Favorable Survival after Aortic Valve Replacement Compared to the General Population

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Background and aim of the study: **A comparison was made between the long-term survival of patients undergoing aortic valve replacement (AVR) for aortic stenosis and of the general Icelandic population, using centralized registries.**
Methods: **A total of 366 AVR patients (231 males, 135 females; mean age 70.1 years) operated on for aortic stenosis in Iceland between 2002 and 2011 was included in the study. Concomitant coronary artery bypass grafting was performed in 54% of cases. Short-term complications and 30-day mortality were analyzed. The patients' overall survival was compared with the survival of Icelanders of the same age and gender. The median follow up was 4.7 years.**
Results: **A bioprosthesis was used in 81% of the patients; the median prosthesis size was 25 mm. Atrial fibrillation (68%) and acute kidney injury (23%) were the most common complications, and the 30-day operative mortality was 6%. Overall survival at one year and five years was 92% and 82%, respectively. There was no difference in survival between the surgical cohorts and expected survival of Icelanders of the same age and gender (p = 0.08), except for the first 30 postoperative days.**
Conclusion: **Despite the significant rate of short-term complications, the long-term survival of patients undergoing AVR for aortic stenosis was good compared to the general population of the same age and gender. These results confirmed the value of AVR as an excellent treatment option for aortic stenosis, as it offers a normalization of the patients' life expectancy.**

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Aortic stenosis is one of the most common valvular heart diseases globally (1,2) and, if untreated, it can significantly reduce patient survival, even when it is asymptomatic (3-6). During the past three decades surgical aortic valve replacement (AVR) has been shown to be an effective treatment for severe aortic stenosis, especially when compared to the natural progress of the disease (3,7,8). In recent years, transcatheter aortic valve implantation (TAVI) has emerged as a treatment option for patients with aortic stenosis that are not candidates for AVR due to their comorbidity burden (9-11). Randomized controlled trials of moderate-risk patients undergoing either AVR or TAVI are currently under way, such as the PARTNER IIA trial and the SURTAVI trial (12,13). It is therefore, important that the outcomes of surgical AVR are actively monitored and re-evaluated (14).

In contemporary studies from high-volume cardiac surgery centers, the operative mortality following AVR ranges from 2% to 7% (15-17). Less is known about long-term outcomes, especially in comparison to that of a whole nation. Such information is useful to compare emerging modalities for the treatment of aortic stenosis in the era of TAVI. Hence, the study aim was to compare the survival of patients with aortic stenosis who underwent AVR to that of the general population of the same age and gender, using centralized registries available in Iceland.

Clinical material and methods

Patients

This retrospective nationwide study included all patients who underwent AVR to treat aortic stenosis at

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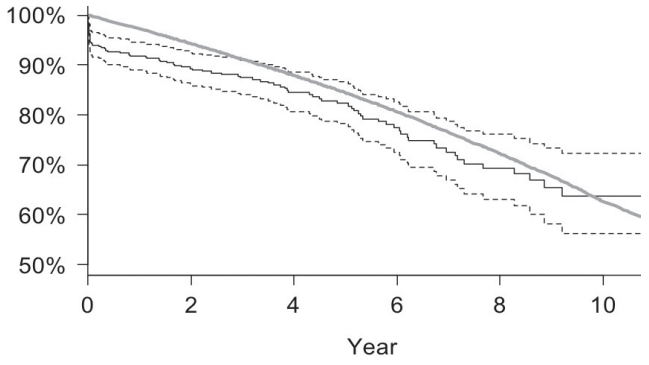

Figure 1: Survival analysis of patients with aortic stenosis who underwent AVR at Landspitali during the period 2002-2011. Kaplan Meier estimate of the observed survival (black line with 95% CI) and the Ederer II estimate of the expected survival (gray line).

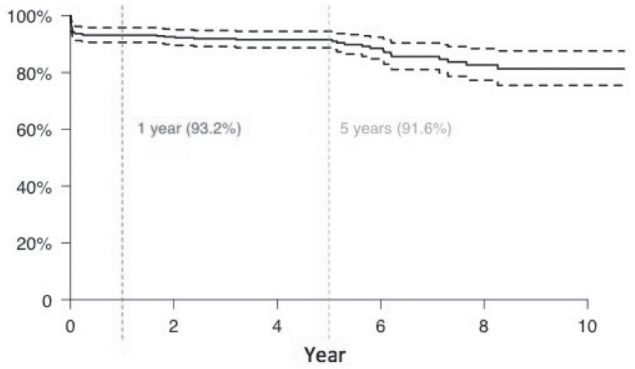

Figure 2: Disease-specific survival of patients with aortic stenosis who underwent AVR at Landspitali during the period 2002-2011, shown at one and five years

Landspitali University Hospital, the single institution performing open-heart surgery in Iceland, between 1 January 2002 and 31 December 2011. The patients were followed until the end of 2013, death, or when reaching the age of 100 years.

