Long-Term Clinical and Echocardiographic Follow-Up of the Freestyle Stentless Aortic Bioprosthesis: the Tel Aviv Medical Center Experience

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ABSTRACT: **Background:** Stentless aortic bioprostheses were designed to provide improved hemodynamic performance and potentially better survival.

Objectives: To report the outcomes of patients after aortic valve replacement with the Freestyle® stentless bioprosthesis at the Tel Aviv Medical Center followed for ≤ 15 years.

Methods and Results: Between 1997 and 2011, 268 patients underwent primary aortic valve replacement with a Freestyle bioprosthesis, 211 (79%) of them in the sub-coronary position. Mean age, Charlson comorbidity index and Euro-score were 71.0 ± 9.2 years, 4.2 ± 1.5 and 10.2 ± 11 respectively, and 156 (58%) were male. Peak and mean trans-aortic gradient decreased significantly (75.0 ± 29.1 vs. 22.8 ± 9.6 mmHg, $P < 0.0001$; and 43.4 ± 17.2 vs. 12.1 ± 5.4 mmHg, $P < 0.0001$ respectively) during 3 months of follow-up. Mean overall follow-up was 4.9 ± 3.1 years and was complete in all patients. In-hospital mortality was 4.1% (n=11) but differed significantly between the first 100 patients operated before 2006 and the last 168 patients operated after January 2006 (8 vs. 3 patients, 8.0% vs. 1.8%, $P = 0.01$). Overall, 5 and 10 year survival rates were 85 ± 2.5% and 57.2 ± 5.7%, respectively. Five year survival was markedly improved in patients operated after January 2006 compared to those operated in the early years of the experience (92.3 ± 2.3% vs. 76.0 ± 4.4%, $P = 0.0009$). All the 21 octogenarians operated after January 2006 survived surgery, with excellent 5 year survival (85.1 ± 7.9%). Six patients required reoperation during follow-up: structural valve deterioration in five and endocarditis in one.

Conclusions: Aortic valve replacement with the Freestyle bioprosthesis provides good long-term hemodynamic and clinical outcomes, even in octogenarians. Valve calcification is the major (and rare) mode of valve deterioration leading to reoperation in these patients.

IMAJ 2013; 15: 538–544

KEY WORDS: aortic stenosis, aortic valve replacement, patient prosthesis mismatch (PPM), echocardiography, stentless valve

Stentless aortic bioprostheses were designed to provide improved hemodynamic performance and greater durability because of lower mechanical stress on the leaflets, with no requirement for long-term anticoagulation [1]. The Freestyle® bioprosthesis (Medtronic Inc, Minneapolis, MN, USA) is a stentless porcine aortic root prepared using a zero-pressure fixation process and anti-calcification treatment. It can be implanted as a sub-coronary valve replacement or as a full aortic root replacement [2]. Multiple recent reports confirm excellent hemodynamic performance associated with stentless aortic valves [3,4]. Furthermore, because aortic valve replacement in patients with small aortic annulus for body surface area is associated with a high incidence of patient prosthesis mismatch [5,6], which in turn is associated with worse survival and clinical outcome [7,8], stentless aortic valves are used whenever PPM is anticipated [9]. The purpose of the present study was to assess the early and late clinical and echocardiographic outcomes, as well as late prosthesis durability among 268 patients who underwent aortic valve replacement with a Freestyle bioprosthesis at the Tel Aviv Medical Center between 1997 and 2011.

PATIENTS AND METHODS

We identified 268 consecutive patients who underwent aortic valve replacement with a Freestyle® stentless bioprosthesis (Medtronic) between January 1997 and November 2011 at the Tel Aviv Medical Center. The operative technique has been described previously [10]. Briefly, all operations were performed through standard midline sternotomy with cardiopulmonary bypass. Excision of the native aortic valve and annular debridement was performed in all cases before valve implantation. Sizing was performed with the sizer provided for the Freestyle stentless bioprosthesis valve, consideration being given to the size at both the annulus and sino-tubular ridge. The Freestyle valve was then inserted in the sub-coronary position (n=211, 79%) or as a full root replacement

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PPM = patient prosthesis mismatch

(n=57, 21%). When sub-coronary insertion was applied a two-layer suture technique was used. Patients received aspirin (80–325 mg/day) for the first 12 postoperative weeks [2,10]. Concomitant coronary artery bypass graft surgery was performed in 146 patients (54.0%).

