Survival of Transcatheter Mitral Valve Repair Compared With Surgical and Conservative Treatment in High-Surgical-Risk Patients

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ABSTRACT

OBJECTIVES The goal of this study was to compare survival between transcatheter mitral valve (MV) repair using MitraClip system (Abbott Vascular, Santa Clara, California), MV-surgery, and conservative treatment in high-surgical-risk patients symptomatic with severe mitral valve regurgitation (MR).

BACKGROUND Up to 50% of patients with symptomatic severe MR are denied for surgery due to high perioperative risk. Transcatheter MV repair might be an alternative.

METHODS Consecutive patients (n = 139) treated with transcatheter MV repair were included. Comparator surgically (n = 53) and conservatively (n = 59) treated patients were identified retrospectively. Surgical risk was based on the logistic European System for Cardiac Operative Risk Evaluation (log EuroSCORE) or the presence of relevant risk factors, as judged by the heart team.

RESULTS The log EuroSCORE was higher in the transcatheter MV repair group (23.9 ± 16.1%) than in the surgically (14.2 ± 8.9%) and conservatively (18.7 ± 13.2%, p < 0.0001) treated patients. Left ventricular ejection fraction was higher in surgical patients (43.9 ± 14.4%, p = 0.003), with similar values for the transcatheter MV repair (36.8 ± 15.3%) and conservatively treated (34.5 ± 16.5%) groups. After 1 year of follow-up, the transcatheter MV repair and surgery groups showed similar survival rates (85.8% and 85.2%, respectively), whereas 67.7% of conservatively treated patients survived. The same trend was observed after the second and third years. After weighting for propensity score and controlling for risk factors, both the transcatheter MV repair (hazard ratio [HR]: 0.41, 95% confidence interval [CI]: 0.22 to 0.78, p = 0.006) and surgical (HR: 0.52, 95% CI: 0.30 to 0.88, p = 0.014) groups showed better survival than the conservatively treated group. The transcatheter MV repair and surgical groups did not differ (HR: 1.25, 95% CI: 0.72 to 2.16, p = 0.430).

CONCLUSIONS Despite a higher log EuroSCORE, high-surgical-risk patients with symptomatic severe MR treated with transcatheter MV repair show similar survival rates compared with surgically treated patients, with both displaying survival benefit compared with conservative treatment. (J Am Coll Cardiol Intv 2014;7:875–81) © 2014 by the American College of Cardiology Foundation.
Operative Risk Evaluation (log EuroSCORE) of at least 20% or were denied for surgery due to a combination of additional factors associated with an increase in mortality judged by the heart team, consisting of an LV ejection fraction (LVEF) <30%, older than 80 years of age, previous cardiac surgery, body mass index >35 or <18 kg/m², pulmonary hypertension, renal insufficiency, previous chest radiation, chronic obstructive pulmonary disease and emphysema, porcelain aorta, and frailty.

We retrospectively analyzed all patients who were discussed by the heart team 2 years before the start date of transcatheter MV repair, during a period when this therapy was not available in our hospital. The therapeutic strategy was reviewed in all patients referred for MV surgery because of symptomatic severe MR. Accepted high-risk surgery patients and patients who were denied surgery (conservatively treated group), who today might be considered for transcatheter MV repair, were considered as control groups. All patients had moderate to severe or severe MR (grade 3+ or 4+) and were symptomatic with or without LV dysfunction (ejection fraction <60%) or LV dilation (LV end-systolic diameter >45 mm) and consequently had an indication for intervention according to the European Society of Cardiology Task Force recommendation (5). High surgical risk was based on log EuroSCORE or the presence of relevant risk factors associated with excessive morbidity and mortality as judged by the heart team. These factors included the same factors considered for risk assessment of transcatheter MV repair patients as mentioned earlier. In the high-risk surgery group, concomitant coronary artery bypass grafting (CABG) was allowed if these lesions could also be treated with a percutaneous intervention. Patients with concomitant aortic valve pathology were excluded.

Individual patient charts were evaluated for clinical characteristics, including patient demographic characteristics, risk factors, and operative data. Follow-up survival information was evaluated by consulting the government death registries by the Social Security number.

