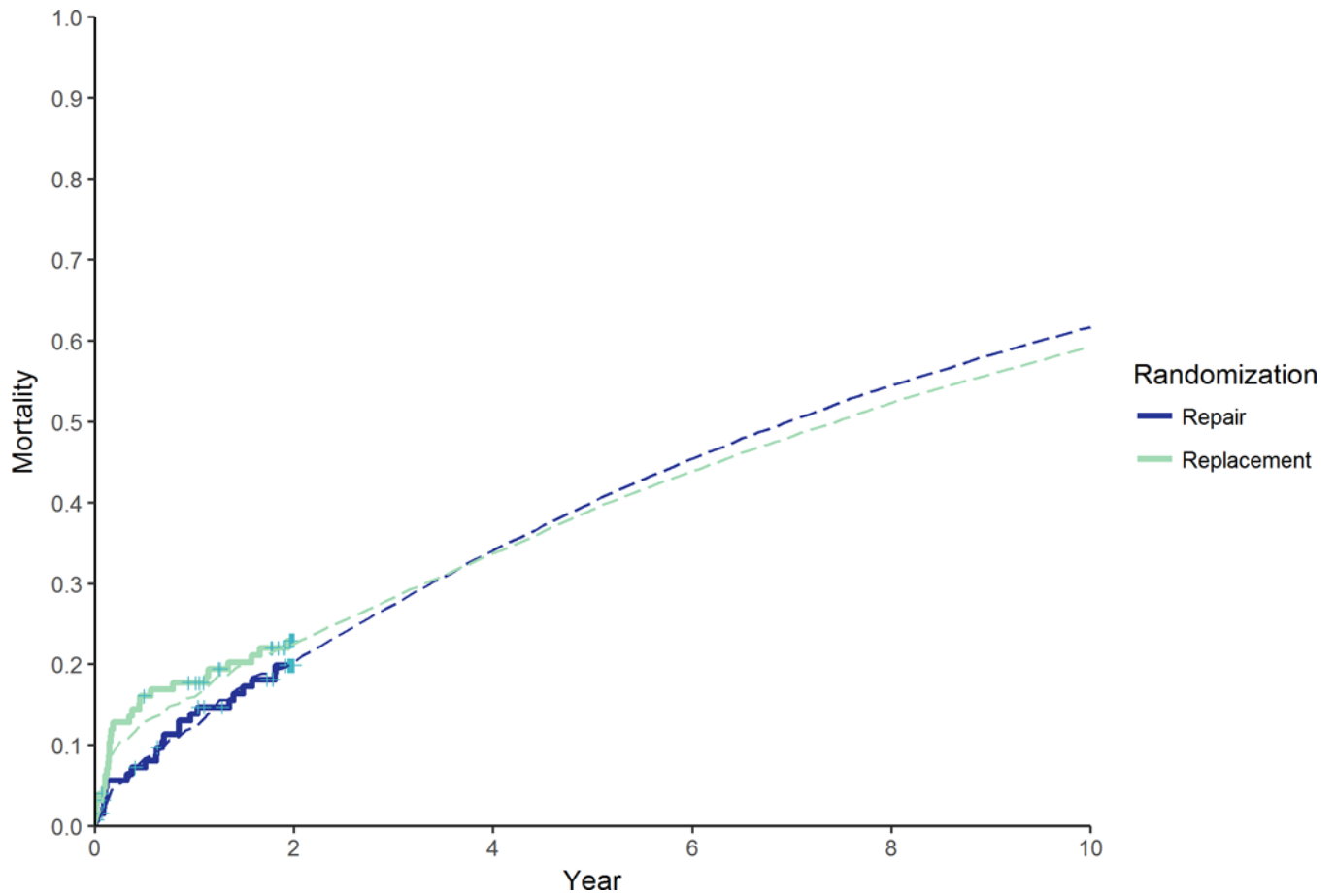


Figure 4. Observed and simulated all-cause mortality estimates by study arm.

