Featured Article

Parsimonious assessment for reoperative aortic valve replacement; the deterrent effect of low left ventricular ejection fraction and renal impairment

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Background: Patient comorbidities play a pivotal role in the surgical outcomes of reoperative aortic valve replacement (re-AVR). Low left ventricular ejection fraction (LVEF) and renal insufficiency (Cr >2 mg/dL) are known independent surgical risk factors. Improved preoperative risk assessment can help determine the best therapeutic approach. We hypothesize that re-AVR patients with low LVEF and concomitant renal insufficiency have a prohibitive surgical risk and may benefit from transcatheter AVR (TAVR).

Methods: From January 2002 to March 2013, we reviewed 232 patients who underwent isolated re-AVR. Patients older than 80 years were excluded to adjust for unobserved frailty. We identified 37 patients with a ≤35% LVEF (low ejection fraction group-LEF) and 195 patients with >35% LVEF (High ejection fraction group-HEF).

Results: The mean age was 68.4±11.5 years and there were more females (86.5% versus 64.1%, P=0.007) in the LEF group. The prevalence of renal insufficiency was higher in LEF patients (27% versus 5.6%, P=0.001). Higher operative mortality (13.5% versus 3.1%, P=0.018) was observed in the LEF group. Stroke rates were similar in both groups (8.1% versus 4.1%, P=0.39). Unadjusted cumulative survival was significantly lower in LEF patients (6.6 years, 95% CI: 5.2–8.0, versus 9.7 years, 95% CI: 8.9–10.4, P=0.024). In patients without renal insufficiency, LEF and HEF had similar survival (8.3 years, 95% CI: 7.1–9.5, versus 9.9 years, 95% CI: 9.1–10.6, P=0.90). Contrarily, in patients with renal insufficiency, LEF led to a significantly lower survival (1.1 years, 95% CI: 0.1–2.0, versus 4.8 years, 95% CI: 2.2–7.3, P=0.050). Adjusted survival analysis revealed elevations in baseline creatinine (HR =4.28, P<0.001) and LEF (HR =5.33, P=0.041) as significant predictors of long-term survival, with a significant interaction between these comorbidities (HR =7.28, P<0.001).

Conclusions: In re-AVR patients, low LVEF (≤35%) is associated with increased operative mortality. Concomitant renal insufficiency in these patients results in a prohibitively low cumulative survival. These reoperative surgical outcomes should warrant expanding the role of TAVR for reoperative patients with LEF and renal impairment.

Keywords: Reoperative AVR; low ejection fraction; (transcatheter aortic valve replacement criteria) TAVR criteria

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Introduction

A patient's underlying comorbidities play a pivotal role in the outcomes of surgical aortic valve replacement (AVR). Contemporary evaluation of these underlying comorbidities is often made through risk predictive models and mortality risk scores, such as the Society of Thoracic Surgeons Predictive Risk of Mortality (STS-PROM) and the European System for Cardiac Risk Evaluation (EuroSCORE) (1-3). One of the few comorbidities consistently present in these predictive models is the

history of a prior sternotomy. In the STS Cardiac Surgery Risk Model (STS-CSRM), reoperative AVR (re-AVR) is associated with 2.1 times the odds of operative mortality (OR: 2.11, 95% CI: 1.78–2.49) (4). However, the aggregated risk of concomitant comorbidities is often underestimated in high-risk populations (5). In these patients, the presence of left ventricular ejection fraction (LVEF) and impaired renal function are consistently associated with worse outcomes (6), with outstanding discriminatory power (7).

Low preoperative LVEF is independently associated with worse outcomes after AVR and is a proxy for the patient's underlying ventricular contractility, an important component in low-gradient aortic stenosis (8,9). In the STS-CSRM, every 10 unit decrease in LVEF is associated with 1.09 times the odds of operative mortality (OR: 1.09, 95% CI: 1.05–1.14) (4).

