JACC: CARDIOONCOLOGY VOL. 3, NO. 3, 2021


ORIGINAL RESEARCH

# Transcatheter Compared With Surgical Aortic Valve Replacement in Patients With Previous Chest-Directed Radiation Therapy

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## ABSTRACT

**BACKGROUND** Cardiac surgery for radiation-induced valvular disease is associated with adverse outcomes. Transcatheter aortic valve replacement (TAVR) is increasingly used in patients with a history of chest-directed radiation therapy and aortic stenosis (CRT-AS).

**OBJECTIVES** We examined outcomes of TAVR compared with surgical aortic valve replacement (SAVR) for patients with CRT-AS.

**METHODS** We identified 69 patients with CRT-AS who underwent TAVR from January 2012 to September 2018. Operative mortality, postoperative morbidities, and length of hospitalization were compared with 117 contemporaneous patients with CRT-AS who underwent isolated SAVR. Age-adjusted survival was evaluated by means of Cox proportional hazards modeling.

**RESULTS** Compared with SAVR patients, TAVR patients were older (mean age 75 ± 11.5 vs 65 ± 11.5 years), with more comorbidities, such as chronic obstructive pulmonary disease, atrial fibrillation, and peripheral vascular disease (all $P < 0.050$). Operative mortality was 4.3% for SAVR vs 1.4% for TAVR ($P = 0.41$). Most SAVR deaths (4 of 5) occurred in the intermediate-/high-risk group (Society for Thoracic Surgeons predicted risk of operative mortality >3%; $P = 0.026$). The ratio of observed to expected mortality was better for low-risk SAVR patients and all TAVR patients (0.72 [95% confidence interval [CI]: 0.59-0.86] and 0.24 [95% CI: 0.05-0.51], respectively) compared with intermediate-/high-risk SAVR patients (2.52 [95% CI: 0.26-4.13]). SAVR patients had significantly longer median intensive care unit and overall length of stay and higher blood transfusion requirements but similar rates of stroke and pacemaker implantation.

**CONCLUSIONS** TAVR was associated with excellent in-hospital outcomes and better survival compared with intermediate-/high-risk SAVR in patients with CRT-AS. While SAVR still has a role in low-risk patients or those for whom TAVR is unsuitable for technical or anatomical reasons, TAVR is emerging as the standard of care for intermediate-/high-risk CRT-AS patients. (J Am Coll Cardiol CardioOnc 2021;3:397-407) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received March 9, 2020; revised manuscript received July 20, 2021, accepted July 20, 2021.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2021.07.005

JACC: CARDIOONCOLOGY, VOL. 3, NO. 3, 2021
SEPTEMBER 2021:397–407

**ABBREVIATIONS AND ACRONYMS**

**CKD** = chronic kidney disease

**CRT-AS** = chest-directed radiation therapy and aortic stenosis

**EMR** = electronic medical record

**ICU** = intensive care unit

**IPT** = inverse probability of treatment

**LOS** = length of stay

**O/E** = observed/expected

**PPM** = permanent pacemaker

**PROM** = predicted risk of operative mortality

**SAVR** = surgical aortic valve replacement

**STS** = Society for Thoracic Surgeons

**TAVR** = transcatheter aortic valve replacement

Severe aortic valve stenosis is a late manifestation of radiation-induced heart disease and is prevalent in approximately 25% of patients with previous chest-directed radiation who are referred for cardiac surgery (1). Surgical treatment of radiation-induced heart disease can be challenging, and a few institutions, including ours, have previously demonstrated worse outcomes in patients with a history of chest-directed radiation therapy and aortic stenosis (CRT-AS) undergoing surgical aortic valve replacement (SAVR) (1-4). The increased short- and long-term risks can be attributed to 3 possible reasons: 1) the need for complex surgical procedures in the setting of concomitant coronary and valvular heart disease; 2) the poor lung ventilatory mechanics due to radiation-induced pulmonary fibrosis, which is known to increase the risk of respiratory complications; and 3) radiation-induced myocardial and pericardial fibrosis, which results in right ventricular dysfunction and diastolic heart failure (1,5).

Although the American College of Cardiology/American Heart Association valve guidelines characterize mediastinal radiation as a "procedure-specific impediment" (6), there is a paucity of reliable data to support the recommendation of transcatheter aortic valve replacement (TAVR) in this unique population, even though TAVR is approved in patients who are deemed to be inoperable and at high (7-9), intermediate (10,11), and low (12) risk of complications after surgery. Existing data to guide clinical decision making are limited to small retrospective studies (13-16) because existing clinical trials were either not designed or could not allow for more granular subgroup comparisons of these two procedures in the context of CRT-AS. To bridge the existing knowledge gap, the present study provided a more nuanced comparison of procedural outcomes and mid-term survival between TAVR and SAVR in a large series of patients with CRT-AS treated at a tertiary medical center.

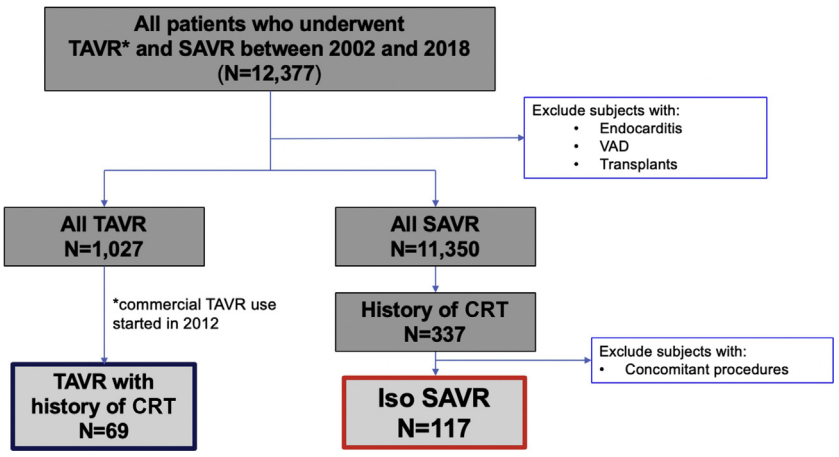
## METHODS

**PATIENT SELECTION.** From a retrospective review of 1,027 commercial TAVR patients at our institution from January 2012 to September 2018, we identified 69 with CRT-AS. For the comparison surgical cohort, 11,350 adult patients aged ≥18 years who underwent SAVR from January 2002 to September 2018 were identified. Patients with concomitant procedures, history of heart transplantation or ventricular assist device implantation, or endocarditis as the indication for surgery were excluded. A total of 117 patients with CRT-AS who underwent isolated SAVR were identified (**Figure 1**). This study was approved by the Partners Healthcare Institutional Review Board with waived consent.