Shown are all-cause mortality estimates based on Kaplan-Meier curves of trial data with censoring at 2-year (solid lines) and simulated mortality estimates within the reference case analysis (dashed lines).

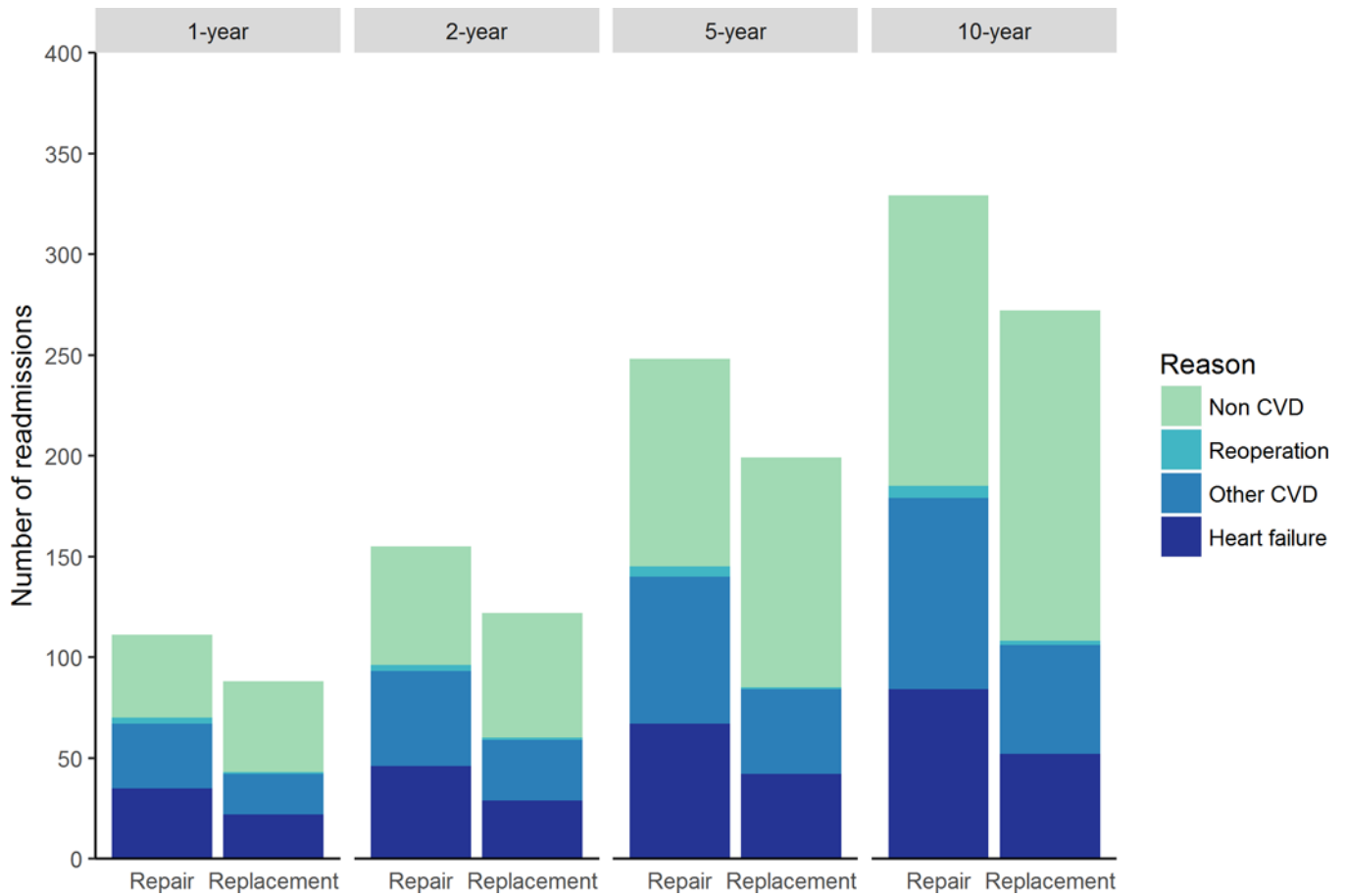


Figure 5. Number of hospital admissions and reoperations during 1-, 2-, 5-, and 10-year follow-up.