Impaired renal function, even when mild, has been associated with increased morbidity and mortality after cardiac surgery (6). Severe renal impairment, defined as dialysis dependence, result in 2.85 times the odds of operative mortality according to the STS-CSRM (OR: 2.85, 95% CI: 2.35–3.45) (4).

Patients undergoing re-AVR who present with low LVEF and concomitant renal impairment represent a unique population whose actual risk of mortality may be underestimated by population-based risk models, given their limited accuracy in high-risk populations (5). The use of select highly-predictive baseline characteristics to assess the surgical risk of these patients has shown encouraging results (7). Our aim was to compare the outcomes of re-AVR patients, stratified by their underlying LVEF and assess its interrelation with concomitant renal impairment. We hypothesized that re-operative AVR patients with low preoperative LVEF and impaired renal function represent a prohibitively high-risk population with poor long-term outcomes, therefore providing a parsimonious risk estimation for patients that may benefit from transcatheter therapies.

Methods

Patients and data collection

With permission from the Partners Institutional Review Board, we identified 232 patients ages 18 to 80 years with a previous sternotomy who underwent isolated, re-AVR, between January 2002 and March 2013 at the Brigham and Women's Hospital. Patients older than 80 years were excluded to reduce possible confounding introduced by unmeasured frailty in this age group. All re-AVR patients were further stratified into groups: "Low" LVEF ≤35% (LEF), n=37 and "High" LVEF >35% (HEF), n=195. Patient characteristics, perioperative data, laboratory test results and in-hospital outcomes were recorded at the time of presentation. Data were extracted from hospital electronic medical records and defined according to the STS Adult Cardiac database version 2.52 unless otherwise noted. STS-PROM were calculated using the 2008 algorithm. Patients were considered to have renal insufficiency if they had a documented history of renal failure or a preoperative creatinine >2.0 mg/dL. Operative mortality was defined as any death occurring in-house during the index admission, or within 30 days of surgery, if discharged. Long-term survival data were obtained from our internal research data repository, routine patient follow-up, and our state Department of Public Health. Follow-up time was calculated in months from the date of surgery to the date of death or May 31, 2014, and censored at last known clinical contact. There was a 99% follow-up for patient survival and the mean follow-up time was 56.8±37.7 months, for a total of 1,117 patient years. Primary outcomes of interest were operative mortality and long-term survival. Secondary outcomes included operative morbidity and length of stay.

Statistical analyses

Normally distributed continuous variables are expressed as mean and standard deviation and were compared using Student's *t*-test with Levene's test for homogeneity of variance. Non-normally distributed variables are expressed as median and interquartile range (IQR) and were compared using Mann-Whitney U tests. Categorical variables are presented as frequencies and percentages and compared using χ^2 or Fisher's exact tests. Longitudinal survival was estimated by Kaplan-Meier analyses. A sparse Cox proportional hazards model was used to evaluate the adjusted risk of low LVEF and renal insufficiency on long-term survival and to test for interactions between them. LVEF and renal insufficiency were selected based on their association with cumulative unadjusted survival and clinical relevance in the scientific literature which mirrored their performance in our unadjusted survival analysis. Age and gender were non-contributory in the survival analysis and were therefore excluded from the final model. All analyses were conducted using IBM SPSS Statistics version 22.0 (IBM Corporation, Armonk, NY, USA) and P≤0.05 was the criterion for significance.

Table 1 Preoperative characteristics of 232 reoperative isolated AVR patients (aged <80 years)

