CHANGES IN OUTCOMES OVER TIME IN INTERMEDIATE-RISK PATIENTS TREATED FOR SEVERE AORTIC STENOSIS

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Abstract

Background:The advent of TAVR changed the practice for treating patients with severe aortic stenosis. Heart-Teams improved their decision-making process to refer patients to the best and safest treatment. Evidence allowed centers to increase funding and TAVR volume and extend indications to different risk category of patients. This study evaluates the outcomes of intermediate-risk patients treated for severe aortic stenosis in an academic center. Methods:Between 2012 and 2019, 812 patients with aortic stenosis underwent TAVR or SAVR. A propensity score-matching analytic strategy was used to balance groups and adjust for time periods. Outcomes were recorded according to the Society of Thoracic Surgeons Guidelines; primary outcome being 30-day mortality and secondary outcomes being perioperative course and complications. Results:No difference in mortality was seen but complications differed: more postoperative transient ischemic attacks, permanent pacemaker implantations and perivalvular leaks in the transcatheter group, while more acute kidney injuries, atrial fibrillation, delirium, postoperative infections and bleeding, tamponade and need for reoperation in the surgical group as well as longer hospital length-of-stay. However, over the years, morbidities/mortality decreased for all patients treated for aortic stenosis. Conclusions:Data showed an improvement in morbidities/mortality for intermediate risk patients treated with SAVR or TAVR. Increased funding allowed for higher TAVR volume by increasing access to this technology. Also, the difference in complications could impact healthcare cost. By incorporating important metrics such as length-of-stay, readmission rates and complications into decision-making, the Heart-Team can improve clinical outcomes, healthcare economics and resource utilization.

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CHANGES IN AORTIC INTERVENTION OUTCOME

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Conclusions: Data showed an improvement in morbidities/mortality for intermediate risk patients treated with SAVR or TAVR. Increased funding allowed for higher TAVR volume by increasing access to this technology. Also, the difference in complications could impact healthcare cost. By incorporating important metrics such as length-of-stay, readmission rates and complications into decision-making, the Heart-Team can improve clinical outcomes, healthcare economics and resource utilization.

240-Words

Introduction

In recent years, management of complex cases with valvular heart disease has evolved markedly with the introduction of the "Heart-Team" concept into the decision-making process. Without it, decisions regarding surgery vs. transcatheter management were likely to be influenced, in part, on which specialist the patient sees first.[1] In the current era of evidence-based practice when patient-centered care is becoming the norm, the Heart-Team approach has become an integral part of care and has received Class I recommendations in the 2017 editions of both the AHA/ACC Focused Update of the 2014 Guideline for the Management of Patients with Valvular Heart Disease and the ESC/EACTS Guidelines for the management of valvular heart disease.[2,3] The Heart-Team plays a central role in the patient care process, from adequate patient selection and procedural planning to improved patient education and follow-up care.[4] While decision-making becomes more complex with a growing number of treatment alternatives, a multidisciplinary assessment allows for optimization of care through better recommendations, shared decision-making and informed patient participation.[4] It is therefore essential for Heart-Team members to remain up-to-date with recent knowledge and evidence-based practice to ensure the best quality of care. Scientifically documenting outcomes also carries the advantage of providing centers with evidence to obtain funding to expand transcatheter aortic valve replacement (TAVR) use to other categories of patients. This study evaluates and compares, over

different time periods (2012-2019), the outcomes of intermediate-risk patients treated for severe aortic stenosis (AS) in a single academic center who were referred to TAVR with those of a matched surgical aortic valve replacement (SAVR) population.[5]

Materials and Methods

Between January 2012 and December 2019, 812 consecutive patients who underwent either TAVR (n=400) or SAVR (n=412) were included in this study. All TAVR patients were systematically evaluated by the Heart-Team; which included interventional cardiologists, cardiac surgeons, imaging cardiologists and a nurse coordinator. Patients deemed neither surgical or transcatheter candidates were excluded from this analysis since they represented a heterogenous group of patients (too frail for either treatment, treatment refusal, life-threatening comorbidity such as incurable cancer, aortic stenosis not severe enough to warrant intervention, or heart condition that was too advanced) not fully captured by the Heart-Team. We included all patients who underwent isolated bioprosthetic SAVR or TAVR with or without prior percutaneous dilatation. The study was approved by the local ethics review board.