All patients included in the study were fully informed about the procedure and signed a written consent form. The study was approved by the hospital’s ethics committee (W13.024 and R&D/Z-13.15). The procedures were performed in accordance with the hospital’s ethics standards and the 1975 Declaration of Helsinki (revised in 2008).

METHODS

PATIENTS. All consecutive patients between January 2009 and April 2013 who underwent transcatheter MV repair, were included. The suitability was determined by the heart team, consisting of cardiac surgeons and interventional, imaging and heart failure cardiologists at our hospital. The patients undergoing transcatheter MV repair therapy were at high-surgical-risk based on the logistic European System for Cardiac Operative Risk Evaluation (log EuroSCORE) (18) of at least 25% (8,9). New transcatheter techniques may introduce an alternative to surgery in high-surgical-risk patients. In the past few years, most evidence on transcatheter MV repair has accumulated for transcatheter edge-to-edge MV repair using the MitraClip system (Abbott Vascular, Santa Clara, California) (10-16). Mimicking the surgical procedure introduced by Alfieri et al. (17), this technique creates a double MV orifice by means of a clip in the midportion of the 2 leaflets. Previous studies, also from our group, proved the MitraClip system’s feasibility and efficacy in high-surgical-risk patients (10,13-16). No data are available comparing outcomes of transcatheter MV repair with surgery and conservative treatment in high-surgical-risk patients. In this study, we aimed to compare survival outcomes in these different treatment strategies in high-surgical-risk patients with symptomatic MR.
retracted during systole, grasping the MV leaflets. This results in permanent leaflet approximation and creation of a double orifice. The clip is a 4-mm-wide cobalt-chromium implant with 2 arms. On the inner portion of the clip arms are small "grippers" to secure the leaflets when the arms are closed. To position the clip device correctly over the mitral orifice, it should be placed perpendicular to the line of leaflet coaptation and above the origin of the MR jet. These factors are mandatory to prevent clip disengagement and to obtain an acceptable MR reduction. A second (or third) clip was placed if further reduction of MR was required. The procedure was performed with patients under general anesthesia and both fluoroscopic and transesophageal echocardiographic (2- and 3-dimensional) guidance (19,20).

The surgical techniques used by the surgeon have been described previously and are considered as standard surgical therapy (21–23). The particular choice of technique was entirely at the discretion of the individual surgeon.

**STATISTICAL ANALYSIS.** Data are given as mean ± SD in the text and in Table 1. The dichotomous variables were tested by the chi-square test. Comparisons between groups were done by analysis of variance, with the least significant difference test as a post-hoc test.

To reduce confounding factors due to imbalances in baseline characteristics, propensity scores were used to weight samples from the transcatheter MV repair, surgery, and control groups so that the distributions of observed baseline characteristics were more comparable across the 3 groups. We computed propensity scores by means of generalized boosted modeling, a machine learning technique that relies on tree-based regression models that are built in an iterative fashion with a multinomial approach trying to obtain an acceptable MR reduction. We used the procedures implemented in the twang package for R (twang: Toolkit for Weighting and Analysis of Nonequivalent Groups; R package version 1.3-18 (R Package for Statistical Computing, Vienna, Austria)).

**RESULTS**

**BASELINE CHARACTERISTICS.** Transcatheter MV repair was carried out in 139 patients (mean age, and/or were known confounders from previous studies (cardiac resynchronization therapy and log EuroSCORE). We used the procedures implemented in the twang package for R (twang: Toolkit for Weighting and Analysis of Nonequivalent Groups; R package version 1.3-18 (R Package for Statistical Computing, Vienna, Austria)) were used. p Values <0.05 (2 tailed) were considered statistically significant.
In 2007 and 2008, a total 307 patients underwent surgical procedures consisting of MV repair or replacement with or without CABG. Of these, 53 patients (mean age, 70.2 ± 9.5 years; 50.9% male) were considered as high risk. The patients undergoing concomitant CABG (n = 12) had coronary lesions (>50% stenosis), which also could be treated with a percutaneous intervention. Surgical MV repair was carried out in 38 patients. Ten and 5 patients underwent MV replacement with a bioprosthesis and mechanoprosthesis, respectively.