Outcomes at 1- and 2-year are based on trial data; outcomes at 5- and 10-year are based on adding simulated outcomes occurring within 2–5 and 2–10 year time intervals within the reference case analysis.

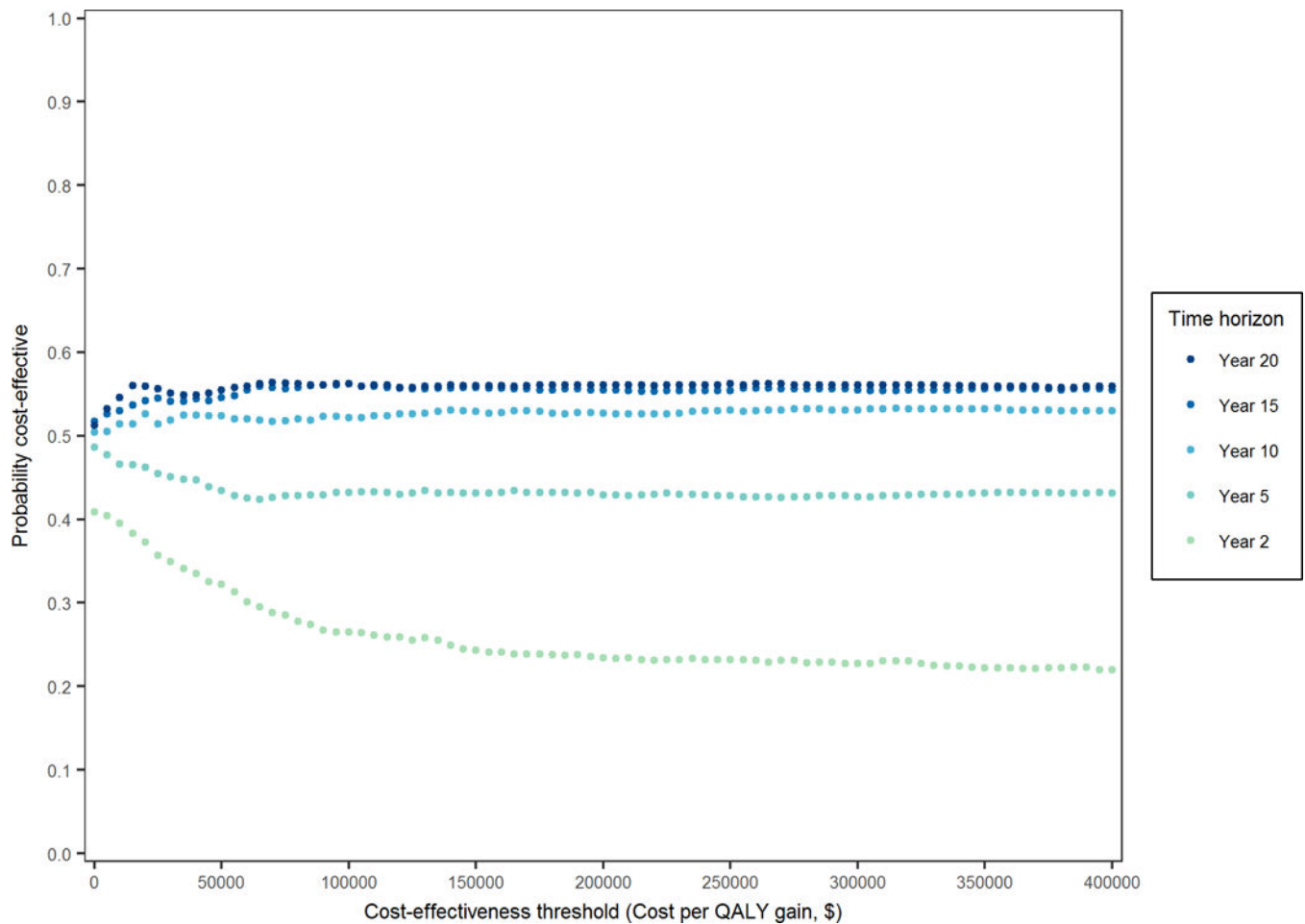


Figure 6. Cost-effectiveness acceptability curves for replacement according to time horizon. These curves indicate the probability of replacement being cost-effective as compared with repair using different time horizons. Each curve equals the proportion of iterations below or to the right of the diagonal (as shown in Figure 3 for time horizons of 1- and 2-year) by changing the slope of the diagonal from 0 to infinity, i.e. increasing the cost-effectiveness threshold. The probability of repair being cost-effective equals 100% minus the depicted probability of replacement being cost-effective.

Table 1.

Reference case cost-effectiveness outcomes (95% UI)

Outcome	Repair N=126	Replacement N=125
Costs, \$		
1-year	90,914 (79,089 to 106,107)	91,762 (81,106 to 107,530)
	-	+848 (-16,160 to 16,995)
