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Transcatheter versus Surgical Aortic Valve Replacement in Patients with Prior Cardiac Surgery in the Randomized PARTNER 2A Trial

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ABSTRACT

Background: Prior cardiac surgery (PCS) is associated with increased surgical risk and post-operative complications following surgical aortic valve replacement (SAVR), but whether this risk is similar in transcatheter aortic valve replacement (TAVR) is unclear.

Objectives: We sought to further evaluate clinical outcomes in patients with and without PCS.

Methods: In the PARTNER 2A trial, 2032 patients with severe AS at intermediate surgical risk were randomized to TAVR with the SAPIEN XT valve or SAVR. Adverse clinical outcomes at 30-days and 2-years were compared using Kaplan Meier event rates and multivariable Cox proportional hazards regression models. The primary end point of the PARTNER 2 trial was all cause death and disabling stroke.

Results: 509 patients (25.1%) had PCS, mostly (98.2%) coronary artery bypass grafting (CABG). There were no significant differences between TAVR and SAVR in patients with or without PCS, in the rates of the primary endpoint at 30 days or 2 years. Nevertheless, an interaction was observed between PCS and treatment arm; while no-PCS patients treated with TAVR had higher rates of 30-day major vascular complications than patients treated with SAVR (adjusted HR 2.66, 95% CI 1.68-4.22), the opposite is true for patients with PCS (adjusted HR 0.27, 95% CI 0.11-0.66) ($p_{interaction}<0.0001$). A similar interaction was observed for life threatening or disabling bleeding.

Conclusions: In the PARTNER 2A Trial of intermediate-risk patients with severe AS undergoing SAVR versus TAVR, the relative risk of two-year adverse clinical outcomes were similar between TAVR and SAVR in patients with or without PCS.

KEY WORDS: Transcatheter aortic valve replacement (TAVR), transcatheter heart valve (THV), aortic stenosis (AS), surgical aortic valve replacement (SAVR).

CONDENSED ABSTRACT

We compared outcomes for intermediate risk patients with or without prior cardiac surgery (PCS) undergoing aortic valve replacement for severe symptomatic aortic stenosis, with SAPIEN XT transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) in the PARTNER 2A trial. By univariate and multivariable analysis, two-year clinical outcomes, including the primary endpoint or its components death and disabling stroke, were similar between TAVR and SAVR in patients with or without PCS. Nevertheless, the relative risk of 30-day major vascular complications and life-threatening/disabling bleeding associated with SAVR was disproportionately higher amongst patients with PCS.

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis
BE = balloon–expandable
TAVR = transcatheter aortic valve replacement
SAVR = surgical aortic valve replacement
CABG = coronary artery bypass surgery
THV = transcatheter heart valve
PCS = prior cardiac surgery
LVEF = left ventricular ejection fraction
CEC = clinical events committee

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has been shown to have similar or even better clinical outcomes than surgical aortic valve replacement (SAVR) in patients with severe symptomatic aortic stenosis (AS) and at least intermediate surgical risk (1-3). Prior cardiac surgery (PCS) is associated with increased morbidity and mortality in patients undergoing cardiac surgery, as it is technically challenging due to scarring of tissues resulting in loss of tissue planes, adhesions and injury to adjacent anatomical structures (4). In patients with prior coronary artery bypass grafting (CABG), there is an increased risk of injury to patent grafts (arterial or venous), during a subsequent cardiac surgery which has been associated with increased mortality and morbidity (5). Furthermore, there are technical issues related to myocardial protection during aortic cross-clamping (6-9). The increased risk associated with PCS is incorporated in the EuroSCORE (I or II) (10,11), and STS (12,13) scores. However, other observational studies have reported no additional risk in patients with PCS undergoing SAVR (14). Irrespective of the increase in surgical risk for patients with PCS, a single-center retrospective study reported comparable clinical outcomes of TAVR and SAVR in high risk patients with PCS (15). Furthermore, an analysis of the PARTNER 1 trial (2) reported that patients with prior CABG and high surgical risk had better 2-year clinical outcomes with SAVR than TAVR, due to higher rates of repeat hospitalizations and a trend towards a higher rate of all-cause death in the TAVR arm (16). On the other hand, another sub-group analysis of patients with prior CABG in the CoreValve high risk study found that TAVR had a significant morbidity advantage with a trend toward improved survival over SAVR at 1 year. (17) Thus, it is not yet clear whether the effect of TAVR versus SAVR is different for patients with and without PCS, especially in patients with intermediate surgical risk.

We sought to assess whether the relative 30-day and 2-year risk of adverse clinical outcomes after TAVR with SAPIEN XT compared to SAVR for patients with severe symptomatic AS and intermediate surgical risk was different for patients with versus without PCS in the PARTNER 2A Trial (3).

METHODS

Study design and population

The design and results of the PARTNER 2A Trial (NCT01314313) have been previously described (3). Briefly, Cohort A of the PARTNER 2 Trial enrolled patients with severe, symptomatic AS at intermediate surgical risk at 57 sites in the United States and Canada. Severe AS was defined as (1) aortic valve area ≤0.8 cm^2 or aortic valve area index ≤0.5 cm^2/m^2 and (2) mean aortic valve gradient greater than 40 mmHg or peak aortic jet velocity greater than 4.0 m/s. Patients were considered to be at intermediate surgical risk if they had a predicted 30-day surgical mortality of 4% to 8% as determined by the Society of Thoracic Surgeons (STS) mortality risk model (possible range of risk, 0%-100%; higher percentages indicate greater risk) (13) and a multidisciplinary heart team. Key exclusion criteria included patients with a congenitally bicuspid aortic valve, severe renal disease, predominant aortic regurgitation, or left ventricular ejection fraction (LVEF) less than 20%. Patients were randomized to receive TAVR with the SAPIEN XT valve or surgical AVR. The current analysis utilized the intention to treat population of patients randomized to TAVR or SAVR in PARTNER 2 Cohort A.