All the patients were followed annually as part of the registry. Baseline clinical data were collected by interviewing the patients and included age, gender, and the presence of hypertension, diabetes mellitus, history of coronary heart disease, as well as operative risk assessment by calculating the logistic Euro-score. Coexisting conditions were evaluated by means of the Charlson comorbiditiy index [11]. The Charlson comorbidity index predicts the 1 year mortality for a patient who may have a wide range of conditions, including heart disease from different causes. It comprises different categories of comorbidities: namely, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia or paraplegia, renal disease, any malignancy including lymphoma and leukemia (except malignant neoplasm of skin), and AIDS/human immunodeficiency virus. Each condition is assigned a score of 1, 2, 3, or 6, depending on the risk of dying associated with this condition. The scores are then summed to give a total score that predicts mortality. Clinical follow-up was obtained by review of medical records, surveys, and telephone interviews. Aortic stenosis severity was defined by the maximal velocity across the aortic valve, mean pressure gradient, and aortic valve area, calculated by the standard continuity equation. Severe aortic stenosis was defined as maximal velocity > 4 m/sec, mean gradient > 40 mmHg, and aortic valve area < 1.0 cm^2.

STATISTICAL ANALYSIS

Continuous normally distributed parameters were presented as means ± SD and compared using the Student's *t*-test or paired *t*-test as appropriate. Ordinal and/or non-normally distributed data were presented by median, first and third quartiles and compared using the Wilcoxon rank sum or Wilcoxon signed rank test. Categorical data were compared between groups using the chi-square test or Fisher's exact test. Unadjusted and adjusted Cox proportional hazards were used to analyze the associations of different clinical parameters with mortality and calculation of hazard ratios and confidence intervals. Event distributions were calculated according to the Kaplan-Meier method and compared by means of the log-rank test. All *P* values were two-sided, and values less than 0.05 were considered statistically significant. All data were analyzed with the JMP System software version 9.0 (SAS Institute, Inc, Cary, NC, USA). All authors participated in designing the study, collecting and analyzing data, and drafting and revising the manuscript.

RESULTS

BASELINE CHARACTERISTICS

Table 1 shows the baseline characteristics of all the patients enrolled (n=268). The mean age of the entire cohort was 71.0 ± 9.3 years, 58% were men, and mean body surface area was 1.9 ± 0.2 m^2. The reason for surgery was degenerative calcific aortic

Table 1. Baseline and echocardiographic characteristics of all 268 patients with severe aortic stenosis before aortic valve replacement

Variables	
Age (yr)	71.0 ± 9.3
Surgery before 2006	
Gender male	58%
COPD (%)	6%
Peripheral vascular disease (%)	10%
Post-CVA (%)	5%
Redo S/P cardiac surgery (%)	13%
Creatinine (mg/dl)	1.2 ± 0.3
Renal failure (creatinine › 1.7%)	11%
Diabetes mellitus (%)	27%
Urgent state (%)	3%
LV ejection fraction (‹ 35%)	6%
Pulmonary hypertension, SPAP › 50 mmHg	17%
Logistic Euro-score*	10.2 ± 11.0
Charlson score*	4.2 ± 1.5
Weight (kg)	76.6 ±14.4
Height (cm)	168.6 ± 8.8
BSA (cm^2/m^2)	1.9 ± 0.2
Ejection fraction (%)	51.9 ± 12.1
LV end-diastolic diameter (mm)	49.7 ± 9.1
Interventricular septum (mm)	13.9 ± 2.7
Posterior wall thickness (mm)	12.3 ± 2.2
LV end-systolic diameter (mm)	32.6 ± 10.1
LVOT diameter (mm)	21.3 ± 2.9
Peak trans-aortic gradient (mmHg)	75.0 ± 29
Mean trans-aortic gradient (mmHg)	43.4 ± 17
Aortic valve area (cm^2)	0.78 ± 0.3
E wave velocity (cm)	97.1 ± 33
E wave deceleration time (msec)	230.9 ± 91
A wave velocity (cm)	96.0 ± 33
Systolic pulmonary pressure (mmHg)	37.1 ± 14.7
≥ Moderate mitral regurgitation (%)	10