**DATA COLLECTION.** Patient characteristics, perioperative data, laboratory test results, echocardiographic reports, and in-hospital outcomes were extracted from patients' electronic medical records (EMRs). The indication for chest-directed radiation therapy was collected for all patients. Owing to the prevalence of remote history of cancer and limitations in the preoperative documentation for cardiac procedures, details regarding doses and duration of chest-directed radiation therapy were frequently absent from the EMR. The time interval between the first round of radiation therapy until TAVR or SAVR was calculated in months. When only the year of radiation was reported (and day and month were missing), July 1 was assumed for interval calculations. Confirmation of previous chest radiation therapy as the cause of the valve disease was determined by referring to cardiologist documentation and/or imaging findings, and absence of other causes was verified through chart and EMR review adjudicated by 2 independent reviewers. To make the comparison groups more contemporaneous and homogeneous regarding cancer types, subgroup analyses were conducted on patients whose procedures were in the TAVR era (2012 and after) and whose indications for CRT were either breast cancer or Hodgkin lymphoma (the 2 most common cancer types); there were 47 TAVR and 47 SAVR patients in these subgroups.

Variables were coded to the Society of Thoracic Surgeons (STS) (17) Adult Cardiac Surgery Database version 2.52 specifications unless otherwise noted. However, the most recent model of the STS predicted risk of operative mortality (PROM) score was used. Chronic kidney disease (CKD) was defined as a preoperative creatinine level ≥2.0 mg/dL or clinical documentation of renal disease. Operative mortality was defined as any death occurring in-house during the index admission, or within 30 days of the procedure if discharged. The decision to perform TAVR versus SAVR was at the discretion of the primary surgeon and the patient. The decision to implant a bioprosthetic versus a mechanical valve at the time of SAVR was at the discretion of the primary surgeon and the patient, considering the patient's age, lifestyle choice, and preferences. Survival data were obtained from our internal research repository,

**FIGURE 1** Study Flow Diagram




All TAVR patients were included from 2012. Only isolated SAVR cases were included. CRT = chest-directed radiation therapy; Iso = isolated cases only; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement; VAD = ventricular assist devices.

routine patient follow-up, and the state's Department of Public Health. Survival follow-up was 100% for this study. Follow-up time was calculated in days from the date of procedure to the date of death or study end (June 30, 2019) if alive.

**OUTCOMES OF INTEREST.** The primary outcomes of interest were all-cause 30-day mortality after the operation and mid-term survival to study end. Secondary outcomes were intensive care unit (ICU) length of stay (LOS), hospital LOS, and postoperative morbidities including stroke, new-onset atrial fibrillation, need for permanent pacemaker (PPM) implantation, acute kidney injury, blood transfusion, reoperation for bleeding, and residual central or paravalvular aortic insufficiency. Observed to expected (O/E) mortality estimates were calculated by dividing the observed rate of 30-day mortality by the mean STS-PROM calculated for the cohort of interest.

**STATISTICAL ANALYSIS.** Normally distributed variables are expressed as mean ± SD and were compared by means of Student *t* tests with Levene test for homogeneity for variance or 1-way analysis of variance with Dunnett post hoc tests for 3-way comparisons. Nonnormally distributed variables are expressed as median (interquartile range [IQR]) and were compared by means of Mann-Whitney *U* tests. Categoric variables are presented as n (%) and were compared by means of chi-square or Fisher exact tests. Comparison of immediate postoperative echocardiographic data between the 2 procedures was also performed. The SAVR cohort was further stratified

**TABLE 1** Baseline Characteristics of Patients With Severe Aortic Stenosis and History of Chest-Directed Radiation Therapy Who Underwent TAVR or SAVR

| | TAVR (n = 69) | SAVR (n = 117) | *P* Value |
|---|---|---|---|
| Age, y | 75.3 ± 11.5 | 64.8 ± 11.5 | 0.001 |
| Female | 46 (66.7) | 81 (69.2) | 0.74 |
| Body mass index, kg/m$^2$ | 25.6± 5.5 | 28.9 ± 7.1 | 0.001 |
| Moderate-severe COPD | 17 (24.6) | 3 (2.6) | 0.001 |
| CKD | 3 (4.3) | 4 (3.4) | 0.71 |
| Diabetes | 16 (23.1) | 20 (17) | 0.16 |
| Hypertension | 48 (69.6) | 67 (57.2) | 0.002 |
| Previous stroke | 6 (8.7) | 2 (1.7) | 0.053 |
| Previous myocardial infarction | 13 (18.8) | 8 (6.8) | 0.016 |
| Previous atrial fibrillation | 23 (33.3) | 12 (10.3) | 0.001 |
| Endocarditis | 0 (0.0) | 1 (0.9) | 1.00 |
| Heart failure | 38 (55.1) | 42 (35.9) | 0.015 |
| Aortic valve gradient, mm Hg | 43.1 ± 12.2 | 45.4 ± 16.4 | 0.39 |
| STS risk score for SAVR, % | 5.73 ± 4.5 | 2.53 ± 2.25 | 0.001 |
| Low (STS ≤3%) | 1.78 ± 0.6 (n = 15) | 1.53 ± 0.72 (n = 88) | 0.15 |
| Intermediate or high (>3%) | 6.84 ± 4.53 (n = 53) | 5.47 ± 2.64 (n = 29) | 0.082 |
| Cancer history | | | |
| Breast | 27 (39) | 48 (41) | 0.87 |
| Right | 12 (17.4) | 18 (15.4) | |
| Left | 14 (12) | 20 (17) | |
| Unknown laterality | 1 (1.5) | 10 (8.5) | |
| Hodgkin/thymic/testicular | 20 (29) | 49 (42) | 0.091 |
| Lung | 9 (13) | 2 (1.7) | 0.003 |
| Right | 2 (3) | 1 (1) | |
| Left | 5 (7.2) | 0 | |
| Unknown laterality | 2 (3) | 1 (1) | |
| Other[a] | 13 (19) | 18 (15.4) | 0.54 |