Procedural technique

The TAVR access site was either trans-femoral (TF), trans-apical, direct trans-aortic, or other (transcaval or transcarotid). Patients underwent TAVR with either a balloon-expandable valve (SAPIEN, SAPIEN XT, or SAPIEN 3, Edwards LifeSciences, Santa Clara, CA), a self-expanding valve (CoreValve, Medtronic Inc, Minneapolis, MN) or other (LOTUS, ACURATE, Boston, Scientific, Natick, MA). TAVR was either performed under general anesthesia with transesophageal echocardiography guidance (mostly non-TF or early cohort cases) or with a minimalist approach of conscious sedation and transthoracic echocardiography as needed.[6] The approach decision was taken by the Heart-Team and the anesthesiologist.

For conventional surgery patients, standard cardio-pulmonary bypass (CPB) and cannulation techniques were used for all cases. Surgical approach, valve prosthesis techniques, and conduct of CPB and myocardial protection were at the discretion of the attending cardiac surgeon. SAVR was performed through a full-length median sternotomy. All surgical patients received a bioprosthetic valve. As per institutional protocol, epi-aortic ultrasonography was performed before cannulation and the aorta was cross-clamped if aortic calcifications or advanced atherosclerosis of the ascending aorta was suspected. Typically, conventional CPB was performed using roller head pumps, membrane oxygenators, cardiotomy suction, arterial filters, cold antegrade and retrograde blood cardioplegia, and moderate systemic hypothermia (34°C). For patients with class 4 or 5 renal failure, the mean arterial blood pressure was maintained [?]70mmHg throughout the duration of CPB. In all cases, the operative field was routinely flooded with carbon dioxide and de-airing maneuvers were performed before releasing the cross clamp. Thirty-day follow-up was obtained in all patients from both groups.

Outcomes of interest were recorded and classified according to the STS Guidelines for Reporting Mortality and Morbidity after Cardiac Valve Interventions.[7] Primary outcome was 30-day mortality and secondary outcomes were perioperative course and complications, including mediastinal bleeding requiring reoperation, myocardial infarction, intensive care unit and hospital length-of-stay, number of red blood cell transfusions, acute renal failure, new permanent pacemaker insertion, atrial fibrillation, stroke or transient ischemic attack (TIA), low cardiac output, infections (pneumonia, urinary tract infection, bacteremia), perivalvular leaks, gastro-intestinal bleeding, retroperitoneal hemorrhage and delirium. All patients were prospectively followed. Valve hemodynamic data were mainly derived from transthoracic echocardiographic studies before discharge from the hospital. Subsequent echography and clinical follow-up were conducted at 1-month after discharge.

We also included the global trend over the years for mortality and morbidities for the entire cohort of patients treated for AS.

Statistical Analysis

Variables are expressed as mean +- standard deviation or median [inter-quartile range] for continuous variables (as appropriate depending on their normality of distribution), and as number (percentage) for cat-

egorical variables. A propensity score-matching analytic strategy was performed as it was deemed more efficient than a traditional multivariable model in adjusting for confounders considering the relatively low event count.

Variables associated with the choice of TAVR vs. SAVR were identified through logistic regression models using least absolute shrinkage and selection operator selection methods. Identified factors in the multivariable logistic regression model to estimate the propensity score included: age, female sex, STS score for major complications, pre-operative creatinine, peripheral vascular disease, pre-operative TIA or stroke, chronic obstructive pulmonary disease, cirrhosis, New York Heart Association classes III & IV heart failure, pre-operative atrial fibrillation, pre-operative hemoglobin and albumin (as markers for frailty). A 4-level categorical variable was included to capture time periods (Y2012-2013, Y2014-2015, Y2016-2017, and Y2018-2019). From 2009 to 2018, limited funding from the Quebec public healthcare system restricted TAVR usage to a pre-determined number of cases in each center. Since 2018, TAVR volume increased markedly with expanding indications across a spectrum of operative risk and improved government funding. Adjustment for time periods was used as a means of reducing potential bias related to changes in funding, technological improvements, procedural flow and indications. Patient characteristics before and after matching were compared using standardized differences; a good match was indicated by an absolute value <20. For all binary outcomes, logit-link generalized estimating equations were used to account for matching in univariable matched analyses.