The patients were identified through two different diagnosis and operation registries at the authors' institution, and there was a 100% cross-match between registries. A total of 436 AVRs was performed during the study period. Patients who had a history of previous cardiac surgery (n = 31), aortic valve regurgitation as a primary indication for replacement (n = 27), and for whom insufficient data were recovered (n = 12) were excluded from the study. Thus, 366 patients were included in the final analysis.

The study was approved by the Icelandic National Bioethics Committee and the Icelandic Data Protection Commission.

Data acquisition

Clinical information was obtained from patient charts and surgical reports and registered in a standardized data sheet. The information collected contained over 130 variables, including patient gender, age, cardiovascular risk profile, height and weight, history of smoking, diabetes (requiring either oral diabetes agents and/or insulin), arrhythmias, and preoperative medication. Patient symptoms were graded according to the NYHA scale for heart failure (18), and the EuroSCORE II (19) was calculated for each patient to classify surgical risk assessment.

Preoperative and postoperative echocardiography results were gathered, including aortic valve gradient, valve size (effective orifice area) calculated with the continuity equation, left ventricular ejection fraction (LVEF), and left ventricular end-diastolic and systolic diameter. Operative factors were registered, including aortic cross-clamp time, cardiopulmonary bypass (CPB) time, skin-to-skin time, prosthetic valve type and size, and whether simultaneous coronary artery bypass grafting (CABG) took place.

Postoperative complications were registered and classified as minor (atrial fibrillation/flutter, urinary tract infection, pneumonia, pleural fluid requiring drainage, superficial surgical wound infection, and renal injury defined as patients in the Risk, Injury, or Failure category according to the RIFLE criteria (20) and major (reoperation for excessive hemorrhage, stroke, myocardial infarction (creatine kinase-MB elevation >70 IU/l and new ST changes or left-bundle branch block), multiple organ failure (MOF), or acute respiratory syndrome.

The amount of blood products given and the amount of chest tube bleeding during the initial 24 h after surgery were registered. Operative mortality was defined as death within 30 days of surgery. Survival data were collected from the centralized Icelandic Directorate of Health as of 1 June 2013. The mean follow up period was 4.7 years (interquartile range 2.7-7.2 years, range 0.003-11.2 years) and none of the patients was lost to follow up. Disease-specific survival, which included cardiac and valve-related deaths, was determined (ICD-10 diagnoses I05-08, I20-I25, I34-I37, I50.9, and I51.9)

Statistical analysis

The R statistics package, version 3.1.3 (R foundation for Statistical Computing, Vienna, Austria) and STATA version 13.1 (StataCorp. 2013. Stata Statistical Software: Release 13, College Station, TX, USA: StataCorp LP) was used for statistical analyses. Continuous variables were compared using Welch's *t*-test or the Mann-Whitney *U*-test, based on tests of normal distribution. Categorical variables were compared using the chi-square test or Fisher's exact test with 2 × 2 tables.

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Survival was estimated using the Kaplan-Meier method, and expected survival was estimated using the Ederer II method, using the 'survexp' function within the R statistical program. Expected survival is the survival in a reference population which is similar to the study cohort of patients at the start of follow up. The reference cohort is matched for age, calendar time, and gender. The mortality tables for Iceland were obtained from the Human Mortality Database (21). The observed number of deaths was compared to the expected number of deaths using a generalized Poisson linear model, using the log of the expected number of deaths as offset. The estimated intercept term of the Poisson model is then equivalent to the log of the mortality ratio between the patient group and the reference population, and the significance test of the intercept is equivalent to the one sample log-rank test of equal number of observed and expected number of deaths (22, 23). The relative survival was also estimated to compare the observed and estimated survival. The relative survival is the ratio of the survival probability of the patient group to the reference population. This was estimated both within time periods and cumulative over time, where the cumulative relative survival is defined as $R(t) = S(t)/S^*(t)$. Here, $S(t)$ is the survival probability in the patient group at time t and $S^*(t)$ is the survival probability in the reference population. The reference survival curve was estimated, as above, using the Ederer II method. The computations were performed using the 'strs' function (24), within STATA and the 'rstpm2' package (25), within the R statistical program. A p-value <0.05 was considered to be statistically significant.