Values are mean ± SD or n (%). [a]Cancer history labeled as "other" includes non-Hodgkin, B-cell, and other lymphomas, esophageal cancer, squamous cell carcinomas, and neuroblastoma.

CKD = chronic kidney disease; COPD = chronic obstructive lung disease; SAVR = surgical aortic valve replacement; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement.

**TABLE 2 Operative Data and Postoperative Outcomes in TAVR and SAVR Patients With Severe Aortic Stenosis and History of Chest-Directed Radiation Therapy**

| | TAVR (n = 69) | SAVR (n = 117) | *P* Value |
|---|---|---|---|
| Operative data | | | |
| Reoperation | 17 (24.6) | 13 (11.1) | 0.022 |
| Valve-in-valve | 6 (8.7) | - | - |
| Perfusion time, min | - | 95 (76–139) | - |
| Cross-clamp time, min | - | 67 (57–90) | - |
| Procedure time, min | 134 (111–177) | - | - |
| In-hospital outcomes | | | |
| Mortality | 1 (1.4) | 5 (4.3) | 0.41 |
| Low-risk SAVR (≤3%) | - | 1 (0.9) | |
| High-risk SAVR (>3%) | - | 4 (3.4) | |
| ICU stay, hours | 0 (0–24) | 47 (25–83) | 0.001 |
| Post-op LOS, days | 2 (1–5) | 7 (5–9) | 0.001 |
| Residual AI[a] | | | 0.001 |
| Mild | 10 (14.5) | 1 (0.9) | |
| ≥Moderate | 2 (2.9) | 0 | |
| Postoperative complications | | | |
| Permanent stroke | 3 (4.3) | 3 (2.6) | 0.67 |
| Reoperation for bleeding | 0 (0.0) | 1 (0.9) | 1.000 |
| New-onset atrial fibrillation | 5 (7.2) | 20 (17.1) | 0.075 |
| New permanent pacemaker | 7 (10.1) | 16 (13.7) | 0.64 |
| Acute kidney injury | 0 (0.0) | 3 (2.6) | 0.29 |
| Transfused with PRBCs | 6 (8.7) | 41 (35) | 0.001 |

Values are n (%) or median (interquartile range). [a]Residual AI data are based on intraoperative transesophageal echocardiography for SAVR and some TAVR patients or immediate post-procedural transthoracic echocardiography for other TAVR patients.

AI = aortic insufficiency; ICU = intensive care unit; LOS = length of stay; PRBCs = packed red blood cells; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

into low-risk (STS PROM ≤3%) and intermediate-/high-risk (STS PROM >3%) based on the most recent STS PROM model, which includes radiation therapy. This cut-off was chosen because it was used in the SURTAVI (Safety and Efficacy Study of the Medtronic CoreValve System in the Treatment of Severe Symptomatic Aortic Stenosis in Intermediate Risk Subjects Who Need Aortic Valve Replacement) trial (11). The STS PROM was used for risk stratification because it is well validated in the literature and is central to the eligibility criteria for TAVR and enrollment in TAVR clinical trials. O/E estimates of 30-day mortality are presented with 95% confidence intervals (CIs). Longitudinal survival was evaluated with the use of Cox proportional hazard modeling, including the subgroups of interest and age, and proportionality assumptions were examined.

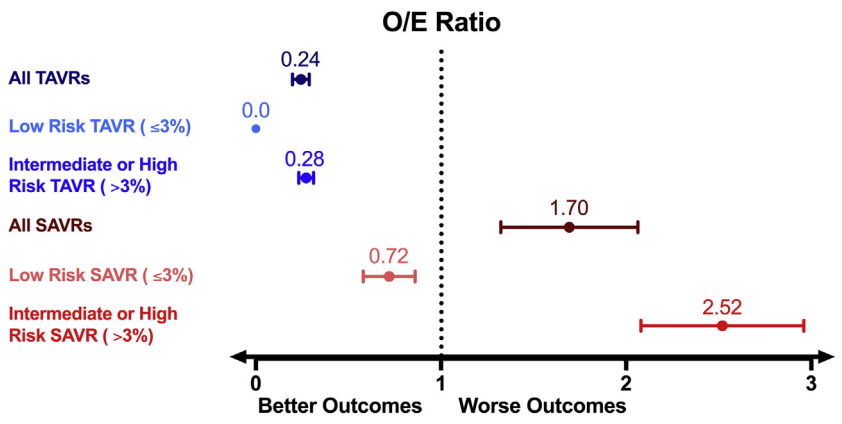
To address bias and confounding due to nonrandomized procedure selection, inverse probability of treatment (IPT) weighting was conducted (18). Initially, forward stepwise logistic regression analyses with an inclusion threshold of $P = 0.15$ were conducted to identify preoperative characteristics predicting the probability of receiving TAVR. Variables directly incorporated into the STS PROM were included in the model, along with prognostically important variables and those known to affect postoperative survival. Continuous variables (age, creatinine, body mass index, ejection fraction, time from CRT) were evaluated both as presented and as splines. A final model including prognostic and treatment-predictive factors was used to generate IPT weights. Because TAVR is indicated for patients with prohibitive surgical risk (who thus have very low chance of receiving SAVR), weights were stabilized and then a 5% trim was applied. The results and model performance diagnostics are presented in Supplemental Tables 4 to 6. IPT-weighted Cox proportional hazard models were generated for the full cohort and contemporaneous subgroup, and effect estimates are presented as hazard ratios (HRs) with 95% CIs. E-value estimates of unmeasured bias were also calculated (19). All analyses were conducted with the use of IBM SPSS Statistics version 23.0 (IBM Corp) with $P < 0.050$ as the criterion for significance.