Post-operative outcomes are presented as defined by the STS Risk Scores. Statistical significance was considered when P-values were <0.05 and simple imputation (mode, mean or median value as appropriate) was used for the few missing data (2%). All statistical analyses were performed using SAS release 9.4 (SAS Institute Inc., Cary, NC).

Results

Between 2009 to 2019, a total of 412 patients (mean age 75+-5years,43.6% female) underwent SAVR and 400 patients (mean age 80+-8years,48.5% female) had TAVR. Applying propensity matching, a total of 139 patients were retained in each group (mean age 77years, [?]50% female). The c-statistic for the propensity match was 0.893. Procedural data for TAVR and SAVR are summarized in Tables 1 and 2, respectively. Preoperative risk factors and status are shown in Table 3 and the breakdown of procedures per year in Table 4.

Primary and secondary outcomes for non-matched and matched analyses are presented in Table 5 and Figure 1. Prior to matching, 30-day mortality was higher in the surgical group (SAVR:4,13%-TAVR:0.5%-p-value<0.001), whiles the matched analysis showed no statistically significant difference in 30-day mortality (SAVR:4.5%-TAVR:0.7%-p-value=0.053) or stroke (SAVR:0.7%-TAVR:3.1%-p-value=0.173). A higher proportion of patients had acute renal failure in the SAVR group (SAVR:6.1%-TAVR:0%-p-value=0.004). There was no statistically significant difference in readmissions to the ICU(SAVR:3.7%-TAVR:0.8%-p-value=0.103), however SAVR patients spent an extra week in hospital (SAVR:9 days–TAVR:2days–p-value<0.001). In addition, more SAVR patients required packed red blood cells transfusions (SAVR:74.1%-TAVR:25%-p-value<0.001) but the unit-per-patient number was similar when transfusion was needed (SAVR:2units-TAVR:3units-p-value=0.153).

The rate of adverse events differed between both groups: TAVR patients had more perivalvular leaks (SAVR:0.7%-TAVR:40.3%-p-value<0.05), transient ischemic attacks (SAVR:0%- TAVR:7.6%-p-value<0.05) and need for permanent pacemaker implants (SAVR:3.7%-TAVR:15.9%-p-value<0.05) while SAVR patients developed more acute kidney injuries (AKI) (SAVR:23.7%-TAVR:11%-p-value<0.05), atrial fibrillation (SAVR:68.7%-TAVR:3.6%-p-value<0.05), delirium (SAVR:25.4%-TAVR:3.8%-p-value<0.05), pneumonia (SAVR:11%-TAVR:0.7%-p-value<0.05), other infections (SAVR:14%-TAVR:0.7%-p-value<0.05) or bacteremia (SAVR:2.9%-TAVR:0%-p-value<0.05), and bleeding or cardiac tamponade with an increased need for re-operation (SAVR:8.2% -TAVR:1.5%-p-value<0.05). (Table 5 and Figure 1)

Figure 2 shows the global trend for mortality and adverse events over the years for all patients who were

treated for AS at our center. Efficacy and safety outcomes after aortic valve treatment improved over time. Indeed, 30-day rates of mortality (4% to 0.4%), stroke (2.5% to 0,9%), renal failure (3.5% to 1.5%), and pneumonia (10% to 1.5%) all decreased over time. In addition, median length-of-stay was shortened from 7 to 2 days.

Comment

The purpose of a Heart-Team in the treatment of valvular disease was confirmed since the advent of transcatheter valvular technologies with scientific studies comparing TAVR versus SAVR in multiple single-center, multicenter, national registries and randomized controlled trials.[8-13] The team must remain cognizant of the literature in order to offer the best treatment for individual patients. There are different risk profiles between patients that carefully need to be assessed; clinical characteristics, comorbidities, anatomical features, socio-economic environment, life expectancy... In Quebec, the Heart-Team approach has become mandatory for high-risk costly procedures such as AVR.[5]

Compared to a matched-SAVR population, this study showed that when we accounted for time period, the Heart-Team performed well at selecting patients who received a TAVR. It is, however, inevitable that complications between the two different approaches differ, as reflected in the current study.