2-year	96,261 (83,950 to 111,619)	97,427 (85,575 to 113,263)
	-	+1,166 (-16,253 to 17,172)
5-year	109,460 (92,212 to 129,023)	108,667 (92,316 to 130,881)
	-	-792 (-20,154 to 18,199)
10-year	119,837 (96,974 to 147,200)	118,023 (96,832 to 148,282)
	-	-1,814 (-27,144 to 22,602)
QALYs		
1-year	0.63 (0.59 to 0.66)	0.60 (0.55 to 0.64)
	-	-0.03 (-0.09 to 0.02)
2-year	1.23 (1.14 to 1.30)	1.18 (1.07 to 1.25)
	-	-0.05 (-0.17 to 0.07)
5-year	2.59 (2.26 to 2.84)	2.58 (2.27 to 2.86)
	-	-0.02 (-0.40 to 0.39)
10-year	3.97 (3.14 to 4.59)	4.06 (3.34 to 4.75)
	-	+0.09 (-0.87 to 1.08)
ICER, \$/QALY		
1-year	Dominant	-
2-year	Dominant	-
5-year	48,270	-
10-year	-	Dominant
Probability CE at \$50K; \$100K; \$200K per QALY threshold, %		
1-year	64; 69; 76	36; 31; 24
2-year	68; 74; 77	32; 26; 23
5-year	57; 57; 57	43; 43; 43
10-year	48; 48; 47	52; 52; 53
Probability dominant, %		
1-year	53	8
2-year	51	12
5-year	33	24
10-year	24	26

Abbreviations: ICER, incremental cost-effectiveness ratio; CE, cost-effective; QALY, quality-adjusted life year.

Table 2.