Fifty-nine patients (mean age, 71.7 ± 9.6 years; 54.2% male) were treated conservatively. Mean follow-up time was 1.7 ± 1.1, 3.8 ± 1.9, and 2.7 ± 2.2 years for the transcatheter MV repair, high-risk surgery and conservatively treated groups, respectively. Table 1 shows the baseline characteristics of the different groups. There were significantly more male patients in the transcatheter MV repair group compared with the other groups. No difference in sex was found between high-risk surgery and conservatively treated patients. Log EuroSCORE was significantly higher in the transcatheter MV repair group than in the other groups. No difference was found for this score between high-risk surgery and conservatively treated patients.

The majority of the patients in all groups had functional MR. Compared with the other groups, the high-risk surgery group displayed relatively more patients with degenerative MR. The prevalence of known CAD was highest in the conservatively treated group (76.3%) and the lowest in the high-risk surgery patients (52.8%). However, when a history of coronary ischemic events (previous myocardial infarction) and treatment (percutaneous coronary intervention and CABG) were considered, the highest frequencies were observed in the transcatheter MV repair group.

In total, pulmonary hypertension was more prevalent in the transcatheter MV repair group, but severe pulmonary hypertension (systolic pulmonary artery pressure >55 mm Hg) was more common in the high-risk surgery and conservatively treated group.
LVEF was significantly higher in the high-risk surgery group, showing similar values for the transcatheter MV repair and conservatively treated patients.

Acute procedural success (MR ≤2+) was achieved in 127 patients (93.4%) in the transcatheter MV repair group.

**SURVIVAL OUTCOMES.** After 1 year of follow-up, the transcatheter MV repair and the high-risk surgery group showed similar survival rates (85.8% vs. 85.2%, respectively), whereas only 67.7% of the patients in the conservatively treated group survived (Fig. 1). The 2- and 3-year survival rates in the conservatively treated group were 52.5% and 45.8%, respectively. The survival rates for the transcatheter MV repair group (75.5% and 62.3% after 2 and 3 years, respectively) and high-risk surgery group (77.8% and 68.5% after 2 and 3 years, respectively) were comparable.

During follow-up, there were 29 cardiac deaths and 6 noncardiac deaths in the transcatheter MV repair group. In the high-risk surgery group, 18 cardiac deaths and 5 noncardiac deaths were reported. Finally, 39 cardiac deaths and 3 noncardiac deaths occurred in the conservatively treated group.

After weighting for propensity score and controlling for cardiac resynchronization therapy and log EuroSCORE, both treatment groups showed superior survival rates compared with the conservatively treated group: transcatheter MV repair versus conservative treatment (HR: 0.41, 95% CI: 0.22 to 0.78, p = 0.006) and surgical treatment versus conservative treatment (HR: 0.52, 95% CI: 0.30 to 0.88, p = 0.014). Both treatment groups did not differ statistically significantly: surgical treatment versus transcatheter MV repair (HR: 1.25, 95% CI: 0.72 to 2.16, p = 0.43). Whether sufficient baseline comparability was achieved with the propensity-weighting analysis is difficult to prove. We therefore undertook an additional analysis by means of propensity matching, keeping only triplets (1 from each treatment modality) of patients who were comparable within 0.25 SE. Eighty-one matching triplets could be used in a conditional Cox proportional hazards model, resulting in a comparable outcome, but with broader confidence intervals. The MitraClip versus conservative treatment comparison was still statistically significant (HR: 0.47, 95% CI: 0.24 to 0.93).

If only patients with functional MR (FMR) were considered, the same trend was observed as described above; transcatheter MV repair versus conservative treatment (HR: 0.46, 95% CI: 0.23 to 0.93, p = 0.03) and surgical treatment versus conservative treatment (HR: 0.54, 95% CI: 0.29 to 1.02, p = 0.057). Both treatment groups did not differ statistically significantly: surgical treatment versus transcatheter MV repair (HR: 0.84, 95% CI: 0.45 to 1.59, p = 0.60).