Definitions and event adjudication

The primary end point of the original study was a composite of death from any cause or disabling stroke at 2 years. The definition of the various end points are provided in the supplementary appendix of the original publication (3). A clinical events committee (CEC),

adjudicated all adverse outcomes. All ECGs and echocardiograms were interpreted by independent core laboratories using methodology previously described (18). The severity of bleeding, vascular complications and acute kidney injury were graded according to the Valve Academic Research Consortium 2 (VARC2) (19). Notably, major vascular complications by this definition include: 1. Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudo-aneurysm; 2. Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio- venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) leading to death, life-threatening or major bleeding, visceral ischaemia or neurological impairment; 3. Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage; 4. The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischaemia or neurological impairment; 5. Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram; 6. Surgery for access site-related nerve injury; 7. Permanent access site-related nerve injury.

Statistical analysis

Continuous variables are presented as mean ± SD and compared by Student's t-test. Categorical variables are reported as percentages and frequencies, and compared by Chi-square test of Fisher's exact test, as appropriate. Time-to-event variables are presented as Kaplan Meier event rates and compared by the log-rank test. Adjusted comparisons of clinical outcomes and echocardiographic parameters were conducted using multivariable Cox proportional hazards regression models. Covariates included in the adjusted models were age, sex, body mass index, diabetes mellitus, hypertension, dyslipidemia, chronic obstructive lung disease (COPD), COPD –

oxygen dependent, chronic kidney disease, LVEF, coronary artery disease, prior myocardial infarction, prior percutaneous coronary intervention and peripheral vascular disease (PVD). Interaction terms were included in the covariate set to assess whether the effect of TAVR vs SAVR differed according to the presence versus absence of PCS.

RESULTS

Patient population and baseline characteristics

Of the 2032 patients included in the current analysis, 509 patients (25.1%) had PCS, 245 (12.1%) in the TAVR group and 264 (13.0%) in the SAVR group. Baseline characteristics are presented in Table 1. Patients with PCS were significantly younger, more frequently male, and had higher rates of diabetes and higher body mass index compared with patients without PCS. Baseline STS score, logistic EuroSCORE, and SYNTAX score were significantly higher in patients with PCS. Expectedly, prior percutaneous intervention and prior myocardial infarction as well as peripheral vascular disease were more common among patients with prior PCS. In both groups (PCS and no-PCS), there were no significant differences between patients randomized to TAVR or SAVR except for higher rates of hypertension and PVD among patients with PCS who were randomized to SAVR compared with those randomized to TAVR.

Baseline Echocardiographic Characteristics

Table 2 presents the baseline echocardiographic characteristics stratified by PCS group (PCS vs no-PCS) and by the randomized treatment (TAVR vs SAVR). Aortic valve area was significantly higher and aortic valve mean gradient as well as left ventricular ejection fraction (LVEF) were both lower in patients with PCS. Comparing TAVR with SAVR patients within each PCS group revealed no significant differences, except for LVEF, which was lower in SAVR than TAVR patients in the no-PCS group.

Procedural characteristics

Procedural variables are displayed, stratified by PCS group, in Table 3. Among patients who underwent TAVR, in both PCS and no-PCS groups, transfemoral access was the most commonly utilized approach. For patients who were not treated transfemorally, transapical approach was more common in patients with PCS than without PCS while the opposite was true for transaortic approach. Prosthesis size in TAVR patients ranged from 23 to 29; 18.1% of PCS patients and 40.5% of no-PCS patients ($p<0.0001$) were implanted with prosthesis sized 23 or smaller. Fluoroscopy duration and the time to discharge post-TAVR were both longer in no-PCS than in PCS patients. However, the volume of contrast media delivered during the procedure did not differ significantly between PCS groups. In contrast, prosthesis size in the SAVR group ranged from 17 to 29 mm with 70.6% of PCS patients and 83.3% of no-PCS patients implanted with prosthesis sized 23 or smaller ($p<0.0001$). Valve size used with SAVR remain significantly smaller than with TAVR, after controlling for the PCS group ($p<0.0001$). In patients treated with SAVR, procedure duration and cross clamp time were significantly longer in patients with PCS.

Clinical outcomes

Overall, patients with PCS had similar 30-day outcomes as patients with no-PCS, with the exception of life-threatening/disabling bleeding which was more frequent in patients with PCS (Table 4 and Figure 1). On the contrary, there was a trend toward higher 30-day rates of primary endpoint and all-cause death among patients with no-PCS. Myocardial infarction (MI), including periprocedural MI, was more common among patients with PCS; however, this did not reach statistical significance. A significant interaction was observed between the PCS group and the treatment arm for major vascular complication ($p_{interaction}<0.0001$). While in patients with no-PCS major vascular complications were significantly more common with TAVR than SAVR, the

opposite is true for patients with PCS. Major vascular complications were mainly access site or access related vascular injury. Bleeding (any) events were more common among patients who underwent SAVR than TAVR in both PCS groups, driven by life threatening or disabling bleeding, but a significant interaction was observed between the PCS group and the treatment arm for any bleeding ($p_{interaction}$=0.003), driven by life threatening or disabling bleeding ($p_{interaction}$=0.01). After multivariable adjustment, PCS remained a moderator of the effect of TAVR versus SAVR on the risk of major vascular complication, bleeding (any), and life threatening or disabling bleeding, with disproportionally lower risk with TAVR versus SAVR among patients with PCS (Table 6).

At 2-years (Median follow-up was 2.0 years, interquartile range 1.7 to 2.0), the primary composite end point occurred more frequently in patients with no-PCS than in patients with PCS (Table 5). This was driven by an increased all-cause death rate, resulting from higher non-cardiovascular death rate. Expectedly, patients with PCS had higher rates of 2-year MI. Nonetheless, the relative risk associated with TAVR versus SAVR did not differ significantly between patients with versus without PCS (Table 5 and Figure 2). No significant interaction was observed between the PCS group and the treatment arm at 2-year follow-up. These results remained similar after multivariable adjustment (Table 6).