Demographics	All patients (n=232)	LEF (LVEF ≤35%) (n=37)	HEF (LVEF >35%) (n=195)	P value
Age (years), mean ± SD	68.4±11.5	70.0±11.7	68.1±11.4	0.351
Females, n (%)	157 (67.7)	32 (86.5)	125 (64.1)	0.007
BMI, mean ± SD	27.9±5.1	27.1±4.3	28.1±6.7	0.010
History of smoking, n (%)	132 (56.9)	25 (67.6)	107 (54.9)	0.205
Diabetes, n (%)	76 (32.8)	17 (45.9)	59 (30.3)	0.084
Renal insufficiency, n (%)	21 (9.1)	10 (27.0)	11 (5.6)	0.001
Preoperative Cr (mg/dL), mean ± SD	0.6±1.2	0.5±1.4	0.6±1.1	0.002
Hypertension, n (%)	185 (79.7)	30 (81.1)	155 (79.5)	1
Peripheral vascular disease, n (%)	57 (24.6)	14 (37.8)	43 (22.1)	0.059
Cerebrovascular disease, n (%)	52 (22.4)	9 (24.3)	43 (22.1)	0.830
Cerebrovascular accident, n (%)	19 (8.2)	3 (8.1)	16 (8.2)	1
Congestive heart failure, n (%)	134 (57.8)	28 (75.7)	106 (54.4)	0.018
NYHA class III/IV, n (%)	114 (49.1)	27 (73.0)	87 (44.6)	0.002

AVR, aortic valve replacement; LVEF, left ventricular ejection fraction; LEF, patients with LVEF ≤35%; HEF, patients with LVEF >35%; BMI, body mass index; Cr, creatinine; NYHA, New York Heart Association.

Results

Baseline and operative characteristics

The baseline characteristics of all the reoperative re-AVR cases are described in *Table 1*. The overall mean age was 68.4±11.5 years and was similarly distributed between LEF (70.0±11.7 years) and HEF (68.1±11.4 years, P=0.351). Patients in the LEF group were more likely to be women (86.5% versus 64.1%, P=0.007), and had a higher frequency of preoperative renal insufficiency (27% versus 5.6%, P=0.001). The prevalence of NHYA class III/IV and congestive heart failure was (as expected) higher for patients in the LEF group (73% versus 44.6%, P=0.002 and 75.7% versus 54.4%, P=0.018, respectively).

The most common previous surgeries were isolated coronary artery bypass graft in 53.9% patients, followed by isolated AVR in 22.4% and were not significantly different between the two groups (*Table 2*). The median interval time from the initial sternotomy to the re-AVR was 9.8 (IQR 6.3–13.5) years in the LEF group and 9.1 (IQR 5.8–12.4) years in the HEF group (P≤0.644). There were 25 patients who underwent a second reoperation; only 4 of them were in the LEF group.

The most common etiologies behind the re-AVR, calcific or bicuspid native valve disease, were present in 75.9% of the patients (89.2% in the LEF group versus 73.3% in the HEF group, P=0.038). Only 6 patients presented with active endocarditis, all in the HEF group. Structural valve degeneration was present in 14.2% of the patients (8.1% in the LEF and 15.4% in the HEF group, P=0.312). Most re-AVR cases (84.5%) had severe aortic stenosis but only 8.2% had concomitant severe aortic insufficiency, with a similar distribution between the two groups (P=0.23). A detailed description of the etiology and indication behind these reoperative cases is shown in *Table 3*.

The cohort's echocardiographic data are shown in *Table 4*. As expected, the LEF group had lower mean and peak aortic valve gradients (35.1±15 versus 44.6±17.5 mmHg, P=0.011 and 57.5±18.5 versus 74.6±27.1 mmHg, P=0.001, respectively). Similarly, the left ventricular end-systolic and end-diastolic diameters were higher in the LEF group (4.8±1.8 versus 4.3±1.3 cm, P=0.038 and 4.9±0.7 versus 3.8±1.1 cm, P=0.002, respectively). The mean AV area was smaller than 1 cm^2 in both groups (0.7±0.2 in LEF and 0.8±0.2 cm in HEF group, P=0.195).