In the PARTNER 2A trial, which randomized intermediate-risk patients to TAVR versus SAVR, there was no difference in mortality between the two groups, but TAVR patients had an increase in peri-procedural strokes and vascular complications, while SAVR patients had a higher incidence of major bleeding. The conclusions were that both approaches were acceptable for intermediate-risk patients.[14] Our results are consistent with these findings, particularly with regards to mortality. However, surgical patients had more complications, which in some patients could tip the balance towards TAVR given the similar mortality rates. The role of the Heart-Team is to help counsel patients as to what is an acceptable risk associated with each procedure and to assess the burden of known complications on quality of life thereafter. This information should be communicated to the referring physicians, the patients and their families to provide the most objective assessment of procedural outcomes and the risk/benefit ratio.[4]

TAVR or SAVR related complications can be costly for the healthcare system. The Heart-Team needs to be informed of the potential effect of complications on healthcare resources. Complications also affect morbidities/mortality. In fact, a review evaluating the impact of AKI on mortality following TAVR found that the 30-day mortality rate in patients with AKI ranged from 13.3% to 44.4%, and was 2-6 folds higher than in patients without AKI.[15] Another study from Florida showed that AKI was associated with increased mortality up to 2 years following TAVR. The investigators also recommended that transfusions should be administered restrictively in order to prevent AKI. In our study, even though transfusions were not directly associated with 30-day mortality, they could potentially lead to AKI, which represents a strong predictor of 30-day mortality. In another propensity-matched analysis, Magruder et al. assessed the impact of severe versus minimal bleeding following cardiac surgery. They found out that patients with bleeds were more likely to experience the primary outcome of any morbidity/mortality (36.8%vs.13.2%,p=0.002), as well as >24hrs ventilation (33.8%vs.7.4 %,p<0.001) and 30-day mortality (11.8%vs.1.5%,p=0.02).[16] A retrospective cohort study that included 4,028 patients who underwent cardiac surgery compared the postoperative complications between patients requiring blood transfusion versus those not requiring transfusion and showed no difference in mortality, however, patients who received transfusions experienced more infections (mediastinitis and respiratory infections), AKI, stroke and sepsis.[17]Mortality associated with AKI was reported to be as high as 60% but appears to range in 15-30% in most studies, depending on the definition of acute respiratory failure and the postoperative period studied (hospital discharge or 30-day mortality).[18-20] In patients who require dialysis, mortality is uniformly high in all studies and averages 60-70%.[21,22] Chertow et al. found that AKI was an independent determinant of death-risk with an odds-ratio of 7.9.[23] The impact of complications and their economic burden should be considered in the assessment of patients.

Our study showed a trend towards increased mortality post-SAVR (SAVR:4.5%vs.TAVR:0.7%). This trend is also found in the components of primary endpoint of propensity-matched analysis comparing TAVR with

SAVR in intermediate-risk patients with AS.[24]

The Heart-Team is a valid concept but could be limited by resources and economics depending on the work environment and healthcare system. This study showed that in the earlier years the attribution of TAVR was limited; it was mostly performed on elective basis. Lowest risk and more urgent patients were directed towards surgery because of cost and because of longer access delays (3-6months). Unfortunately, this translated into a higher risk of procedural morbidities/mortality. We also know that complications could be related to later mortality that is not captured by the 30-day mortality endpoint assessed. Beyond individualized patient care, the Heart-Team is also tasked with the role of rationing resources to improve health system outcomes by directing costly interventions to those who stand to benefit the most. By creating local databases and documenting important metrics such as length-of-stay, readmission rates and complications that could become costly for the system, the Heart-Team contributes to the improvement of health system economics and outcomes.[25] Finally, this study indirectly supports the benefits of increased funding for TAVR throughout the years since the increased volume was associated with a reduction in mortality, adverse events, and length-of-stay.

Conclusion

Over different time periods, the more contemporary data showed an improvement in morbidities/mortality for intermediate-risk patients treated either with SAVR or TAVR. Increased funding allowed for an increase in TAVR volume, thus allowing more patients to have access to this technology. Differences in complications between the two approaches could substantially impact healthcare costs. By incorporating important metrics such as length-of-stay, readmission rates and complications into treatment allocation decisions, the Heart-Team could potentially continue to improve clinical outcomes, healthcare economics and resource utilization.