When analyses were restricted to the as treated population (n = 1938; PCS: 485 and no-PCS: 1453), or to only those patients who had undergone prior CABG (excluding the 12 patients who underwent sternotomy for other reasons besides CABG), these results remained consistent.

DISCUSSION

The major finding from this sub-analysis of the PARTNER 2A Trial comparing the outcomes of TAVR and SAVR in intermediate-risk patients stratified by PCS is that patients

with and without PCS undergoing TAVR with SAPIEN XT valve have similar short and long-term clinical outcomes compared with patients treated with SAVR. However, major vascular complications and life-threatening bleeding were disproportionally more common among patients with PCS who underwent SAVR. The present study thus supports the long-term efficacy of both TAVR and SAVR in patients with PCS, with a possible early safety advantage for TAVR versus SAVR.

The similar mortality and repeat hospitalization rates observed between treatment arms in patients with PCS are in line with a previous small retrospective study (15), but in contradiction to a previous publication reporting a trend toward increased all-cause mortality rate and increased repeat hospitalization rate among patients with PCS who underwent TAVR compared with SAVR in the PARTNER 1 trial (16). This discrepancy might be explained by differences in the baseline risk of the study populations. The PARTNER 1 trial enrolled patients at high operative risk, while PARTNER 2 enrolled those at intermediate risk. In both trials, risk was defined using STS score, and prior cardiac surgery factors prominently in this calculation. Thus, in intermediate-risk patients, the relative weight of PCS in the STS score calculation is high, as these patients have relatively low rates of other co-morbidities. This is likely the reason for the observed lower rate of 2-year all-cause death, specifically non-cardiovascular death, in PCS patients compared to no-PCS in both treatment arms. On the contrary, in high risk patients, the relative weight of PCS is low as the STS score may be driven by other co-morbidities. Thus, the comparatively low comorbidity rates of patients with PCS in the current (intermediate risk) study likely counteracts the disadvantage of having PCS, resulting in similar long term clinical outcomes. The last potential explanation is methodological, as the previous study did not

examine the interaction between PCS group and treatment arm and only compared TAVR to SAVR in patients with PCS, hence rendering its results less statistically valid (20,21).

An improvement in procedural skills among TAVR operators due to accrued experience with the procedure, or by iterative device improvements between the two studies (SAPIEN classic in PARTNER 1 versus SAPIEN XT in PARTNER 2) (22) may also explain the current results. For example, 30-day moderate/severe paravalvular leak rates, which have been shown to affect prognosis (23-25), decreased from 12.2% in PARTNER IA to less than 4% in PARTNER 2A (2,3). The clinical impact of this reduction may be especially pronounced in patients with PCS, as the presence of ischemic heart disease makes them particularly vulnerable to the negative influence of aortic regurgitation on coronary flow reserve (26).

In the current study, higher rates of major vascular complications observed in patients with PCS who underwent SAVR compared with TAVR were driven by access site related complications. This is unlike the overall patient population, in which major vascular complications were significantly more common in TAVR compared with SAVR (3). There is a noticeably increased vascular complication rate in PCS patients who underwent SAVR, likely because the operating field is not naïve: post-surgery adhesions might complicate the access, and repeat surgery poses a risk of iatrogenic injury to the patent coronary graft (5). Compounding this interaction, we see decreased vascular complication rates with TAVR in PCS patients compared to those without PCS. This is likely due to the comparatively low comorbidity burden of patients with PCS compared to those without PCS, as explained previously. The relatively low vascular complication rate in patients with PCS who underwent TAVR might also be attributed to significant differences in access route as transapical was relatively common and transaortic less common compared with no-PCS patients. In the sub-analysis of patients who had prior

CABG from the PARTNER 1 trial, higher rates of vascular complications were observed in TAVR compared with SAVR in patients with PCS (16). The discrepancy with our findings might be explained by the advances in device configuration, including the ability to mount the valve on the deployment balloon inside the abdominal aorta, allowing a decrease in the delivery system size that occurred between the two trials.

Finally, bleeding was significantly more common among patients with PCS who underwent SAVR than TAVR, driven by life threatening or disabling bleeding. This finding is fairly expected, given that repeated sternotomy and lysis of adhesions are required during the SAVR procedure, and it is in line with the increase in access related major vascular complications and with previous publications reporting higher rates of bleeding and blood transfusion among patients with PCS who underwent SAVR compared with TAVR (15,16,27). It is noteworthy that the increase in bleeding event rates had no effect on mortality or length of hospitalization in the current study.

Limitations

The present study is a post-hoc analysis of a randomized trial and is therefore subject to the usual limitations for this type of analysis. The PARTNER 2A Trial was not powered to examine outcomes according to the presence of PCS. Despite utilizing an intention to treat population, and the fact that our findings regarding elevated major vascular complication and life- threatening bleeding rates among patients with PCS treated with SAVR remained statistically significant after multivariable adjustment, we cannot rule out the possibility that the analysis is confounded by other unmeasured factors that are correlated with PCS. Although the study identified differences in major vascular complications and bleeding events as defined by

VARC2, the prognostic significance of these events may differ between patients treated with SAVR and TAVR.

CONCLUSIONS

In conclusion, in the PARTNER 2A Trial, patients with severe AS at intermediate surgical risk and PCS had similar 2-year clinical outcomes when treated with SAPIEN XT TAVR or SAVR. However, 30-day major vascular complication and life-threatening bleeding events were disproportionally more common with SAVR than with TAVR in patients with versus without PCS. Thus, compared to SAVR, TAVR may be associated with a relatively lower risk of peri-procedural complications for patients with PCS.

PERSPECTIVES

WHAT IS KNOWN?

Prior cardiac surgery (PCS) is associated with increased surgical risk and post-operative complications following surgical aortic valve replacement (SAVR), but whether this risk is similar in transcatheter aortic valve replacement (TAVR) is unclear.

WHAT IS NEW?

Two-year clinical outcomes, including the primary endpoint or its components death and disabling stroke, were similar between TAVR and SAVR in patients with or without PCS. However, the relative risk of 30-day major vascular complications and life-threatening/disabling bleeding associated with SAVR was disproportionately higher amongst patients with PCS.