The majority (72.8%) of the implanted valves were bioprosthetic and were similarly distributed between the LEF and HEF (78.4% versus 71.8%, P<0.55). Despite

Table 2 Previous cardiac surgery of the 232 reoperative isolated AVR patients

Previous surgery	All patients (n=232)	LEF (LVEF ≤35%) (n=37)	HEF (LVEF >35%) (n=195)	P value
AVR, n (%)	52 (22.4)	5 (13.5)	47 (24.1)	0.199
AVR+ CABG, n (%)	9 (3.9)	2 (5.4)	7 (3.6)	0.638
AVR + other, n (%)	13 (5.6)	0 (0)	13 (6.7)	0.232
CABG, n (%)	125 (53.9)	24 (64.9)	101 (51.8)	0.155
CABG + other (non-AVR), n (%)	8 (3.4)	5 (13.5)	3 (1.5)	0.003
Other valve, n (%)	12 (5.2)	1 (2.7)	11 (5.6)	0.696
Misc cardiac surgery, n (%)	13 (5.6)	0 (0)	13 (6.7)	0.232
Follow-up time, median (IQR)	4.2 (2.3–7.1)	3.9 (2.0–7.0)	4.2 (2.3–7.2)	0.261

CABG, coronary artery disease; Misc, miscellaneous; IQR, interquartile range.

Table 3 Underlying etiology and indication for reoperative isolated AVR

Factor	All patients (n=232)	LEF (LVEF ≤35%) (n=37)	HEF (LVEF >35%) (n=195)	P value
Etiology				
Calcific/bicuspid, n (%)	176 (75.9)	33 (89.2)	143 (73.3)	0.038
Active endocarditis, n (%)	6 (2.6)	0 (0)	6 (3.1)	0.593
Healed endocarditis, n (%)	4 (1.7)	1 (2.7)	3 (1.5)	0.503
SVD, n (%)	33 (14.2)	3 (8.1)	30 (15.4)	0.312
Other, n (%)	13 (5.6)	0 (0)	13 (6.7)	0.232
Indication				
AI none/trace, n (%)	134 (57.8)	21 (56.8)	113 (57.9)	0.232
Mild, n (%)	49 (21.1)	13 (35.1)	36 (18.5)	–
Moderate, n (%)	30 (12.9)	1 (2.7)	29 (14.9)	–
Severe, n (%)	19 (8.2)	2 (5.4)	17 (8.7)	–
Severe AS, n (%)	196 (84.5)	32 (86.5)	164 (84.1)	0.845

SVD, structural valve degeneration; AI, aortic insufficiency; AS aortic stenosis.

Table 4 Echocardiographic data

Echocardiographic data	All patients (n=232)	LEF (LVEF ≤35%) (n=37)	HEF (LVEF >35%) (n=195)	P value
Ejection fraction, median [range]	55 [45–60]	30 [25–35]	60 [50–65]	–
LV end-diastolic diameter (cm), mean ± SD	4.4±1.4	4.8±1.8	4.3±1.3	0.038
LV end-systolic diameter (cm), mean ± SD	4±1.1	4.9±0.7	3.8±1.1	0.002
IVS (cm), mean ± SD	1.3±0.4	1.1±0.2	1.3±0.4	0.02
Mean AV gradient (mmHg), mean ± SD	43.3±17.4	35.1±15	44.6±17.5	0.011
Peak AV gradient (mmHg), mean ± SD	71.8±26.7	57.5±18.5	74.6±27.1	0.001
AV area (cm), mean ± SD	0.7±0.2	0.7±0.2	0.8±0.2	0.195

LV, left ventricular; IVS, inter ventricular septum; AV, aortic valve.