## RESULTS

**BASELINE CHARACTERISTICS.** The baseline characteristics of the entire cohort are presented in **Table 1**. Compared with TAVR patients, SAVR patients were significantly younger (age 64.8 ± 11.5 years vs 75.3 ± 11.5 years), and had fewer comorbidities, including a lower prevalence of moderate-to-severe chronic obstructive pulmonary disorder (2.6% vs 24.6%), peripheral vascular disease (10.3% vs 26.1%), previous myocardial infarction (6.8% vs 18.8%), and heart failure (36% vs 55%) (all $P < 0.050$). TAVR patients had a higher prevalence of previous stroke (8.7% vs 1.7%; $P = 0.053$) but there were no significant differences in CKD, endocarditis, or mean aortic valve gradients (all $P > 0.050$). STS PROM was significantly higher in TAVR patients compared with SAVR patients (5.7% ± 4.5% vs 2.5% ± 2.2%; $P < 0.001$).

The most common indications for CRT were Hodgkin lymphoma or breast cancer, which did not differ significantly between the two groups (both $P > 0.050$), but lung cancer was significantly higher in the TAVR cohort (13% vs 1.7%; $P = 0.003$). Additional details on the laterality of breast cancer and lung cancer are included in **Table 1**. The median times between the first exposure to CRT and the TAVR and SAVR procedures were 17.5 (IQR: 7-37) and 23.0 (IQR: 9-35) years, respectively ($P = 0.67$). Supplemental Table 1 demonstrates baseline characteristics of the subgroup of patients after excluding less common types of cancers and excluding SAVR patients before

**FIGURE 2** Ratio of Observed to Expected Operative Mortality




Ratio of observed to expected (O/E) operative mortality demonstrated among low-, intermediate-, and high-risk SAVR and TAVR patients with history of chest radiation. Abbreviations as Figure 1.

the year 2012 (before the TAVR era) to maximize homogeneity (n = 47 in each group) as a sensitivity analysis.

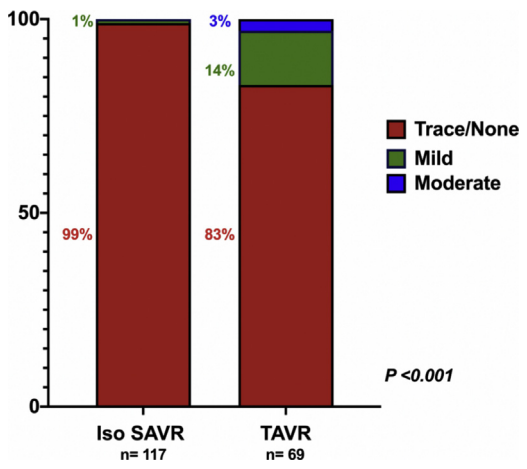
**OPERATIVE AND IN-HOSPITAL OUTCOMES.** More TAVR patients had previous cardiac surgery than the SAVR group (25% vs 11%; $P = 0.022$) (Table 2). The transfemoral approach was used in most TAVR patients (n = 57) followed by the transaortic (n = 6) and transapical approaches (n = 4). General anesthesia was used in 20 TAVR patients (29%). Among the SAVR cases, mechanical valves were implanted in 57 patients (49%). Supplemental Table 2 displays operative data and postoperative outcomes for the subgroup of patients after excluding less common types of cancer and excluding cases before 2012.

The overall operative mortality was 1.4% (n = 1) in the TAVR group and 4.5% (n = 5) in the SAVR group ($P > 0.050$). However, 4 of the 5 SAVR deaths occurred in the intermediate-/high-risk group (13.8%; n = 29), with the remainder in the low-risk SAVR cohort (1.1%; n = 88) ($P = 0.028$). When comparing the O/E ratios in our subgroup analysis, the low-risk SAVR patients, with a mean STS PROM of 1.5% ± 0.7%, experienced lower than expected mortality (O/E ratio: 0.72; 95% CI: 0.59-0.86)). All TAVR patients, with a mean STS PROM of 5.7% ± 4.5%, also experienced lower observed mortality than predicted (O/E ratio: 0.24; 95% CI: 0.05-0.51). However, the intermediate-/high-risk SAVR patients, with a mean STS PROM of 5.4% ± 2.6%, experienced more mortality events than predicted by their STS PROM score (O/E ratio: 2.52; 95% CI: 0.26-4.13) (Figure 2).

SAVR patients had significantly longer ICU time (47 [IQR: 25-83] hours vs 0 [IQR: 0-25] hours) and LOS (6 [IQR: 5-9] days vs 2 [IQR: 1-5] days), and were more likely to require postoperative blood transfusions (36.9% vs 7.1%) compared with TAVR patients (all $P < 0.001$). However, on immediate postoperative echocardiography, there were more SAVR patients with trace or no residual (central or paravalvular) aortic insufficiency (99% vs 83%; $P < 0.001$) (Figure 3). There were otherwise no statistical differences in rates of new PPM requirement, new-onset atrial fibrillation, or acute kidney injury. Postoperative outcomes by etiology of cancer types are summarized in Supplemental Table 3. In general, TAVR patients appeared to have favorable clinical outcomes for most cancer types, although they did not reach statistical significance owing to the low numbers.