Sensitivity analyses using a 10-year time horizon

Variable	Costs repair, \$	Costs replacement, \$	costs replacement vs repair, \$	QALYs repair	QALYs replacement	QALYs replacement vs repair	ICER, \$/QALY replacement vs repair
Discount rate							
0%	123,641	121,405	-2,236	4.44	4.57	+0.12	Dominant
5%	117,701	116,127	-1,574	3.70	3.78	+0.08	Dominant
Distribution for extrapolation of baseline mortality rates							
Spline-Weibull	125,579	122,604	-2,975	4.54	4.59	+0.06	Dominant
Weibull	125,181	122,222	-2,959	4.48	4.56	+0.08	Dominant
Log-logistic	124,937	122,424	-2,514	4.47	4.56	+0.08	Dominant
Distribution for extrapolation of baseline readmission rates							
Weibull	120,528	116,090	-4,438	3.98	4.08	+0.10	Dominant
Log-logistic	118,312	114,445	-3,867	3.98	4.09	+0.10	Dominant
Hazard ratio of repair vs replacement for heart failure readmissions >2-year follow-up							
Lower limit (0.899)	117,488	118,023	+6,146	3.97	4.06	+0.09	6,146
Upper limit (2.610)	124,467	118,023	-6,443	3.95	4.06	+0.11	Dominant
Hazard ratio of repair vs replacement for other cardiovascular readmissions >2-year follow-up							
Lower limit (0.790)	116,082	118,023	+1,941	3.98	4.06	+0.08	23,247
Upper limit (3.227)	128,024	118,023	-10,000	3.95	4.06	+0.11	Dominant
Hazard ratio of repair vs replacement for non-cardiovascular readmissions >2-year follow-up							
Lower limit (0.569)	115,538	118,023	+2,486	4.00	4.06	+0.06	38,376
Upper limit (1.220)	126,406	118,023	-8,382	3.94	4.06	+0.12	Dominant
Hazard ratio of repair vs replacement for mortality >2-year follow-up							
Lower limit (0.494)	124,915	118,023	-6,891	4.48	4.06	-0.41	16,618*
Upper limit (2.087)	114,247	118,023	+3,777	3.41	4.06	+0.65	5,797
Hazard ratio of hospital readmission for mortality >2-year follow-up							
Lower limit (2.517)	122,340	119,887	-2,453	4.04	4.08	+0.04	Dominant
Upper limit (6.972)	113,814	112,667	-1,147	3.08	3.14	+0.06	Dominant
Reoperation risk in replacement ≈ repair >2-year follow-up	119,837	118,741	-1,096	3.97	4.06	+0.09	Dominant

Variable	Costs repair, \$	Costs replacement, \$	costs replacement vs repair, \$	QALYs repair	QALYs replacement	QALYs replacement vs repair	ICER, \$/QALY replacement vs repair
100% higher reoperation risk in repair >2-year follow-up	120,595	118,023	-2,572	3.97	4.06	+0.09	Dominant
300% higher reoperation risk in repair >2-year follow-up	121,845	118,023	-3,822	3.97	4.06	+0.09	Dominant
Clock set back to zero following reoperation, cross-over to replacement following reoperation in repair	120,750	118,326	-2,423	3.97	4.06	+0.09	Dominant
Costs heart failure readmissions							
Lower limit (11,400)	115,732	117,078	+1,346	3.97	4.06	+0.09	14,593
Upper limit (24,855)	124,008	122,311	-1,697	3.97	4.06	+0.09	Dominant
Costs other cardiovascular readmissions							
Lower limit (12,630)	114,834	114,116	-718	3.97	4.06	+0.09	Dominant
Upper limit (33,690)	129,305	122,463	-6,842	3.97	4.06	+0.09	Dominant
Costs non-cardiovascular readmissions							
Lower limit (14,635)	114,237	110,380	-3,856	3.97	4.06	+0.09	Dominant
Upper limit (28,610)	128,867	127,074	-1,793	3.97	4.06	+0.09	Dominant
Age-dependent analyses							
Age 50	133,207	121,057	-12,149	4.86	4.97	+0.11	Dominant
Age 55	129,526	120,379	-9,146	4.78	4.68	+0.11	Dominant
Age 60	126,431	119,988	-6,444	4.49	4.61	+0.12	Dominant
Age 65	122,835	118,980	-3,855	4.27	4.31	+0.04	Dominant
Age 70	120,138	117,933	-2,205	4.00	4.01	+0.01	Dominant
Age 75	118,091	117,141	-950	3.67	3.65	-0.03	33,764 *
Age 80	116,093	115,185	-908	3.36	3.29	-0.07	12,726 *
Age 85	113,267	114,307	+1,040	2.99	2.88	-0.11	Dominated

*Incremental cost-effectiveness ratios (ICERs) are here calculated with replacement as reference. Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.