Table 5 Operative data and outcomes

Factor	All patients (n=232)	LEF (LVEF ≤35%) (n=37)	HEF (LVEF >35%) (n=195)	P value
Operative data				
Valves implanted				
Bioprosthetic, n (%)	169 (72.8)	29 (78.4)	140 (71.8)	0.546
Mechanical, n (%)	63 (27.2)	8 (21.6)	55 (28.2)	0.546
Size (mm), median (IQR)	23 [21–25]	23 [21–25]	23 [21–25]	1
≤21 mm, n (%)	85 (36.6)	8 (21.6)	77 (39.5)	0.042
More than 1 previous cardiac surgery, n (%)	25 (10.8)	4 (10.8)	21 (10.8)	1
Emergent status, n (%)	2 (0.9)	0 (0)	2 (1)	1
Preoperative IABP, n (%)	1 (0.4)	0 (0)	1 (0.5)	1
Intraoperative IABP, n (%)	16 (6.9)	7 (18.9)	9 (4.6)	0.006
Perfusion time (min), median (IQR)	145 [125–202]	150 [136–237]	143 [120–197]	0.046
Cross-clamp time (min), median (IQR)	82 [68–115]	84 [74–125]	80 [66–114]	0.685
Postoperative outcomes				
Postoperative IABP used, n (%)	1 (0.4)	1 (2.7)	0 (0)	0.159
Reoperation for bleed, n (%)	6 (2.6)	1 (2.7)	5 (2.6)	1
Permanent stroke, n (%)	11 (4.7)	3 (8.1)	8 (4.1)	0.398
Renal insufficiency, n (%)	8 (3.4)	3 (8.1)	5 (2.6)	0.118
ESRD requiring dialysis, n (%)	6 (2.6)	3 (8.1)	3 (1.5)	0.053
Ventilation time (h), median (IQR)	10 [6–19]	15 [7–36]	9 [5–18]	0.026
>24 h, n (%)	40 (17.2)	12 (32.4)	28 (14.4)	0.015
ICU stay (h), median (IQR)	66 [34–117]	90 [55–167]	51 [28–115]	0.003
Postop LOS (days), median (IQR)	8 [6–12]	12 [8–16]	7 [6–12]	0.001
Operative mortality, n (%)	11 (4.7)	5 (13.5)	6 (3.1)	0.018

IABP, intra-aortic balloon pump; ESRD, end stage renal disease; ICU, intensive care unit; LOS, length of stay.

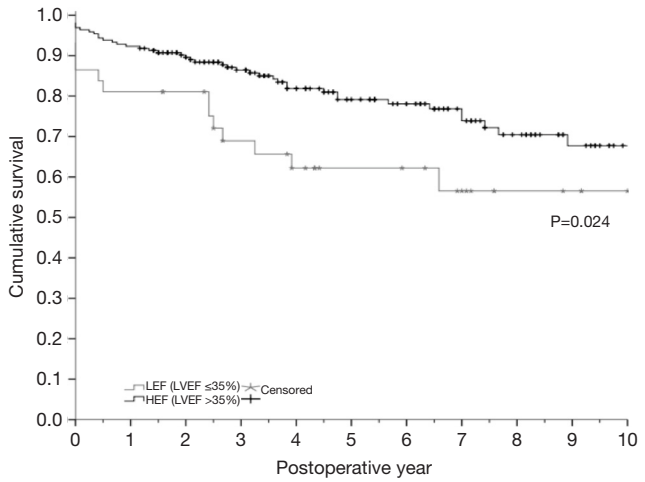
similar cross-clamp times [84 (IQR 74–125) for LEF and 80 (IQR 66–114) for HEF, P=0.685], patients in the LEF group had significantly longer median perfusion times [150 (IQR 136–237) min versus 143 (IQR 120–197) min, P=0.046]. The use of intraoperative intra-aortic balloon pump (IABP) was higher in patients with LEF (18.9% versus 4.6%, P=0.006).

Operative outcomes

Overall, operative mortality was 4.7% and was significantly higher in the LEF group (13.5% versus 3.1%, P=0.018). Additionally, LEF patients had significantly longer ventilation time [15 (IQR 7–36) h versus 9 (IQR 5–18) h, P=0.026], ICU [90 (IQR 55–167) h versus 51 (IQR 28–115) h, P=0.003] and hospital length of stay [12 (IQR 8–16) days versus 7 (IQR 6–12) days, P=0.001]. There were no differences in the use of postoperative IABP, reoperation for bleeding, and new onset renal insufficiency (*Table 5*). Although not statistically significant, postoperative stroke (8.1% versus 4.1%, P=0.398) and dialysis (8.1% versus1.5%, P=0.053) were higher in the LEF group.