Table II: Early complications of patients with aortic stenosis who underwent AVR.

Complication*	No. identified (total = 366)
Major complications	
Myocardial infarction	50 (13.6)
Stroke	6 (1.6)
Deep wound infection with mediastinitis	3 (0.8)
MOF	38 (10.4)
Reoperation for bleeding	55 (15.0)
All major complications	117 (32.0)
Operative mortality	22 (6.0)
Minor complications	
Atrial fibrillation	191 (67.6)
Acute kidney injury	83 (22.7)
Urinary tract infection	39 (10.6)
Pneumonia	41 (11.2)
Pleural fluid requiring drainage	49 (13.4)
Superficial wound infection	30 (8.2)
All minor complications	254 (69.2)

*Note: Each patient could have more than one complication.
Values in parentheses are percentages.
MOF: Multiple organ failure.

Table I: Preoperative variables of the patients.

Variable	Value
Mean age (years)	71 (range: 26–88)
Male gender (n)	231 (63.1)
BMI (kg/m^2)*	27.6 ± 4.5
History of smoking (n)	240 (65.6)
History of hypertension (n)	254 (69.4)
History of diabetes (n)	55 (15.0)
Ejection fraction (%)*	57 ± 8.8
Maximum gradient (mmHg)*	70 ± 25.8
EOA (cm^2)*	0.7 ± 0.25
NYHA class III/IV (n)	221 (60.4)
EuroSCORE II (%)*	3.8 ± 6.2
Concomitant CABG (n)	199 (54.4)
Mechanical prosthesis (n)	68 (18.6)
Bioprosthesis - stentless (n)	84 (50.3)
Bioprosthesis - stented (n)	114 (31.1)
Duration of surgery (skin-to-skin) (min)*	286 ± 118

*Values are mean ± SD.
Values in parentheses are percentages.
BMI: Body mass index; CABG: Coronary artery bypass grafting; EOA: Effective orifice area.

Results

Patient characteristics

Of the 366 patients in the study, 231 (63.1%) were males, the mean age was 70.1 years (range: 26 to 88 years) and the mean body mass index was 27.6 kg/m^2. In addition, 240 patients (65.6%) had a history of smoking, 254 (69.4%) had a history of hypertension, and 55 (15.0%) had diabetes. The mean LVEF was 57 ± 8.8% and the maximal gradient across the valve was 70 ± 25.8 mmHg. The mean aortic valve area was 0.7 ± 0.25 cm^2 and the mean EuroSCORE II 3.8 ± 6.2%) (Table I).

More than half of the patients underwent concomitant CABG (54.4%), and 298 (81.4%) received a bioprosthesis, 60% of which were stentless (Freestyle™) valves. The median size of the implanted valves was 25 mm (range: 21 to 29 mm). The mean total operation time was 286 ± 118 min, the mean CPB time 162 ± 55 min, and the mean aortic cross-clamp time 116 ± 35 min.

Early complications

The most common early complication was new-onset atrial fibrillation (Table II), which was diagnosed in 191 patients (67.6%). Acute kidney injury occurred in 83 patients (22.7%) according to the RIFLE criteria. Of those patients, 40 (10.9%) were classified as Risk, 29 (7.9%) as Injury, and 14 (3.8%) as Failure.

Mortality and long-term survival

The 30-day mortality was 6.0% (n = 22). The overall

Table III: Survival analysis of patients with aortic stenosis who underwent AVR.

Time period (years after operation)	Patients remaining	Observed deaths during period	Expected deaths during period	Difference
0-1	366	30	9.7	+20.3
1-2	336	9	10.1	-1.1
2-4	301	14	18.2	-4.2
4-6	217	14	14.5	-0.5
6-8	122	11	10.3	+0.7
8-12	68	6	6.8	-0.8

survival of the AVR patients was compared to the expected survival of Icelanders of the same age and gender. At the time of completion of follow up (1st August 2013) 84 patients had died. The expected number of deaths based on the reference population was 69.6. The Kaplan Meier estimate of survival, with the expected survival superimposed, is shown in Figure 1.

Overall, the mortality ratio between cases and the reference population was 1.21 [95% confidence interval (CI) 0.98-1.50], but this was not statistically different from a ratio of 1 (p = 0.08). The largest contribution to the mortality ratio was deaths occurring during the first 30 days of follow up. The difference in observed and expected numbers of deaths, based on time periods after surgery, are listed in Table III.