**MID-TERM SURVIVAL.** The median follow-up time was 37 months (IQR: 19-72 months) for a total of 806 patient-years. During this period, there were 44 deaths from all causes. Cox models controlling for age showed similar survival between SAVR and TAVR patients (SAVR HR: 1.12; 95% CI: 0.51-2.47; $P = 0.27$) (Figure 4A). In the risk-stratified subgroups, survival between low-risk SAVR and TAVR patients did not differ (HR for low-risk SAVR: 0.46; 95% CI: 0.21-1.01; $P = 0.27$) (Figure 4B). However intermediate-/high-risk SAVR patients had significantly worse survival than TAVR patients (HR: 2.94; 95% CI: 1.57-5.55; $P < 0.001$; Figure 4B). Notably, cancer type was not a significant risk factor for operative mortality ($P = 0.47$) or mid-term survival ($P = 0.20$).

**FIGURE 3 Residual Aortic Insufficiency**




Degree of aortic insufficiency (central or paravalvular) on immediate postoperative assessment in each group. There were proportionally more SAVR patients with trace or no residual aortic insufficiency (99% vs 83%; $P < 0.001$). Abbreviations as in Figure 1.

**IPT-WEIGHTED COX PROPORTIONAL HAZARDS MODELING.** Figure 5 shows the weighted and adjusted survival between low-risk SAVR, intermediate-/high-risk SAVR, and TAVR patients for the whole cohort, and Supplemental Figure 1 shows the weighted and adjusted survival for the contemporaneous subgroup as the sensitivity analysis. There was a significant survival penalty associated with the SAVR intermediate-/high-risk subgroup compared with TAVR (HR: 3.96 [95% CI: 3.78-4.15] for all patients; HR: 2.80 [95% CI: 2.50-3.07] for the subgroup sensitivity analysis; both $P < 0.001$). Sensitivity analyses for potential effect size of unmeasured confounding or bias revealed an E-value estimate of 2.54 for the whole cohort and 5.04 for the contemporaneous subgroups (lower limits of 1.00 for each).