Survival outcomes

There were 55 deaths during the study period. Long-term



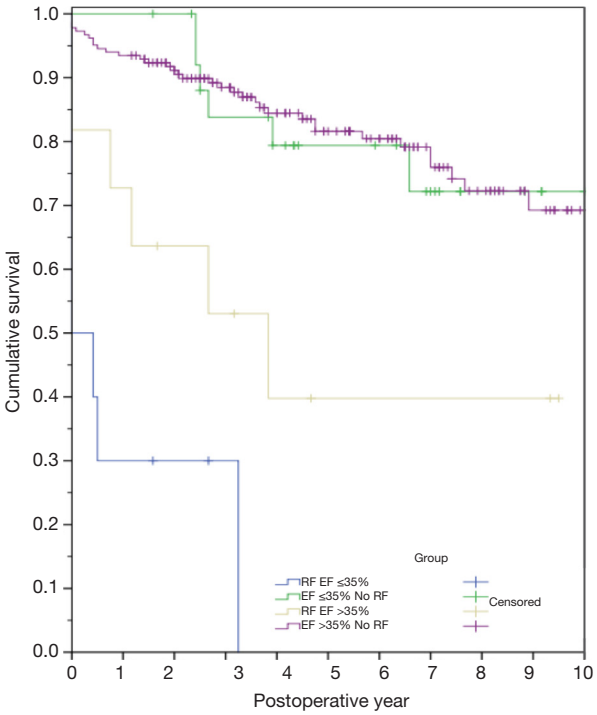
Mean estimated survival	Estimated years	95% CI	
Overall	9.3	8.7	10.0
LEF (preoperative LVEF ≤35%)	6.6	5.2	8.0
HEF (preoperative LVEF >35%)	9.7	8.9	10.4

Figure 1 Kaplan-Meier survival curves for LEF and HEF patients. Cumulative survival curves show significantly higher survival for patients with left ventricular ejection fraction (LVEF) >35% (HEF) compared to patients with LVEF ≤35% (LEV) (P=0.024).

survival was significantly lower for LEF, compared to HEF patients (6.6 years, 95% CI: 5.2–8.0 versus 9.7 years, 95% CI: 8.9–10.4, P=0.024) (*Figure 1*). Unadjusted survival analysis, stratified according to the presence of renal insufficiency, revealed the influence of renal impairment in the survival of LEF and HEF patients. In patients without renal insufficiency, there was no difference in the mean survival between LEF and HEF groups (8.3 years, 95% CI: 7.1–9.5 versus 9.9 years, 95% CI: 9.1–10.6, respectively, P=0.90). Contrary, in patients with renal insufficiency, the mean cumulative survival was significantly lower for patients in the LEF group (1.1 years, 95% CI: 0.1–2.0 versus 4.8 years, 95% CI: 2.2–7.3, P=0.05). Additionally, there was a significant difference between LEF patients with renal insufficiency and without, P=0.001, and HEF patients with renal insufficiency and without, P=0.001 (*Figure 2*). Pairwise comparisons for cumulative survival, stratified by LVEF and renal function are shown in *Table S1*.

Multivariable analysis

In order to determine the adjusted effect of low LVEF and creatinine on long-term survival, we ran a sparse Cox proportional hazards model. In this high-risk population,



Mean estimated survival	Estimated years	95% CI	
Overall	9.3	8.7	10
EF >35 no RF (LVEF >35% and normal renal function)	9.9	9.1	10.6
EF ≤35 no RF (LVEF ≤35% and normal renal function)	8.3	7.1	9.5
RF EF >35 (LVEF >35% and renal failure)	4.8	22	73
RF EF ≤35 (LVEF ≤35% and renal failure)	1.1	0.1	2