**DISCUSSION**

This is the first study to compare transcatheter MV repair with surgical and conservative treatment in high-surgical-risk patients with symptomatic MR. We show that this relatively new transcatheter technique is superior to conservative treatment and that the survival rates after transcatheter MV repair are comparable to classic surgery, despite a higher log EuroSCORE.

Agricola et al. (2) reported that conservative treatment of symptomatic moderate to severe MR is associated with a 50% risk of mortality at 4-year follow-up. Similar mortality rates were reported recently by Goel et al. (7) after 5 years of follow-up. The baseline characteristics of the patients enrolled in that study resemble those of our MV repair study group in terms of LV dysfunction, age, and other comorbidities. In our study, the mortality rate of conservatively treated patients was even higher with 54.2% mortality after 3 years. Therefore, transcatheter MV repair with a survival rate of 62.3% after 3 years could be the preferred treatment in high-surgical-risk patients and/or patients denied surgery. These findings are comparable with the high-risk registry data from the EVEREST II (Endovascular Valve Edge-to-Edge Repair) trial showing superior survival rates with transcatheter MV repair compared with conservative treatment (16).

The “standard” treatment of MR is surgery. Logically, the patients denied for surgery must be at increased surgical risk. Indeed, it has been suggested that the patient risk factors differ significantly between surgical patients and transcatheter MV repair patients, favoring surgical patients (25). In an era in which up to 50% of patients are denied surgery, simply because of that high risk, transcatheter MV repair would be the only alternative therapy! The landmark EVEREST II trial, in which patients at low and moderate risk were also included, showed that the survival rates were similar between transcatheter MV repair and surgery groups (12,26). Our report expands the EVEREST II data on high-surgical-risk patients, suggesting that transcatheter MV repair may even be as good as surgical therapy. Further improvement of the survival rates may be expected by gaining experience leading to improved durability and completeness of MV repair (27).

Finally, there is controversy in the literature concerning surgical treatment of FMR in terms of survival.
benefits. In fact, it has been suggested that surgical treatment is not better than conservative therapy in high-surgical-risk patients with FMR (28). In our cohort, 77% of the transcatheter MV repair patients and 81% of the conservatively treated group had FMR. Despite this high percentage and high periprocedural risk, the transcatheter MV repair group showed superior survival gain compared with conservative therapy. Patients with FMR may even benefit the most from transcatheter MV repair, as has been suggested by others (10,13,29). Indeed, the European Guidelines recommend transcatheter MV repair, if feasible at low procedure risk, to treat patients with FMR without severe tethering to provide short-term improvement in functional class and LV function (5). In our study, if only patients with FMR were considered, the same trend was observed as described for the total group. To further investigate the hypothesis that transcatheter MV repair has superior survival benefits over conservative therapy in high-surgical-risk patients with FMR, 2 randomized clinical trials have been designed to compare transcatheter MV repair in addition to optimal standard medical therapy with optimal standard of care therapy alone; the COAPT (Clinical Outcomes Assessment of the MitraClip Percutaneous Therapy for High Surgical Risk Patients) trial and the RESHAPE-HF (Randomized Study of the MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation), both in the recruitment phase.

**STUDY LIMITATIONS.** These include the nonrandomized character and the fact that the comparator groups were recruited retrospectively. Despite its retrospective and nonrandomized character, we believe that our study advocates enough potential for transcatheter MV repair to be a good alternative to high-risk surgery and a serious treatment option for patients denied surgery. Another limitation is that we did not describe secondary endpoints such as residual MR grade, signs of reverse LV remodeling, NYHA functional classification, and rehospitalization. Our only objective was to investigate the primary endpoint of mortality in the 3 different treatment strategies, and the investigation of secondary endpoints was beyond the scope of our study. The upcoming randomized clinical trials will provide data on these topics.

**CONCLUSIONS**

Despite higher log EuroSCORE, high-surgical-risk patients with severe symptomatic MR treated with the transcatheter MV repair show similar survival rates compared with those undergoing surgery, with both showing survival benefit compared with conservative treatment.

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**REFERENCES**

(Endovascular Valve Edge-to-Edge Repair)


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