WHAT IS NEXT?

Since this analysis was conducted on patients with intermediate surgical risk who underwent TAVR with SAPIEN XT valve between the years 2011 and 2013, it is possible that contemporary TAVR with improved screening methods, improved operators' experience, and

newer generation valves, is safer and will have an advantage over SAVR in patients with PCS. Further research is needed to determine whether the same pattern holds for patients with low surgical risk.

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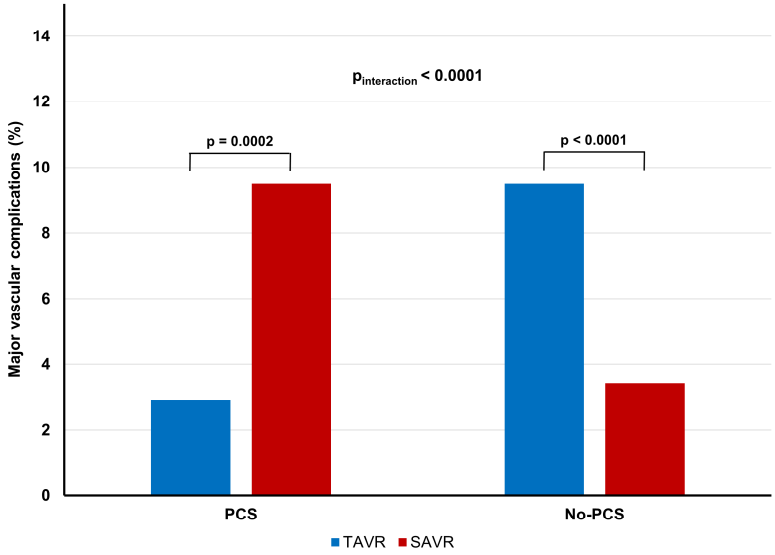
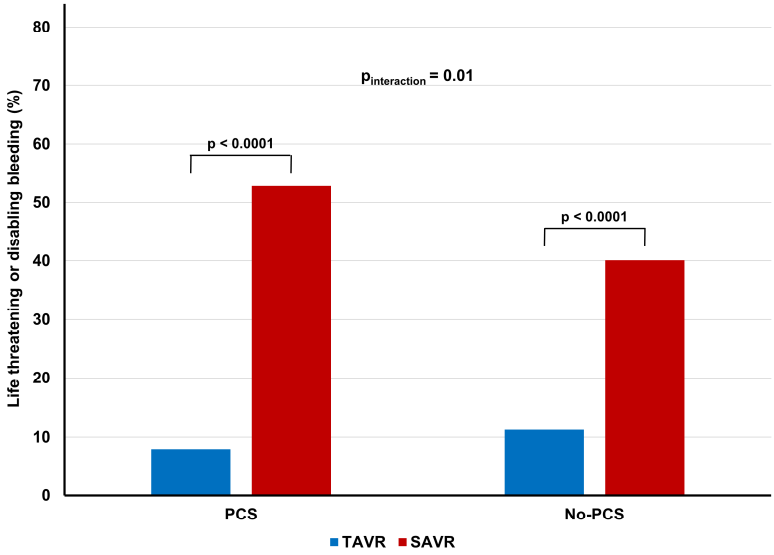
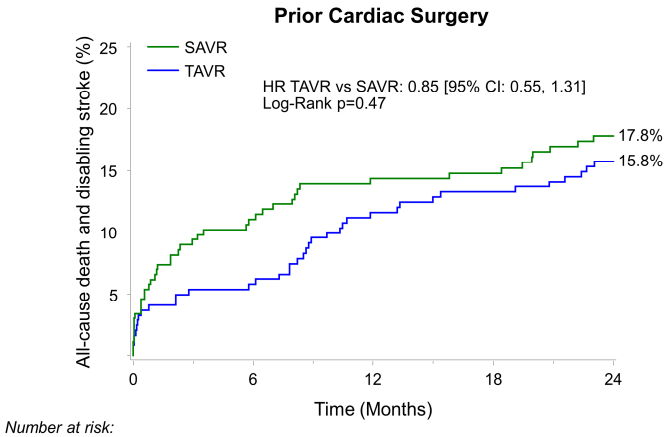
FIGURE LEGENDS

Figure 1. 30-day rates of bleeding and vascular complications in patients undergoing TAVR or SAVR stratified by prior cardiac surgery (PCS). (A) major vascular complications; (B) Life threatening or disabling bleeding. TAVR = transcatheter aortic valve replacement; SAVR = surgical aortic valve replacement.

Figure 2. Kaplan-Meier failure rates in patients undergoing TAVR or SAVR stratified by prior cardiac surgery (PCS). (A) all-cause death and disabling stroke; (B) all-cause death; (C) cardiovascular death. CI = confidence interval; HR = hazard ratio. TAVR = transcatheter aortic valve replacement; SAVR = surgical aortic valve replacement.

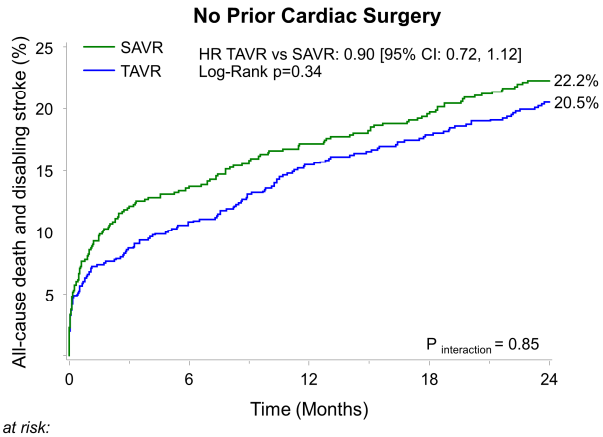






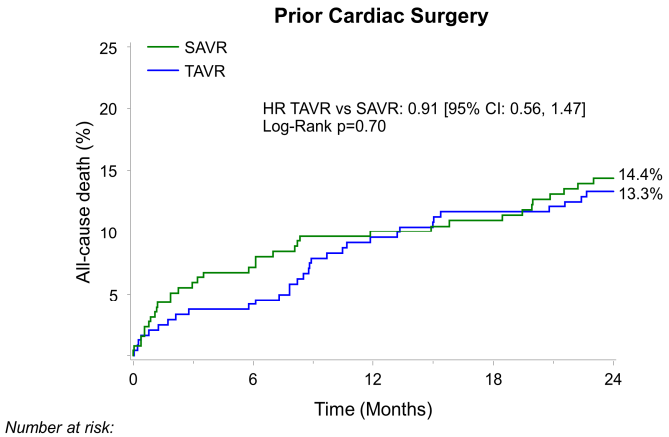
Number at risk:

SAVR	264	214	204	197	186
TAVR	245	227	212	207	197



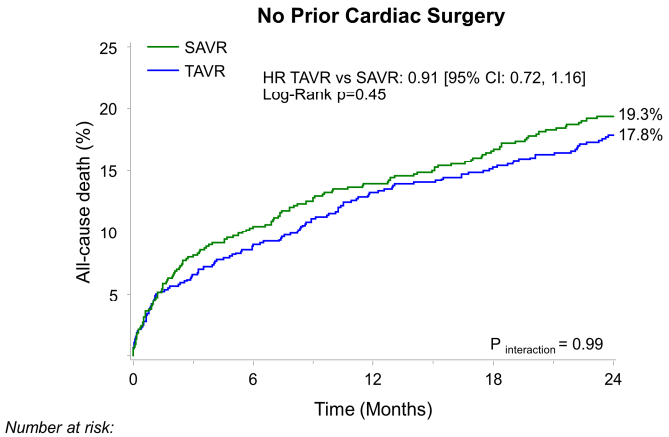
Number at risk:

SAVR	757	598	567	538	509
TAVR	766	674	630	604	577



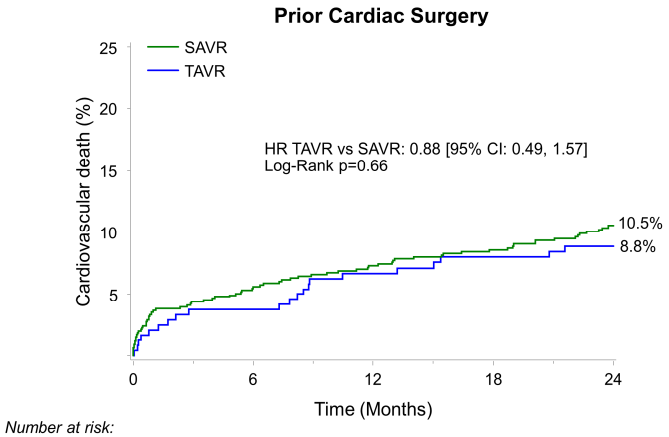
Number at risk:

SAVR	264	224	215	207	194
TAVR	245	231	217	211	202



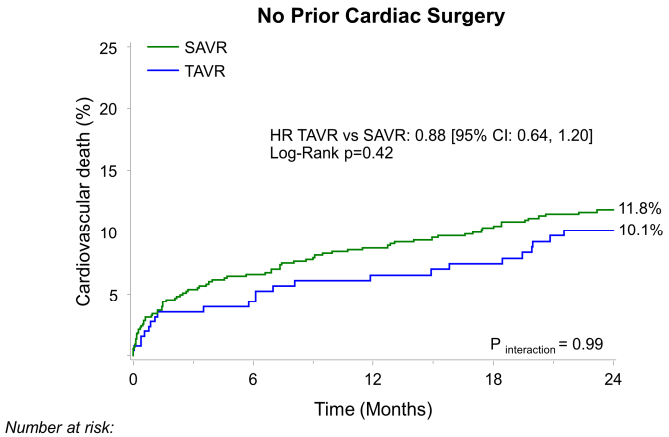
Number at risk:

SAVR	757	619	587	555	525
TAVR	766	688	647	624	596



Number at risk:

SAVR	245	231	217	211	202
TAVR	264	224	215	207	194



Number at risk:

SAVR	757	620	587	555	525
TAVR	766	688	647	625	596

Table 1. Baseline Characteristics

	Prior Cardiac Surgery (n = 509)				No Prior Cardiac Surgery (n = 1523)				Overall p Value
	TAVR (n=245)	SAVR (n=264)	P Value	Overall	TAVR (n=766)	SAVR (n=757)	P Value	Overall	
Age, years	78.5 (7.0)	79.4 (6.5)	0.13	79.0 (6.7)	82.5 (6.3)	82.5 (6.6)	0.98	82.5 (6.5)	<0.0001
Male sex	82.9 (203/245)	81.8 (216/264)	0.76	82.3 (419/509)	45.0 (345/766)	45.4 (344/757)	0.87	45.2 (689/1523)	<0.0001
Body mass index	29.4 (5.9)	29.1 (6.0)	0.64	29.2 (5.9)	28.4 (6.2)	28.0 (6.3)	0.29	28.2 (6.2)	0.001
STS score	6.1 (2.1)	6.1 (2.0)	0.88	6.1 (2.0)	5.8 (2.1)	5.7 (1.8)	0.73	5.7 (1.9)	0.002
Logistic EuroSCORE	10.6 (8.5)	10.3 (8.3)	0.64	10.4 (8.4)	5.4 (4.7)	5.4 (4.9)	0.79	5.4 (4.8)	<0.0001
NYHA functional class									
II	22.9 (56/245)	27.0 (71/263)	0.28	25.0 (127/508)	22.5 (172/766)	22.9 (173/757)	0.85	22.7 (345/1523)	0.28
III	65.7 (161/245)	56.3 (148/263)	0.03	60.8 (309/508)	57.6 (441/766)	57.9 (438/757)	0.91	57.7 (879/1523)	0.22
IV	11.0 (27/245)	16.7 (44/263)	0.06	14.0 (71/508)	20.0 (153/766)	19.3 (146/757)	0.74	19.6 (299/1523)	0.004
III or IV	76.7 (188/245)	73.0 (192/263)	0.33	74.8 (380/508)	77.5 (594/766)	77.1 (584/757)	0.85	77.3 (1178/1523)	0.24
CAD	95.5 (234/245)	95.1 (251/264)	0.82	95.3 (485/509)	60.8 (466/766)	56.5 (428/757)	0.09	58.7 (894/1523)	<0.0001
SYNTAX score	6.5 (9.2)	7.7 (11.8)	0.65	7.1 (10.5)	4.4 (6.0)	3.8 (5.5)	0.18	4.1 (5.8)	0.0002
Prior MI	31.8 (78/245)	30.3 (80/264)	0.71	31.0 (158/509)	14.0 (107/766)	13.1 (99/757)	0.61	13.5 (206/1523)	<0.0001
Prior PCI	37.6 (92/245)	39.0 (103/264)	0.73	38.3 (195/509)	23.8 (182/766)	23.6 (179/757)	0.96	23.7 (361/1523)	<0.0001
Prior CABG	97.6 (239/245)	98.9 (261/264)	0.26	98.2 (500/509)	0.0 (0/766)	0.0 (0/757)	N/A	0.0 (0/1523)	<0.0001