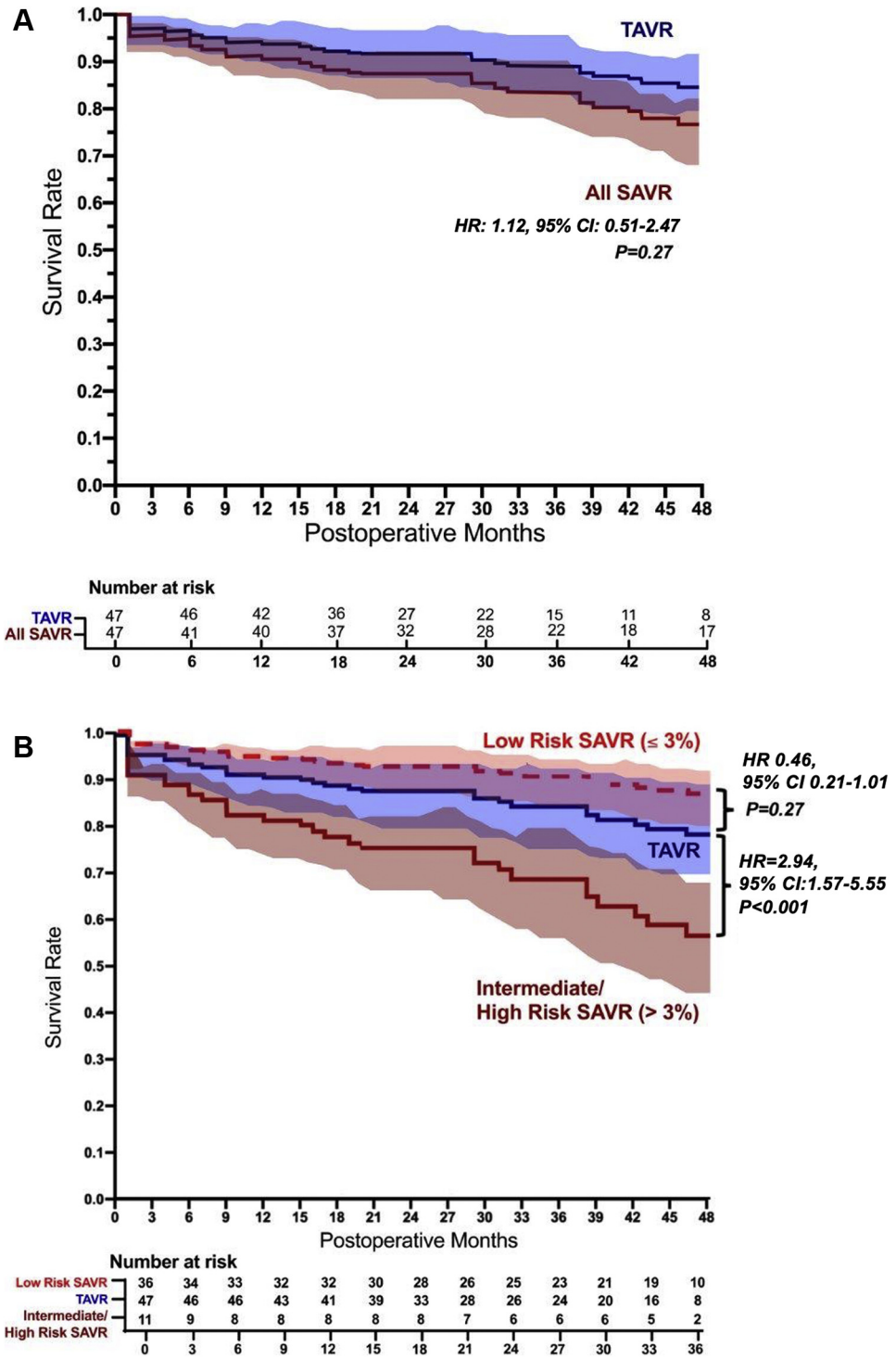
## DISCUSSION

Patients with a history of CRT and symptomatic AS represent a unique cohort with inherent clinical and procedural challenges. This study, to our knowledge, is one of the largest to compare outcomes of isolated SAVR and TAVR in CRT-AS patients. This study has 2 key findings. First, we demonstrate that TAVR was associated with excellent in-hospital outcomes in terms of ICU and hospital LOS and the need for postoperative blood transfusions. However, there were no significant differences in postoperative rates of new PPM, new-onset atrial fibrillation, or acute kidney injury. Second, low-risk SAVR patients had outcomes similar to those with TAVR, but high-risk SAVR patients had significantly worse mid-term survival and higher O/E mortality ratio compared with TAVR patients. These results were consistent with matching through the use of an IPT-weighted Cox model and for the cohort subgroup with more homogeneous cancer types and same time period of TAVR or SAVR. Together, these findings propose an algorithmic approach to managing this complex disease, with TAVR as a first option and SAVR as an alternate option in low-risk patients with anatomic or technical impediments to TAVR (Central Illustration).

As cancer survival outcomes have continued to improve in recent years, there has been considerable interest in understanding the long-term occurrence of drug-related or radiation-related adverse cardiovascular effects, particularly in the context of cancer therapeutics (20). However, there are limited supporting data to help guide clinical decision making in the context of TAVR versus SAVR in patients with CRT-AS, as the field of cardio-oncology evolves (13,14). Our study findings build on existing studies albeit with a larger and more homogeneous cohort. For example, Zhang et al (13) compared outcomes of 55 TAVR and 55 SAVR patients with CRT-AS and demonstrated that TAVR patients had a lower O/E ratio of short-term mortality (0.33 vs 5.0) and significantly shorter LOS (4 vs 6 days) and lower 1-year mortality after adjusting for patient STS PROM scores. Although our findings are similar to theirs, there are important differences that must be taken into account. First, their study included concomitant cases (eg, 25% had previous coronary artery bypass grafting) although our study included only isolated cases to ensure a homogeneous comparison between groups. Second, their SAVR PPM rate was lower compared with our study (7.3% vs 13.7%), even though both studies found no significant differences in PPM rates between TAVR and SAVR patients. Third, we stratified our SAVR cohort into low-risk and high-risk patients to ensure valid comparative groups and found an operative and overall survival benefit for TAVR over the high-risk SAVR cohort only. Finally, our study had longer follow-up and reported mid-term outcomes beyond 1 year and up to 48 months.

In lieu of a randomized controlled trial comparing TAVR and SAVR in patients with CRT-AS, this head-to-head comparative study provides the best available benchmark evidence in the contemporary era. This is because the PARTNER (Placement of Aortic Transcatheter Valve) trials were not stratified to a

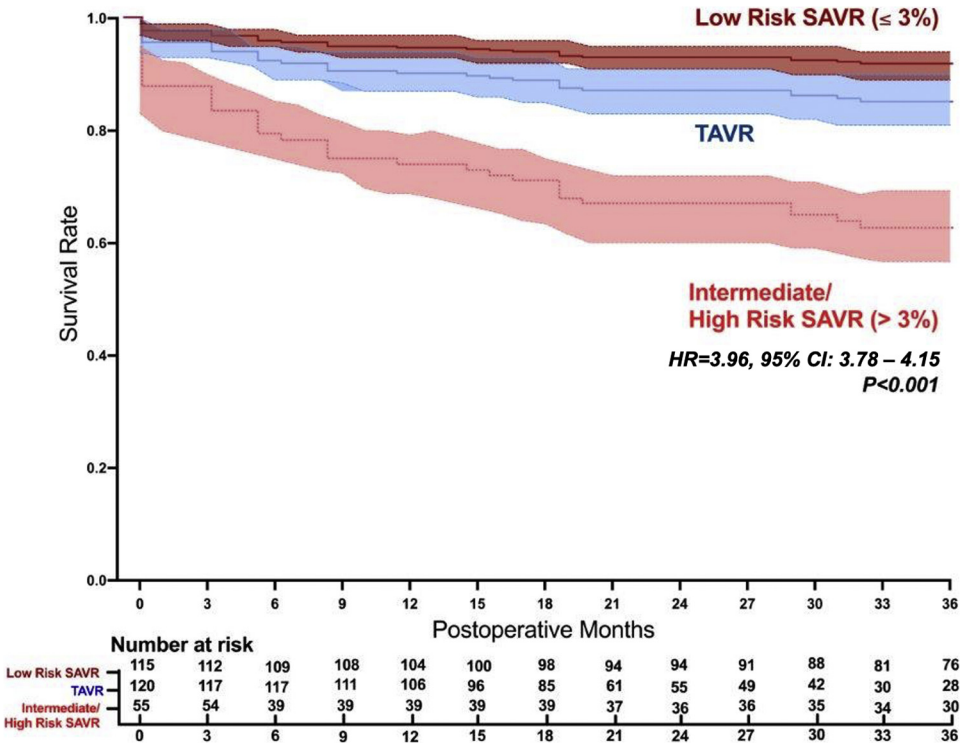
**FIGURE 4** Age-Adjusted Survival




**(A)** Age-adjusted survival for the entire cohort. With the use of Cox proportional hazards modeling, 48-month survival of all TAVR patients was compared with that of all SAVR patients, all with history of chest radiation. There were no significant differences in survival between the 2 patient groups (hazard ratio [HR]: 1.12; 95% confidence interval [CI]: 0.51-2.47; $P = 0.27$). **(B)** Age-adjusted survival for the subgroups. With the use of Cox proportional hazards modeling, 48-month survival of all TAVR patients was compared with that of low-risk and high-risk SAVR patients, all with history of chest radiation. Intermediate-/high-risk SAVR patients had significantly worse survival than TAVR patients (HR: 2.94; 95% CI: 1.57-5.55; $P < 0.001$). Abbreviations as in Figure 1.