*Calculated as described in the methods section

COPD = chronic obstructive pulmonary disease, CVA = cerebrovascular accident, LV = left ventricle, SPAP = systolic pulmonary arterial pressure, LVOT = left ventricular outflow tract, BSA = body surface area, SPAP = systolic pulmonary arterial pressure

Table 2. Clinical postoperative outcomes of all patients stratified into the first 100 patients implanted before January 2006 and the latter 268 patients

		Before January 2006	After January 2006	*P* value
Early mortality (< 30 days)	11 (4.1%)	8 (8.33%)	3 (1.7%)	0.009
Valve size (mm)	24.5 ± 2.5	23.7 ± 2.3	25.0 ± 2.5	< 0.001
Surgery details				
Concomitant procedures (%)*	59%	67%	55%	0.07
CABG procedure (%)	54%	71%	45%	0.04
Mitral valve replacement (%)	3%	3%	3%	0.8
Sub-coronary implantation (%)	79%	82%	76%	0.3
Root replacement (%)	21%	18%	24%	0.3
Ascending aortic aneurysm (%)	13%	11%	14%	0.5
Aortic aortic interposition graft (%)	14%	11%	15%	0.3
Cardiopulmonary bypass time (min)	121.6 ± 47.1	132.5 ± 49.6	115.7 ± 44.8	0.008
Aortic cross-clamp time (min)	93.3 ± 35.0	100.9 ± 36.2	89.2 ± 33.7	0.01
Hospital stay (days)	8.6 ± 6.7	9.47 ± 9.14	8.1 ± 4.9	0.2
Postoperative complications				
Wound infection (%)	0.4%	0%	1%	0.4
Myocardial infarction (%)	0.4%	0%	1%	0.4
Cerebrovascular accident (%)	3%	1%	4%	0.2
Atrial fibrillation (%)	28%	29%	28%	0.9
Atrioventricular block (%)	1%	1%	1%	0.7
Sepsis (%)	3%	5%	2 %	0.2
Pneumonia (%)	2%	3%	1%	0.3
Acute renal failure (%)**	8%	14%	4%	0.008
Mediastinal bleeding (%)	1%	2%	1%	0.3

*Including and concomitant coronary, valvular or aortic procedure
**Including need for dialysis, or increase in creatinine by at least 0.5 mg/dl

disease in 230 (86%) and bicuspid aortic valve in 38 (14%). All patients were symptomatic (New York Heart Association class ≥ III). The average logistic Euro-score was 10.2 ± 11 and the average Charlson comorbidity index was 4.2 ± 1.5. Previous sternotomy was performed in 13% of patients, and previous aortic valve replacement in 5%. Seven procedures were performed urgently due to high risk of immediate mortality (five patients with acute aortic regurgitation due to endocarditis, one patient immediately after myocardial infarction and cardiogenic shock, and one patient with severe uncontrolled left and right heart failure). Baseline echocardiographic examination showed the following mean values: aortic peak pressure gradient 75.0 ± 29 mmHg, aortic mean pressure gradient 43.4 ± 17 mmHg, aortic valve area 0.78 ± 0.3 cm^2. Comparison between the first 100 patients having surgery before and the last 168 patients implanted after January 2006 showed that patients implanted after 2006 were younger, had lower Euro-score and Charlson score and a lower incidence of previous sternotomy, peripheral vascular disease, and critical state before surgery ($P < 0.05$ for all).