Prior sternotomy (non-CABG)	2.9 (7/245)	1.9 (5/264)	0.47	2.4 (12/509)	0.0 (0/766)	0.0 (0/757)	N/A	0.0 (0/1523)	<0.0001
Frailty	0.8 (2/245)	0.4 (1/264)	0.52	0.6 (3/509)	1.3 (10/766)	1.9 (14/755)	0.39	1.6 (24/1521)	0.09
PVD	31.0 (76/245)	47.7 (126/264)	0.0001	39.7 (202/509)	26.9 (206/766)	27.7 (210/757)	0.71	27.3 (416/1523)	<0.0001
Porcelain aorta	0.0 (0/245)	0.0 (0/264)	N/A	0.0 (0/509)	0.0 (0/766)	0.1 (1/755)	0.31	0.1 (1/1521)	0.56
CVD	16.3 (40/245)	18.6 (49/264)	0.51	17.5 (89/509)	18.0 (138/766)	16.4 (124/757)	0.40	17.2 (262/1523)	0.88
Hypertension	94.3 (231/245)	98.1 (259/264)	0.02	96.3 (490/509)	94.4 (723/766)	93.7 (709/757)	0.55	94.0 (1432/1523)	0.053
Dyslipidemia	91.8 (225/245)	91.7 (242/264)	0.94	79.8 (1216/1523)	80.9 (620/766)	78.7 (596/757)	0.28	82.8 (1683/2032)	<0.0001
Diabetes mellitus	44.9 (110/245)	41.3 (109/264)	0.41	43.0 (219/509)	35.4 (271/766)	31.7 (240/757)	0.13	33.6 (511/1523)	0.0001
Renal disease (Cr ≥2 mg/dL)	5.3 (13/245)	4.2 (11/264)	0.54	4.7 (24/509)	5.0 (38/766)	5.5 (42/757)	0.61	5.3 (80/1523)	0.63
Liver disease	1.2 (3/245)	1.1 (3/264)	0.93	1.2 (6/509)	2.1 (16/766)	3.0 (23/757)	0.24	2.6 (39/1523)	0.07
COPD	29.2 (71/243)	29.3 (77/263)	0.99	29.2 (148/506)	32.7 (250/764)	30.5 (229/751)	0.35	31.6 (479/1515)	0.32
Oxygen dependent COPD	2.1 (5/243)	1.5 (4/262)	0.65	1.8 (9/505)	3.8 (29/760)	3.8 (28/745)	0.95	3.8 (57/1505)	0.03
Pulmonary hypertension	2.4 (6/245)	2.7 (7/264)	0.88	2.6 (13/509)	3.0 (23/766)	2.4 (18/755)	0.46	2.7 (41/1521)	0.86
Chest wall radiation	0.0 (0/245)	0.0 (0/264)	N/A	0.0 (0/509)	0.1 (1/766)	0.0 (0/755)	0.32	0.1 (1/1521)	0.56
Permanent pacemaker	14.3 (35/245)	14.4 (38/264)	0.97	14.3 (73/509)	10.8 (83/766)	11.2 (85/757)	0.81	11.0 (168/1523)	0.05

Values are mean (SD) or % (n/N).

BAV = balloon aortic valvuloplasty; CAD = coronary artery disease; Cr = creatinine; COPD = chronic obstructive pulmonary disease; CVD = cerebrovascular disease; EuroSCORE = European System for Cardiac Operative Risk Evaluation; MI = myocardial infarction; NYHA = New York Heart Association;

PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; STS = Society of Thoracic Surgeons.

Table 2. Baseline Echocardiographic Characteristics

	Prior Cardiac Surgery (n = 509)				No Prior Cardiac Surgery (n = 1523)				Overall p Value
	TAVR (n=245)	SAVR (n=264)	P Value	Overall	TAVR (n=766)	SAVR (n=757)	P Value	Overall	
AV peak velocity, cm/s	425.7 (57.5)	425.9 (52.2)	0.97	425.8 (54.8)	444.0 (62.3)	443.1 (58.2)	0.77	443.6 (60.3)	<0.0001
AV mean gradient, mm Hg	41.6 (11.7)	41.7 (11.2)	0.92	41.6 (11.4)	46.0 (13.8)	45.7 (12.8)	0.66	45.8 (13.3)	<0.0001
Aortic valve area, cm^2	0.74 (0.17)	0.73 (0.21)	0.55	0.73 (0.19)	0.69 (0.17)	0.68 (0.19)	0.25	0.68 (0.18)	<0.0001
Aortic valve annulus diameter, cm	2.27 (0.34)	2.29 (0.39)	0.54	2.28 (0.37)	2.19 (0.31)	2.18 (0.31)	0.36	2.18 (0.31)	<0.0001
LVEF*	51.3 (12.4)	52.6 (11.8)	0.27	52.0 (12.1)	56.3 (10.6)	54.8 (11.9)	0.01	55.6 (11.3)	<0.0001
AR: moderate / severe	11.9 (26/218)	12.9 (31/240)	0.75	12.4 (57/458)	11.1 (80/719)	11.4 (78/685)	0.88	11.3 (158/1404)	0.49
MR: moderate / severe	16.1 (33/205)	16.8 (39/232)	0.84	16.5 (72/437)	17.0 (118/694)	19.9 (132/662)	0.16	18.4 (250/1356)	0.35
TR: moderate / severe	14.5 (28/193)	17.9 (40/224)	0.36	16.3 (68/417)	17.4 (116/668)	17.5 (110/630)	0.96	17.4 (226/1298)	0.60