Figure 2 Kaplan-Meier survival curves for LEF and HEF patients, stratified by renal function. Cumulative survival curves show the effect of creatinine across different levels of LVEF. The poorest survival is observed in patients with LVEF ≤35% (LEF) and renal insufficiency, followed by patients with LVEF >35 (HEF) and renal insufficiency. (EF ≤35 no RF versus EF >35% no RF, P=0.90; RF EF >35 versus EF ≤35% no RF, P=0.014; RF EF>35 versus EF >35% no RF, P=0.001; RF EF>35% versus RF EF ≤35, P=0.050). See *Table S1* for all pairwise comparisons. EF, ejection fraction; RF, renal failure.

both creatinine, expressed in 1 mg/dL increments, (HR =4.29 95% CI: 1.830–10.032, P=0.001) and LEF group (HR =5.36, 95% CI: 1.068–26.638, P=0.041) were significant predictors of decreased cumulative survival. In accordance with our unadjusted survival analysis, we observed a significant interaction between LVEF and preoperative creatinine (HR =7.28, 95% CI: 3.120–17.003, P=0.001), explaining the effect of renal impairment across the different levels of LVEF. Age, was non-contributory in our

analysis and was therefore not included in the final model.

Discussion

Our study has several noteworthy findings. Patients undergoing re-AVR with low LVEF have a significantly higher operative mortality and longer ventilation, ICU, and hospitalization times. Unadjusted long-term survival was also lower in patients with low LVEF. Interestingly, when stratified by renal function, we observed an unfavorable survival difference for patients with low LVEF in patients with renal insufficiency (preoperative creatinine >2.0 mg/dL) but not in patients with normal renal function. This finding was further confirmed in our adjusted survival analysis, which revealed that low LVEF (<35%) and renal impairment were significant predictors for cumulative survival. Expectedly, we found an interaction between high and low LVEF and renal function, explaining the changing effect of renal function across different levels of LVEF. The prohibitively low cumulative survival seen in re-AVR patients with low LVEF and concomitant renal insufficiency underscores the importance of identifying significant interactions in the patients' underlying comorbidities and provides a parsimonious approach to recognize these high-risk patients, who are likely to benefit from transcatheter AVR (TAVR).

A 68-year-old (mean age in our study) 174 cm, 70 kg, re-AVR male patient with low LVEF (35%), creatinine of 2.1 mg/dL (renal impairment) and no other comorbidity would have a 2.55% STS-PROM. This is below the intermediate risk threshold (3.0%), for which TAVR is currently indicated, despite the high mortality and low survival observed in LEF patients with concomitant renal insufficiency.

Our study confirms the results from previous publications on isolated re-AVR in which early mortality and decreased long-term survival have been associated with low LVEF and NYHA III/IV (8-12). The steep operative mortality in the LEF group (13.5%) was considerably higher compared to the published mortality of non-reoperative (first time) cardiac surgery patients with low LVEF (5.6% to 11%) (13-15) and to the previously published operative mortality in all re-AVR patients (4.5% to 5.1%) (8,9), to which the 3.2% mortality of our re-AVR HEF group compares favorably. The contrasting outcomes of re-AVR LEF patients to both HEF and historic groups stress the increased risk conferred by the presence of low ventricular contractility and a prior sternotomy.

Long-term survival was significantly shorter in LEF patients. Interestingly, after further stratifying the two groups by renal insufficiency, the interplay between these two variables became evident. The best survival was observed among reoperative AVR patients with no renal insufficiency regardless of their LVEF status, followed by all patients with renal insufficiency in whom the presence of low LVEF resulted in a grim mean survival of 1.1 years. Consequently, an unadjusted difference in the survival function was observed for decreased LVEF across different levels of renal function.