EARLY CLINICAL OUTCOMES

Table 2 shows the postoperative outcomes in all patients, divided into those who had surgery before or after January 2006. Total cardiopulmonary bypass time was 121.6 ± 47 minutes and aortic cross-clamp time 93.3 ± 35.0 minutes, both significantly reduced in the latter group. The mean duration of hospitalization was 8.6 ± 6.7 days. Overall in-hospital mortality was 4.1% (n=11), of whom 3 patients were in critical condition before surgery (1 with uncontrolled right and left heart failure, and 2 with acute aortic regurgitation due to endocarditis and root abscess), and 7 had concomitant procedures (coronary artery bypass graft in 3, mitral valve replacement in 2, septal myectomy in 1, and maze procedure in 1). Causes of early death were low cardiac output state (n=3), sepsis (n=2), multi-organ failure (n=4), and uncontrolled bleeding (n=2). We compared patients who survived to hospital discharge with those who did not, and discovered a significantly higher Euro-score (19.9 vs. 9.7, $P = 0.05$), higher Charlson score (5.5 ± 1.5 vs. 4.1 ± 1.5, $P = 0.03$), smaller implant size (22.8 ± 1.7 vs. 24.6 ± 2.5 mm, $P = 0.004$), longer bypass time (174.8 ± 54 vs. 119.4 ± 46 minutes, $P = 0.01$), and a higher incidence of critical state (27% vs. 1.5%, $P = 0.001$), peripheral vascular disease (30% vs. 10%, $P = 0.04$), and the need for mitral valve replacement (18% vs. 3%, $P = 0.04$) among the patients who died. There were no significant differences in severity of aortic stenosis based on echocardiography between those who did or did not survive surgery. There was no significant difference in early mortality between the patients who had a sub-coronary valve replacement compared to a complete aortic root replacement ($P = 0.6$).

Nominal logistic regression analysis showed that the only parameters significantly associated with early mortality were the presence of critical state before surgery (odds ratio 23.7, 95% confidence interval 4.1–126, $P = 0.001$), increased Euro-score (OR 1.06. 95%CI 1.03–1.09 for each increase of 1 in the score, $P < 0.0001$), increased Charlson score (OR 1.7, 95%CI 1.1–2.5, $P = 0.01$), small implant valve size (OR 0.43, 95%CI 0.001–0.55 for each mm, $P = 0.02$), concomitant mitral valve replacement (OR 7.8, 95%CI 1.07–38.5, $P = 0.02$), and increased bypass time (OR 1.02, CI 1.01–1.03 for each minute, $P = 0.004$). Interestingly, age ($P = 0.3$), gender ($P = 0.2$), presence of pulmonary disease ($P = 0.3$), renal disease ($P = 0.4$), pulmonary hypertension (> 50 mmHg, $P = 0.5$) and low ejection fraction (< 35%, $P = 0.3$) were not associated with operative mortality. The performance of sub-coronary valve replacement compared to a complete aortic root replacement did not influence operative mortality either. We found a significant difference in early mortality between the first 100 patients operated on before January 2006 and the 168 patients after (8.0% vs. 1.8%, $P = 0.01$). When looking at the 168 patients implanted after January 2006, we found that the only significant association with early mortality was the presence of a critical state before surgery (OR 84, 95% CI, 2.7–279, $P = 0.01$).