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Table1:Procedural factors for propensity-matched patients who underwent TAVR

Variables	*TAVR(n=139)*
Patients with bicuspid valve	7(2.9)
Patients with concomitant PCI	2(0.8)
Valve-in-valve procedure	14(5.9)
Type and Size of TAVR valve	
Accurate (Boston Scientific)	10(4.2)
Small	4(0.4)
Medium	4(0.4)
Large	2(0.2)
CoreValve Evolut Pro	3(1.3)
29mm	3(100)
CoreValve Evolut R (Medtronic)	5(2.1)
23mm	1(20.0)
26mm	2(40.0)
34mm	2(40.0)
Lotus	26(11.0)
23mm	5(19.2)
25mm	11(42.3)
27mm	10(38.5)
Sapien	4(1.7)
23mm	1(25.0)
26mm	3(75.0)
Sapien XT	77(32.5)
20mm	4(5.2)
21mm	1(1.3)
23mm	32(41.6)

Variables	*TAVR(n=139)*
26mm	29(37.7)
29mm	11(14.3)
Sapiens 3 (Edwards)	110(46.4)
20mm	4(3.6)
23mm	34(30.9)
26mm	56(50.9)
29mm	16(14.5)
Access Vessel	
Direct aortic access	8(3.4)
Suprasternal	1(0.4)
Trans-apical	16(6.8)
Trans-axillary	4(1.7)
Trans-carotid	3(1.3)
Trans-femoral	203(85.6)
Pre-Dilation	165(69.6)
Post-Dilation	42(17.7)
Type of Sedation	
General anesthesia	124(52.3)
Minimal sedation	113(47.7)
Valve fracture	0(0)
CPB needed	2(0.8)

CPB: cardio-pulmonary bypass – PCI: percutaneous coronary intervention – TAVR: transcatheter aortic valve replacement. Categorial data are expressed in N(%), continuous variables in mean±SD and Median[IQR]

Table2:Procedural factors for propensity-matched patients who underwent SAVR

Variables	*SAVR(n=139)*
CPB total time (minutes)	83.2±21.2 79[69,91.5]
Cross-clamping time (minutes)	65.6±19.5 62[52.5,72]
Type of Aortic bioprosthetic implant	
C-E Pericardial Magna	92(66.2)
C-E Porcine Standard (Perimount)	30(21.6)
Others	14(10.1)
Size of aortic implant	
19	14(10.1)
21	52(37.4)
23	49(35.3)
25	19(13.7)
27	3(2.2)
Surgical Approach	
Sternotomy	137(98.6)
Mini-Sternotomy	2(1.4)
Arterial Cannulation	
Aortic	139(100)
Other	0(0)
CPB Hemofiltration	24(17.3)
Cardioplegia	

Variables	*SAVR(n=139)*
Antegrade	50(36.0)
Antegrade+Retrograde	87(62.6)
Minimum body temperature during CPB	34.5±0.4 34.5[34.4,34.7]

CPB: cardio-pulmonary bypass – SAVR: surgical aortic valve replacement. Categorial data are expressed in N(%), continuous variables in mean±SD and Median[IQR]

Tables 3: Preoperative risk factors for matched patients

Variables	*SAVR(n=139)*	*TAVR(n=139)*	*Standardized differences*
Age (years)	77±5	77±9	-1.0
Female Gender	67(48.2)	69(49.6)	2.9
Hypertension	109(78.4)	127(91.4)	36.8
Diabetes	56(40.3)	53(38.1)	-4.4
Body Mass Index	29±5	28±7	-21.9
Body Surface Area	1.9±0.2	1.8±0.2	-23.8
Preop serum Creatinine (µmol/L)	84[70,106]	83[65,106]	-2.3
Chronic Kidney Disease	51(36.7)	75(54.0)	35.2
Preop renal failure requiring dialysis	3(2.2)	4(2.9)	4.6
Preop hemoglobin (gr/L)	120±17	122±18	8.9
Preop albumin, (gr/L)	39±4	39±4	6.1
Prior Stroke	9(6.5)	11(8.0)	5.6
Prior TIA	5(3.6)	5(3.6)	-0.1
Peripheral Vascular Disease	18(12.9)	20(14.4)	4.2
COPD	32(23.0)	33(23.7)	1.7
Prior Cardiac Surgery	6(4.3)	57(41.0)	97.5
Prior PCI	10(7.2)	65(46.8)	99.6
Preop Afib	34(24.5)	30(21.6)	-6.8
Preop Pacemaker	9(6.5)	9(6.5)	0.0
Cirrhosis	4(2.9)	3(2.2)	-4.6
Emergent or Urgent	35(25.2)	1(0.7)	-78.2
Preop NYHA class III or IV	80(57.6)	85(61.2)	52.1
LVEF (%)	57±10	57±12	-3.0
Pulmonary Hypertension	12(8.6)	18(12.9)	13.9
Hemodynamics			
Mean aortic valve gradient (mmHg)	44±12	47±15	20.7
AVA (cm^2)	0.80±0.16	0.81±0.18	5.6
Moderate or severe aortic valve insufficiency	13(9.4)	1(0.7)	44.2
STS predicted 30-Day Mortality	4.5%±0.3%	4.8%±0.3%	10.1
STS predicted Permanent Cerebrovascular Accident	1.7%±0.1%	2.7%±0.1%	82.3
STS predicted Renal Failure	5.3%±0.3%	4.1%±0.5%	-28.8