JACC: CARDIOONCOLOGY, VOL. 3, NO. 3, 2021
SEPTEMBER 2021:397–407

**FIGURE 5 Weighted and Adjusted Survival for Entire Cohort**



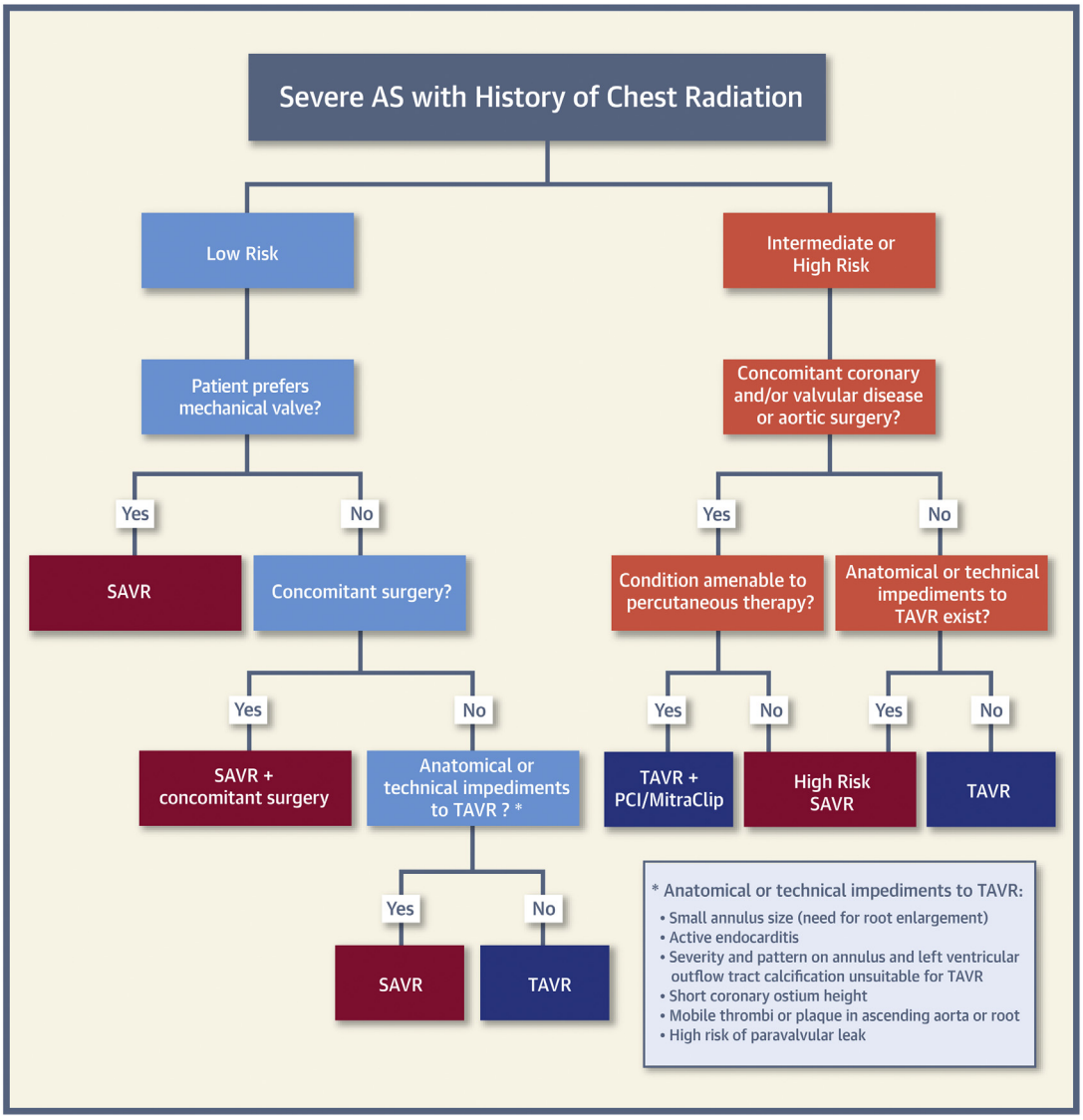

Inverse probability of treatment-weighted Cox proportional hazard modeling comparing 36-month survival of TAVR patients with low- and intermediate-/high-risk SAVR patients, all with chest radiation. Abbreviations as Figures 1 and 4.

level that would allow for randomized comparisons between TAVR and SAVR in this patient population. For example, most patients with CRT-AS in the PARTNER 1 trial were classified as having a "hostile chest" and were deemed technically inoperable. These patients were excluded from surgery and instead were randomized to TAVR or standard therapy, which mostly included balloon valvuloplasty (21). Although TAVR demonstrated significant reductions in LOS and improvements in 1-year survival compared with standard care, there was a lack of a surgical comparison arm in that study. Similarly, no specific outcomes for the 29 patients with CRT-AS, who were considered to be inoperable for technical reasons, were reported in a subsequent analysis of inoperable patients who underwent TAVR in the PARTNER 1B trial (22). These patients were grouped together in a cohort of patients with porcelain aorta, chest wall deformity, the potential for injury to previous bypass graft on reentry, and previous chest-directed radiation, with combined 30-day and 1-year mortalities of 4.7% and 14.1%, respectively (22).

In addition, patients with CRT-AS undergoing either TAVR or SAVR present unique challenges in terms of risk stratification, which may not correlate with our expected outcomes. For example, the overall mean STS PROM score in our study cohort was closer to the range of intermediate risk (3%-8%) before subgroup (low risk vs intermediate/high risk) analysis, and the TAVR patients were much sicker in terms of their comorbidity burden compared with the SAVR patients. However, the mortality of the TAVR patients in our study was lower than those extrapolated from the PARTNER 1 trial, but similar to those reported in the PARTNER 2 trial, which included intermediate-risk patients (10).