OR = odds ratio
CI = confidence interval

ECHOCARDIOGRAHIC FINDINGS AND PATIENT PROSTHESIS MISMATCH

Baseline echocardiographic parameters of ventricular function and native aortic valve hemodynamics are shown in Table 1. Peak and mean trans-prosthetic gradients at discharge were 18.5 ± 8.5 and 10.2 ± 4.5 mmHg, a significant improvement compared to pre-surgical values ($P < 0.0001$ for all). Calculation of aortic valve area was performed in 157 patients pre-discharge and showed a marked improvement over pre-surgical values (1.9 ± 0.8 cm^2, $P < 0.0001$). Mean aortic valve area index was 1.09 ± 0.5 cm^2/m^2, and the pre-discharge incidence of ≥ mild (aortic valve area index < 0.85 cm^2/m^2) patient prosthesis mismatch was 33.7%, and that of severe PPM (aortic valve area index < 0.65 cm^2/m^2) was 11.4%. Doppler echocardiographic data at 3 months follow-up showed that peak trans-valvular gradient (15.6 ± 7.5 mmHg, $P = 0.04$), mean trans-valvular gradient (8.7 ± 4.3 mmHg, $P = 0.0001$), aortic valve area (2.0 ± 0.6 cm^2, $P = 0.1$), and aortic valve area index (1.11 ± 0.4 cm^2/m^2, $P = 0.1$) improved further compared with the values at discharge. The incidence of ≥ mild PPM and severe PPM 3 months post-surgery decreased to 20% and 6.0%, respectively. Patients with severe PPM had lower ejection fraction before surgery (46.6 ± 11.4 vs. 55.3 ± 8.3%, $P = 0.005$), were younger (72.9 ± 7.5 vs. 79.1 ± 9.1 years, $P = 0.004$), weighed more (86.6 ± 14.9 vs. 72.6 ± 13.7 kg, $P = 0.0009$), were taller (169.4 ± 8.6 vs. 163.8 ± 9.3 cm, $P = 0.01$) and had larger body surface area (1.97 ± 0.2 vs. 1.78 ± 0.2 cm^2/m^2, $P = 0.0005$) compared to patients without PPM after surgery. There was no difference in peak, mean trans-aortic gradients, or aortic valve area before surgery between patients who developed or did not develop PPM. The proportion of female gender and patients implanted with smaller valves (19 or 21 mm) was similar between the PPM and non-PPM groups (66.6% vs. 57.5%, $P = 0.4$ and 11.1% vs. 11.5%, $P = 0.9$, respectively). Actuarial survival was comparable for patients irrespective of PPM severity, respectively ($P = 0.8$ for both comparisons).

LONG-TERM OUTCOMES

The mean follow-up duration after surgery was 4.9 ± 3.1 years. Of the 257 patients who survived surgery, 47 (18%) died during follow-up and 6 required a second cardiac surgery for the aortic valve. The cause of mortality in patients who survived the index surgery was progressive heart failure in seven patients, sudden arrhythmic cardiac death in two, endocarditis in one, other types of infection in eight, stroke in six, cancer in nine, and ischemic heart disease in two. The cause of death was undetermined in 12 patients. Of the patients who needed a second aortic valve surgery, five had prosthesis structural deterioration (calcific deterioration in four and leaflet tear with severe regurgitation in one), and one had prosthesis endocarditis. At the end of follow-up 205 patients (77%) remained event free. The overall survival rates were 93.6 ± 1.5%, 85.0 ± 2.5% and 57.2 ± 5.7 at 1 year, 5 years and 10 years respectively. The overall freedom from death or need for second surgery was 93.2 ± 1.5%, 84.7 ± 2.5% and 54.3 ± 5.9% at 1 year, 5 years and 10 years respectively.

Table 3. Unadjusted Cox hazard analysis of survival by demographic, clinical and echocardiographic parameters

	Hazard ratio for death
Surgery performed before January 2006	3.1 (1.6,6.3) 0.0009
Weight (kg)	0.99 (0.97,1.02) 0.6
Height (cm)	0.98 (0.93,1.05) 0.6
BSA (cm^2/m^2)	0.41(0.02,12.2) 0.6
Age (yr)	1.08 (1.04,1.13) 0.0001
Gender (male %)	1.3 (0.76,2.2) 0.3
Prior sternotomy (%)	2.7 (1.09,5.5) 0.03
Low ejection fraction (‹ 35%) (%)	2.3 (0.90,5.1) 0.08
Pulmonary hypertension (SPAP › 50 mmHg) (%)	2.2 (1.12,3.9) 0.02
Peak pressure gradient (mmHg)	0.98 (0.97,0.99) 0.01
Mean pressure gradient (mmHg)	0.98 (0.96,0.99) 0.01
AVA (cm^2)	0.40 (0.05,1.9) 0.3
Ejection fraction (%)	0.96 (0.90,1.02) 0.1
Valve size (mm)	0.90 (0.80,1.01) 0.09
Bypass time (min)	1.07 (1.03,1.11) 0.001
Cross-clamp time (min)	1.08 (1.02,1.16) 0.01
Concomitant CABG	0.76 (0.44,1.3) 0.3
Concomitant mitral surgery	3.3 (1.0, 8.1) 0.05
Critical state before surgery	3.7 (1.13,9.2) 0.03
Sub-coronary procedure	0.81(0.45,1.62) 0.5
COPD	2.4 (0.93,5.3) 0.07
Diabetes	1.4 (0.73,2.4) 0.3
Renal failure (creatinine › 1.7)	2.2 (1.03,4.2) 0.04
Logistic Euro-score*	81.6 (15.8,357) 0.0001
Charlson's score*	1.5 (1.34,1.9) 0.0001