Relative survival estimates by time periods after operation are shown in Table IV. Survival in the patient group relative to the reference population was significantly lower in the first year only, with a relative survival estimate of 0.95 (95% CI: 0.91-0.97). After the second year, the relative survival within intervals was estimated to be about 1, and the cumulative relative survival remained stable around 0.95 (due to non-significant excess mortality within time intervals), and was not significantly lower than 1 at the end of follow up, indicating similar survival in the patient group and the reference population.

The disease-specific survival of the study group at one year and five years was 93.2% and 91.6%, respectively (Fig. 2). Data on disease-specific survival in the comparison group was unattainable, and was therefore not calculated.

Discussion

The results of the present study demonstrated an excellent long-term outcome of AVR in Iceland, reflected by the fact that patients who underwent AVR had a similar long-term survival to that of the general population of the same age and gender. The overall mortality ratio between cases and the reference population was not statistically different, although a trend towards a less favorable survival amongst the patients was observed (p = 0.08), mainly attributed to operative mortality. Comparable results have been described in a Swedish single-center study (26), where patients who underwent AVR had a similar survival rate to that of the general population for the first two years after surgery. However, after six years the surgical group had fared worse than the comparison group, which was matched for age and gender. Any comparison to the present study was limited by the use of only a single type of prosthetic valve and a high ratio of the patients over the age of 80 years.

Various potential explanations have been proposed for the normalization of life expectancy after

Table IV: Survival analysis of patients with aortic stenosis who underwent AVR.

Time period (year after operation)	Interval survival probability	Expected interval survival probability	Relative survival (95% CI)	Cumulative survival	Expected cumulative survival	Cumulative relative survival (95% CI)
0-1	0.92	0.97	0.95 (0.91-0.97)	0.92	0.97	0.95 (0.91-0.97)
1-2	0.97	0.97	1.00 (0.98-1.02)	0.89	0.94	0.95 (0.91-0.98)
2-4	0.95	0.94	1.01 (0.98-1.03)	0.85	0.88	0.96 (0.91-1.00)
4-6	0.92	0.93	0.99 (0.94-1.03)	0.78	0.82	0.95 (0.89-1.01)
6-8	0.89	0.90	0.99 (0.90-1.04)	0.69	0.74	0.94 (0.85-1.02)
8-12	0.84	0.80	1.05 (0.85-1.16)	0.58	0.59	0.99 (0.81-1.14)

undergoing AVR for aortic stenosis. The most significant is evidently a reversal of the detrimental pathological effects of aortic stenosis following AVR. Additionally, a close medical follow up after the operation could modulate cardiovascular risk factors and thereby increase life expectancy. Selection bias could also play a role if the study cohort were to consist of lower-risk patients. This was unlikely in the present cohort, as indicated by an average EuroSCORE II of 3.8%, which was comparable to that in other studies (27).

The number of early complications was high, especially atrial fibrillation and bleeding requiring reoperation. The operative mortality of 6.0% was on par with that of similar cohorts (15), but somewhat higher than in single-center studies performed in high-volume institutions (16).

The main strength of the present study was a prolonged long-term follow up of all patients operated on for aortic stenosis within an entire nation. Furthermore, all of the patients were operated on at a single center by five surgeons. The present authors' method of using relative survival in order to achieve a valid comparison with the entire Icelandic population of the same age and gender is well defined and has been used for comparisons of survival analysis for sepsis patients (28). To the present authors' knowledge, this method offers a novel approach for analyzing the survival of patients who have undergone major cardiac surgery, although it has been shown to be applicable also in coronary heart disease (29). Most importantly, the method allows a comparison to be made of excess mortality after AVR compared to that of the general population.

Study limitations

The main limitations of the present study were its retrospective design and the relatively low number of operations performed. A complete understanding of the long-term results of AVR is important, especially in the current era of an evolving TAVI technology being applied to increasing numbers of groups (16). Today, conventional open AVR remains the 'gold-standard' in the treatment of aortic stenosis, while the high cost of TAVI still limits its use in many hospitals (30,31). Clearly, more evidence is required demonstrating the advantages of TAVI over AVR before it can be applied on a more regular basis.

In conclusion, the results of the present study demonstrate the good outcome of patients who undergo AVR in Iceland, and confirm the legitimacy of AVR as an excellent treatment option for aortic stenosis, as it offers a normalization of the patients' life expectancy. Nonetheless, it is firmly believed that AVR remains a viable procedure that has the potential to improve still further.

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