For the IPT-weighted Cox models, the lowest-risk patients—SAVR patients with STS PROM <3%—had the best mid-term survival, which might be expected. However, the survival penalty associated with intermediate-/high-risk SAVR was significant in each case, with HRs of 3.96 overall and 2.80 in the subgroup analysis. Furthermore, the results of the E-value estimations as sensitivity analyses suggest that very

**CENTRAL ILLUSTRATION** **Proposed Algorithmic Management of Symptomatic Severe AS in Patients With a History of Chest Radiation**




**Yazdchi, F. et al. J Am Coll Cardiol CardioOnc. 2021;3(3):397–407.**

AS = aortic stenosis; PCI = percutaneous coronary intervention; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

large sources of confounding would need to be posited to negate the survival protective benefits that TAVR appears to confer. Although the present study contains a comparatively small total cohort, the risk factors associated with postoperative survival in these patients has been the subject of extensive study and are fairly well understood; confounders with effect sizes of >2.5 (entire cohort) and 5.0 (subgroup) that predict both treatment assignment and survival may certainly exist but would require further study to identify.

Our findings have important implications for patient care in the current TAVR landscape (12,23). In light of our findings, TAVR should remain the mainstay treatment option in most patients with CRT-AS given the excellent short- and mid-term

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benefits. However, the favorable outcomes in the low-risk SAVR group provides important data for counseling low-risk patients with CRT-AS who may have anatomic or technical impediments that preclude TAVR (eg, inadequate annulus size, active endocarditis, symmetric valve calcification, short coronary ostium height, and mobile thrombi in the ascending aorta [24]) or future concerns associated with bioprosthetic valve failure due to structural valve deterioration or clinically significant paravalvular leaks. Because the spectrum of disease progression (ie, fibrosis) and amount of calcification in the annulus or left ventricular outflow tract varies among patients with a history of mediastinal radiation, some patients may end up with smaller TAVR valves, which can limit the option of future valve-in-valve therapies. Predilation with the use of balloon valvuloplasty and TAVR may be deemed too risky in situations with significant calcification and/or fibrosis, and could potentially increase the risk of conduction abnormalities requiring PPM. All anatomic, access-related, and patient-related factors must be assessed carefully by the multidisciplinary heart team before a patient-centered decision on TAVR or SAVR is made for a patient with CRT-AS.

**STUDY LIMITATIONS.** The present study has limitations related to its retrospective and observational design. Thus, there are inherent biases that may affect the generalizability of our findings. Although this study is one of the largest on this subject, the overall small sample size limits the power of our statistical inferences, including comparison of our outcomes data. The TAVR patients represented a more contemporary cohort than the SAVR patients, and it is possible that changes in postoperative management practices may have influenced some of the observed outcome differences. Although we used stabilized and trimmed IPT scores, no propensity or regression methodology can rule out unmeasured bias. Furthermore, because both our grouping criteria and the standards used to refer patients to TAVR during this time period were dependent on the STS PROM and other measures of patient severity, it is possible that our IPT weighting model violates the positivity assumption. The subgroup analysis, however, intentionally identified subjects who theoretically would have a nonzero chance of being assigned to either treatment. Regarding our subgroup analysis of O/E operative/30-day mortality ratios, we acknowledge that the expected STS PROM is derived from the surgical literature, and thus using STS PROM score might be considered a limitation when evaluating the TAVR population in the O/E analysis despite its extensive use in TAVR clinical trials.

In addition, we could not confirm the cause of death in some of the patients. Likewise, we were unable to ascertain patients' cancer stage and radiation dose. Heterogeneity of the cancer types was another limitation. Given that most patients were referred from outside facilities, and despite our extensive chart review and use of our robust multiinstitutional EMR, echocardiographic follow-up beyond 30 days was lacking, which limited our ability to perform additional analysis. We also did not have access to computed tomographic images of patients to compare the calcium scores between the two groups. Finally, we cannot evaluate how cancer recurrence might have affected survival as a competing risk event. Our results should be interpreted with these caveats in mind.

## CONCLUSIONS

In this relatively large single-center study, TAVR was associated with excellent in-hospital outcomes and better survival than intermediate/high-risk SAVR in patients with CRT-AS. While SAVR still has a role in low-risk patients or those for whom TAVR is unsuitable for technical or anatomic reasons, TAVR is emerging as the standard of care for intermediate- and high-risk patients with CRT-AS.

## FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Nohria is a consultant for Takeda and receives research support from Amgen. Dr Shah is a speaker and proctor for Edwards Lifesciences. Dr Kaneko is a speaker for Edwards Lifesciences and Medtronic and a consultant for Baylis Medical and 4C. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** This study provides evidence that intermediate- and high-risk patients (STS-PROM >3%) with a history of CRT-AS have a survival advantage with TAVR compared with SAVR. However, in low-risk patients (STS-PROM ≤3%), surgery results in similar survival and can be safely performed, if indicated. Examples of such indications include cases in which anatomic or technical impediments to TAVR exist, or if the strategy of "surgery first followed by future valve-in-valve TAVR" might be chosen for a younger patient.

**TRANSLATIONAL OUTLOOK:** Future studies should consider an expanded subgroup analysis of the PARTNER and CoreValve randomized clinical trials in a larger cohort of patients with a history of CRT-AS. These studies would provide useful clinical data for low-risk patients (who are candidates for both SAVR and TAVR) and would also facilitate the development of predictive risk models (that would also incorporate factors such as type of cancer, radiation dose, etc) to allow accurate identification of those at higher risk for surgery.

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**KEY WORDS** outcomes, thoracic oncology, valvular disease

**APPENDIX** For supplemental tables and a figure, please see the online version of this paper.


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