*Calculated as described in the methods section

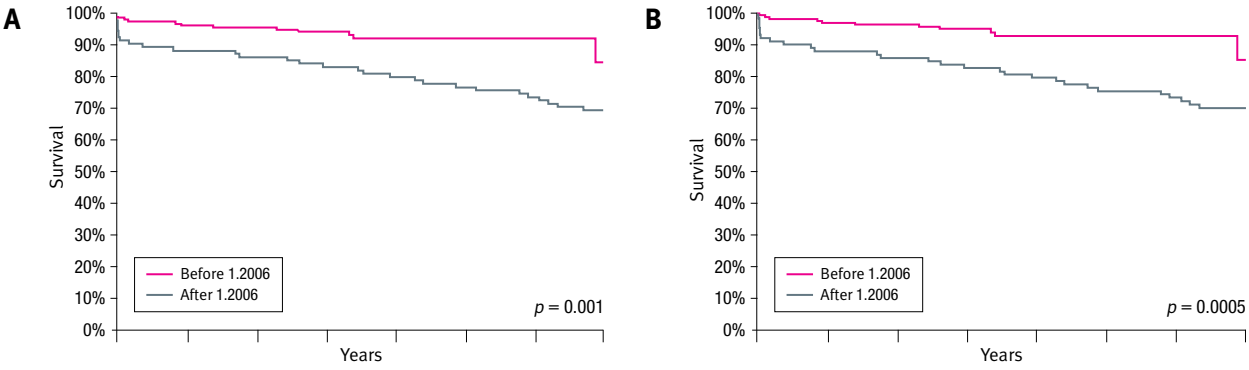
BSA = body surface area, SPAP = systolic pulmonary arterial pressure, AVA = aortic valve area, COPD = chronic obstructive pulmonary disease

Table 3 shows the results of unadjusted Cox proportional hazard analysis for all-cause mortality in all patients. The clinical parameters associated with increased mortality were year of operation after January 2006 (hazard ratio 3.1, 95%CI 1.6–6.3, $P = 0.0009$), older age (HR 1.08, 95%CI 1.04–1.13 for each year, $P = 0.0001$), Charlson comorbidity index (HR 1.5, 95%CI 1.34–1.9 for 1 grade, $P < 0.0001$), Euro-score (HR 1.04, 95%CI 1.03–1.06 for 1 grade, $P < 0.0001$), renal failure defined as creatinine > 1.7 mg/dl (HR 2.2, 95%CI 1.03–4.2, $P = 0.04$), and prior sternotomy (HR 2.7, 95%CI 1.09–5.5,

HR = hazard ratio

Figure 1. [A] Non-adjusted post-interventional survival in patients with severe aortic stenosis undergoing aortic valve replacement with the Freestyle stentless bioprosthesis before January 2006 (pink line) or after January 2006 (gray line). The survival was lower among the first 100 patients who underwent replacement in the first years of the cohort ($P = 0.001$)

[B] Non-adjusted post-interventional survival without need for aortic valve re-replacement in patients with severe aortic stenosis undergoing aortic valve replacement with the Freestyle stentless bioprosthesis before January 2006 (pink line) or after January 2006 (gray line). The survival without need for a second aortic valve surgery was lower among the first 100 patients who underwent replacement in the first years of the cohort ($P = 0.0005$)