We assess the interrelation between LVEF, renal impairment, and long-term survival using a sparse Cox proportional hazards model. Both low LVEF and renal impairment were significant predictors of cumulative survival. More importantly, we confirmed the presence of a significant interaction between these two variables. Calculating for different clinical scenarios, and compared to HEF patients without renal impairment, HEF patients with renal impairment would have 4.28 times the risk of death (calculated HR =4.28). Correspondingly, for a patient in the LEF group with concomitant renal impairment that risk increases 166.49 times (calculated HR =166.49). The detrimental influence of decreased LVEF and impaired renal function on survival has been previously described (6,16,17). However, in re-AVR patients, the aggregated mortality risk of these comorbidities probably supersedes the predicted risk associated with each independent risk factor.

LVEF is a surrogate marker of cardiac decompensation and deteriorating hemodynamic reserve. Interestingly, the long-term influence of this low LVEF was negligent in patients with normal renal function, and augmented in those with concomitant renal insufficiency. However, the concomitant presence of these three characteristics (reoperative status, low LVEF and renal insufficiency) should serve as a parsimonious warning to the poor outcomes observed in these patients.

Although TAVR has become a popularized intervention for high-risk patients, it lacks the necessary long-term follow-up data (18-21). Greason and colleagues published the outcomes of a high-risk subgroup of reoperative patients from the PARTNER trial (cohort-A), which did not show a significant mortality difference or a conclusive survival benefit with TAVR over surgical AVR (20). More recently, Lauten and associates studied the outcomes of TAVR in patients with low ejection fraction through a sample of low-flow, low-gradient aortic stenosis from the multicenter German TAVI registry (22). Low grade patients suffered higher operative mortality (12.8%) compared to high grade patients (7.4%), although, low grade survivors experienced significant symptomatic improvements at 30 days and 1-year

follow-up. These results call for continuous identification of reoperative and low LVEF cases which, based on their underlying comorbidities, would benefit the most from TAVR. Especially in patients with prohibitive reoperative risk, TAVR could offer more than eliminating the risk surgical chest reentry.

Limitations

This study has all the inherent limitations of a retrospective design. The small size of the LEF group precluded further subgroup analysis or a continuous evaluation of LVEF. We decided to adopt LVEF ≤35% as a definition for low LVEF to be aligned with previous publications (23,24). Data on the inotropic reserve of low LVEF patients would help elucidate its role in the observed outcomes and its association with other baseline comorbidities. Unfortunately, Dobutamine stress results were seldom available in our study. However, the underlying inotropic reserve does not predict ventricular recovery in patients who survive the AVR (25), and could be less important in the assessment of long-term outcomes.

Despite recent publications with excellent outcomes of re-AVR in the elderly (10,26), age is still incorporated in the major cardiac surgery risk scores as a significant predictor of postoperative adverse outcomes (3,27,28). The exclusion of patients older than 80 aimed to decreased the variability introduced by unmeasured frailty in the elderly. However, it limits the generalizability of our findings to populations with a similar age distribution. The results of this study should be interpreted with these considerations in mind.

Conclusions

Patients presenting for an isolated re-AVR are a complex and growing population. In our study, re-AVR patients with LVEF <35% experienced higher mortality and longer ventilation, ICU, and hospitalization time, compared to those with higher ejection fraction. Long-term outcomes were heavily influenced by the concomitant presence of renal impairment and low LVEF. Patients undergoing re-AVR who have low LVEF and renal insufficiency represent a prohibitively high-risk population who might benefit from transcatheter therapies.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary

Table S1 Pairwise comparisons for cumulative survival, stratified by LVEF and renal function

Comparison groups	RF EF35 (LVEF ≤35 and renal insufficiency)	EF35 no RF (LVEF ≤35 and normal renal function)	RF EF >35 (LVEF >35 and renal insufficiency)	EF >35 no RF LVEF >35 and normal renal function)
RF EF35 (LVEF ≤35 and renal insufficiency)	–	0	0.05	0
EF35 no RF (LVEF ≤35 and normal renal function)	0	–	0.014	0.908
RF EF >35 (LVEF >35 and renal insufficiency)	0.05	0.014	–	0.001
EF >35 no RF (LVEF >35 and normal renal function)	0	0.908	0.001	–

EF, ejection fraction; RF, renal failure.