Afib: atrial fibrillation – AVA: aortic valve area – COPD: chronic obstructive pulmonary disease – LVEF: left ventricular ejection fraction – NYHA: New York Heart Association – PCI: percutaneous coronary intervention – Preop: pre-operative – SAVR: surgical aortic valve replacement – TAVR: transcatheter aortic valve replacement – TIA: transient ischemic attack. Categorial data are expressed in N(%), continuous variables in mean±SD or Median[IQR].

Table4:Patient distribution per year of procedure

Variables	*SAVR(n=139)*	*TAVR(n=139)*	*Standardized differences*
2012-2013	18(12.9)	18(12.9)	4.8
2014-2015	35(25.2)	34(24.5)	
2016-2017	42(30.2)	40(28.8)	
2018-2019	44(31.7)	47(33.8)	

SAVR: surgical aortic valve replacement – TAVR: transcatheter aortic valve replacement

Table5:Post-operative outcomes of patients: unadjusted, and matched for time-periods

Variables	*unadjusted SAVR(n=412)*	*unadjusted TAVR(n=400)*	*P-value*	*SAVR(n=139)*	*TAVR(n=139)*	*P-value*
30-Day Mortality	17(4.13)	2(0.5)	<0.001	6(4.5)	1(0.7)	0.053
Permanent Cerebrovascular Accident	4(0.97)	7(2.03)	0.224	1(0.7)	4(3.1)	0.173
Renal Failure	20(4.95)	1(0.30)	<0.001	8(6.1)	0(0)	0.004
Readmission to ICU	14(3.38)	10(2.95)	0.113	5(3.7)	1(0.8)	0.103
Hospital length-of-stay (days)	9[7,13]	2.0[1.0,5]	<0.001	9[7,13]	2.0[1.0,5]	<0.001
Any Transfusion	117(74.1)	34(24.5)	<0.001	100(74.1)	33(25.0)	<0.001
Any pRBC used	282(67.95)	92(26.74)	<0.001	97(71.9)	33(25.0)	<0.001

ICU: intensive care unit – pRBC: packed red blood cells – SAVR: surgical aortic valve replacement – TAVR: transcatheter aortic valve replacement.

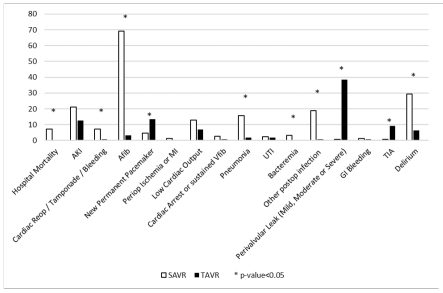
Figure1:Post-operative outcomes (percentage) of patients A) unadjusted and B) matched for time-periods

Afib: atrial fibrillation – AKI: acute kidney injury – GI: gastrointestinal – MI: myocardial ischemia – Periop: peri-operative – Postop: post-operative – Reop: re-operation – SAVR: surgical aortic valve replacement – TAVR: transcatheter aortic valve replacement – TIA: transient ischemic attack – UTI: urinary tract infection – Vfib: ventricular fibrillation

Figure2:Trends in morbidities/mortality at 30-days over time periods for all patients treated for aortic stenosis

LOS: length-of-stay (in days). All other complications are in percentage (%)

A



B