Values are mean (SD) or % (n/N). *Visual or Simpson

AV = aortic valve; IVSd = interventricular septum diastolic diameter; LV = left ventricular; LVED = left ventricular end-diastolic; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; AR: aortic regurgitation; MR = mitral regurgitation; TR = tricuspid regurgitation.

Table 3. Procedural Characteristics

TAVR	Prior Cardiac Surgery (n = 245)	No Prior Cardiac Surgery (n = 766)	p Value
Access route			
Transfemoral	74.7 (183/245)	77.3 (592/766)	0.40
Transapical	23.3 (57/245)	15.3 (117/766)	0.004
Transaortic	2.0 (5/245)	7.4 (57/766)	0.002
Prosthesis size			
23 mm	18.1 (43/237)	40.5 (299/738)	<0.0001
26 mm	57.0 (135/237)	43.9 (324/738)	0.0005
29 mm	24.9 (59/237)	15.6 (115/738)	0.001
Post-dilation	24.4 (58/238)	19.5 (145/742)	0.11
Hemodynamic support (IABP)	1.3 (3/238)	1.6 (12/742)	0.70
Rapid cardiac pacing*	96.2 (229/238)	97.0 (720/742)	0.53
Concomitant PCI	1.7 (4/238)	2.0 (15/742)	0.74
Volume of Contrast Media (mL)	123.7 (86.0)	125.7 (86.8)	0.76
Fluoroscopy duration (min)	18.9 (8.7)	20.8 (10.9)	0.01
Procedure duration** (min)	100.8 (46.5)	103.3 (52.9)	0.51
Time to discharge post-TAVR, days	5.5 (3.0)	6.5 (5.2)	0.003
SAVR	**Prior Cardiac Surgery (n = 264)**	**No Prior Cardiac Surgery (n = 757)**	**p Value**
Prosthesis size			
17 mm	0.0 (0/242)	0.1 (1/694)	0.55
19 mm	4.5 (11/242)	14.6 (101/694)	<0.0001
21 mm	27.7 (67/242)	33.7 (234/694)	0.08
23 mm	38.4 (93/242)	34.9 (242/694)	0.32
25 mm	22.3 (54/242)	13.8 (96/694)	0.002
27 mm	6.2 (15/242)	2.4 (17/694)	0.006

29 mm	0.8 (2/242)	0.4 (3/694)	0.47
Concomitant CABG	9.1 (22/243)	16.5 (115/698)	0.005
Difficulty to wean from bypass	4.5 (11/243)	2.2 (15/695)	0.053
Cross clamp time	118.5 (53.4)	99.6 (41.5)	<0.0001
Procedure duration** (min)	294.0 (95.2)	216.8 (74.1)	<0.0001
Time to discharge post-SAVR, days	10.5 (6.8)	10.8 (7.0)	0.52

Values are mean (SD) or % (n/N).
*During valve deployment.
**Skin incision to closure.
CABG = coronary artery bypass grafting; IABP = intra-aortic balloon pump other abbreviations as in Table 2.

Table 4. 30-day Clinical Outcomes

	Prior Cardiac Surgery (n = 509)				No Prior Cardiac Surgery (n = 1523)				Overall p Value	$P_{interaction}$
	TAVR (n=245)	SAVR (n=264)	P Value	Overall	TAVR (n=766)	SAVR (n=757)	P Value	Overall		
Death or disabling stroke	4.1 (10)	6.2 (16)	0.30	5.2 (26)	6.8 (52)	8.6 (64)	0.20	7.7 (116)	0.056	0.69
All-cause death	2.1 (5)	3.1 (8)	0.46	2.6 (13)	4.5 (34)	4.5 (33)	1.00	4.5 (67)	0.07	0.50
Cardiovascular	2.1 (5)	2.7 (7)	0.63	2.4 (12)	3.7 (28)	3.4 (25)	0.75	3.5 (53)	0.21	0.57
Non-cardiovascular	0.0 (0)	0.4 (1)	0.33	0.2 (1)	0.8 (6)	1.1 (8)	0.54	1.0 (14)	0.10	0.99
Repeat hospitalization*	5.8 (14)	7.6 (19)	0.49	6.7 (33)	6.7 (50)	6.1 (43)	0.54	6.4 (93)	0.78	0.36
Stroke	5.3 (13)	4.9 (13)	0.85	5.1 (26)	5.5 (42)	6.4 (48)	0.48	6.0 (90)	0.49	0.63
Disabling stroke	2.9 (7)	3.0 (8)	0.90	3.0 (15)	3.3 (25)	4.7 (35)	0.17	4.0 (60)	0.30	0.62
Myocardial infarction	1.2 (3)	3.4 (9)	0.10	2.4 (12)	1.2 (9)	1.3 (10)	0.79	1.3 (19)	0.08	0.26
Periprocedural	0.4 (1)	3.0 (8)	0.02	1.8 (9)	1.0 (8)	1.2 (9)	0.79	1.1 (17)	0.26	0.11
Major vascular complications**	2.9 (7)	9.5 (25)	0.002	6.3 (32)	9.5 (73)	3.4 (26)	<0.0001	6.5 (99)	0.86	<0.0001
Access site related	2.5 (6)	8.4 (22)	0.004	5.5 (28)	8.5 (65)	2.7 (20)	<0.0001	5.6 (85)	0.94	<0.0001
Hemorrhagic event (any)**	36.4 (89)	78.3 (206)	<0.0001	58.1 (295)	46.9 (359)	72.6 (547)	<0.0001	59.7 (906)	0.64	0.003
Life threatening or disabling**	7.8 (19)	52.8 (139)	<0.0001	31.1 (158)	11.3 (86)	40.1 (303)	<0.0001	25.6 (389)	0.01	0.01
Acute kidney injury**	17.7 (43)	29.9 (77)	0.002	23.9 (120)	19.7 (149)	33.7 (250)	<0.0001	26.6 (399)	0.24	0.81
New permanent pacemaker	6.2 (15)	7.4 (19)	0.63	6.8 (34)	9.2 (70)	6.6 (49)	0.05	7.9 (119)	0.37	0.18

Values are % (n), K-M estimated probabilities, at 30 days. *For symptoms of aortic stenosis and / or complications of valve procedure. ** According to VARC 2 definition.

Table 5. 2-year clinical outcomes

	Prior Cardiac Surgery (n = 509)				No Prior Cardiac Surgery (n = 1523)				Overall p Value	$P_{interaction}$
	TAVR (n=245)	SAVR (n=264)	P Value	Overall	TAVR (n=766)	SAVR (n=757)	P Value	Overall		
Death or disabling stroke	15.8 (38)	17.8 (44)	0.47	16.8 (82)	20.5 (154)	22.2 (158)	0.34	21.3 (312)	0.03	0.85
All-cause death	13.3 (32)	14.4 (35)	0.70	13.9 (67)	17.8 (134)	19.3 (135)	0.45	18.6 (269)	0.02	0.99
Cardiovascular	8.8 (21)	10.1 (24)	0.65	9.5 (45)	10.5 (76)	11.8 (80)	0.42	11.1 (156)	0.29	0.99
Non-cardiovascular	4.9 (11)	4.3 (10)	0.85	4.6 (21)	8.2 (58)	8.6 (55)	0.82	8.4 (113)	0.008	0.79
Repeat hospitalization*	19.4 (45)	20.8 (49)	0.70	20.1 (94)	19.6 (138)	16.0 (107)	0.14	17.9 (245)	0.33	0.28
Stroke	10.2 (24)	9.0 (22)	0.71	9.6 (46)	9.2 (67)	8.8 (63)	0.92	9.1 (130)	0.81	0.77
Disabling stroke	5.9 (14)	5.8 (14)	0.97	5.9 (28)	6.3 (45)	6.6 (47)	0.64	6.5 (92)	0.60	0.78
Myocardial infarction	5.7 (13)	7.5 (18)	0.37	6.7 (31)	2.8 (20)	2.8 (19)	0.98	2.8 (39)	0.0002	0.52
Renal failure	33.4 (79)	40.1 (100)	0.054	36.9 (179)	33.6 (247)	42.4 (304)	<0.0001	38.0 (551)	0.53	0.58

Values are % (n), K-M estimated probabilities, at 30 days. *For symptoms of aortic stenosis and / or complications of valve procedure.

Table 6. Adjusted 30-day and 2-year clinical outcomes

Event of Interest	Hazard Ratio* TAVR vs SAVR (95% Confidence Interval)		$p_{interaction}$**
	Prior Cardiac Surgery	No Prior Cardiac Surgery	
30 days			
Death or disabling stroke	0.70 (0.31, 1.61)	0.77 (0.52, 1.12)	0.86
All-cause death	0.64 (0.19, 2.14)	0.90 (0.54, 1.49)	0.61
Cardiovascular	0.74 (0.21, 2.57)	0.95 (0.54, 1.70)	0.72
Non-cardiovascular	N/A	0.73 (0.25, 2.12)	N/A
Repeat hospitalization***	0.80 (0.40, 1.61)	1.21 (0.79, 1.86)	0.32
Stroke	1.06 (0.48, 2.35)	0.88 (0.58, 1.34)	0.68
Disabling stroke	1.02 (0.37, 2.84)	0.73 (0.43, 1.24)	0.57
Myocardial infarction	1.49 (0.18, 12.63)	0.84 (0.24, 2.90)	0.67
Periprocedural	0.41 (0.03, 5.59)	1.10 (0.26, 4.66)	0.53
Major vascular complication	0.27 (0.11, 0.66)	2.66 (1.68, 4.22)	<0.0001
Bleeding (any)	0.32 (0.25, 0.42)	0.50 (0.43, 0.57)	0.004
Life threatening or disabling bleeding	0.13 (0.08, 0.21)	0.24 (0.19, 0.31)	0.02
2 years			
Death or disabling stroke	0.95 (0.61, 1.48)	0.89 (0.71, 1.13)	0.82
All-cause death	1.01 (0.62, 1.66)	0.91 (0.71, 1.17)	0.71
Cardiovascular	0.91 (0.50, 1.66)	0.86 (0.62, 1.19)	0.86
Non-cardiovascular	1.30 (0.53, 3.15)	0.99 (0.68, 1.45)	0.59
Repeat hospitalization***	0.91 (0.60, 1.39)	1.26 (0.97, 1.63)	0.21
Stroke	1.12 (0.62, 2.03)	1.00 (0.71, 1.43)	0.76
Disabling stroke	1.12 (0.53, 2.38)	0.90 (0.59, 1.38)	0.62
Myocardial infarction	0.95 (0.31, 2.91)	0.76 (0.35, 1.66)	0.75

*Adjusted for: age, sex, body mass index, diabetes mellitus, hypertension, dyslipidemia, chronic obstructive lung disease (COPD), COPD – oxygen dependent, chronic kidney disease, left ventricular ejection fraction (LVEF), coronary artery disease, prior myocardial infarction, prior percutaneous coronary intervention, peripheral vascular disease, and the interaction term.
**Interaction term: the effect of TAVR vs SAVR according to the presence versus absence of prior cardiac surgery.
***For symptoms of aortic stenosis and / or complications of valve procedure.