Before 1.2006	100	86	84	81	77	74	69
After 1.2006	168	162	141	98	72	46	21

Before 1.2006	100	85	83	80	76	73	68
After 1.2006	168	162	141	98	72	46	21

$P = 0.03$). Presence of liver or pulmonary disease, diabetes, gender, weight or height, and body surface area did not affect mortality rates. The hemodynamic parameters associated with increased mortality were pulmonary hypertension before surgery defined as systolic pulmonary pressure > 50 mmHg (HR 2.2, 95%CI 1.12–3.9, $P = 0.02$), lower trans-aortic peak pressure gradient (HR 0.98, 95%CI 0.97–0.99 for each mmHg, $P = 0.01$), and lower trans-aortic mean pressure gradient (HR 0.98, 95%CI 0.96–0.99, $P = 0.01$). Surprisingly, ejection fraction and aortic valve area before surgery did not have a significant association for long-term mortality. The surgical parameters associated with increased mortality were longer bypass time (HR 1.07, 95%CI, 1.03–1.11 for every 10 minutes, $P = 0.001$), longer cross-clamp time (HR 1.08, 95%CI 1.02–1.16 for every 10 minutes, $P = 0.01$), need for concomitant mitral valve surgery (HR 3.3, 95%CI 1.13–9.2, $P = 0.03$), but not the performance of concomitant CABG or sub-coronary procedure as compared to root replacement.

The association between better survival in patients having surgery after January 2006 remained significant even after adjustment for differences in age and comorbidity (Euroscore and Charlson comorbidity scores) between the cohorts (HR 0.47, 95%CI 0.22–0.95, $P = 0.03$ in favor of the latter group). Furthermore, the overall survival rates in patients implanted after 2006 were excellent (96.4 ± 1.4% and 92.3 ± 2.3 at 1 year and 5 years, respectively) [Figure 1A]. The overall freedom from death or need for second surgery was 96.4 ± 1.4% and 92.4 ± 2.3% at 1 year and 5 years respectively, and significantly improved in the cohort implanted after 2006 [Figure 1B]. Importantly, there was no operative mortality in the 21 octogenarians implanted after January 2006, and their 1 year and 5 year survival rates were excellent as well (95.2 ± 4.6 and 85.1 ± 7.9, respectively).

CABG = coronary artery bypass graft

DISCUSSION

Recently, excellent clinical outcomes and long-term results have been reported with stentless aortic valves [4]. However, despite these data, the proportion of stentless aortic valves in aortic valve surgery practice remains small (≈10%) [12]. The present study analyzed short and long-term outcomes after aortic valve replacement with the Freestyle aortic valve in a large, single-center cohort prospectively followed for up to 15 years.

SHORT AND LONG-TERM OUTCOME

Overall in-hospital mortality was 4.1%, mostly among patients who were in critical condition before surgery or had concomitant procedures. Non-adjusted 5 and 10 year survival rates were 85.0 ± 2.5% and 57.2 ± 5.7, and freedom from death or need for second surgery was 84.7 ± 2.5% and 54.3 ± 5.9% respectively, comparable or better than previously published studies of stentless bioprostheses [4,13]. Importantly, the short and long-term outcomes in patients implanted after 2006 were significantly better than outcomes in the first 100 patients in our cohort, even when adjusting for the differences between the groups, including comorbidity and other confounders, possibly

reflecting the learning curve of the procedure. Furthermore, the present 5 year survival in a small (21 patients) selected cohort of octogenarians with minor comorbidity was excellent, stressing the continued role of aortic valve replacement in selected older patients with minimal comorbidities.

STRUCTURAL VALVE DETERIORATION

The recent increase in the use of aortic bioprostheses, in contrast to mechanical prostheses, among younger patients emphasizes the importance of valve durability [14]. The present study confirms good long-term durability of the Freestyle stentless bioprosthesis, comparable to, and possibly better than the freedom from structural deterioration observed with most currently available stented bioprostheses. Inflammatory and immune responses have been implicated in the degenerative process of bioprostheses [15]. The Freestyle stentless bioprosthesis is a porcine aortic root pretreated with amino oleic acid, an anti-calcification agent shown to reduce porcine leaflet calcification [16]. Our data suggest an attenuated calcification process in the Freestyle valve because only four explanted valves showed significant macroscopic calcium deposition, although our follow-up time was limited to less than 5 years in most patients, limiting the strength of our conclusions. Among patients with structural deterioration, only in one patient was it related to leaflet tear, contradictory to previous reports showing that the major mode of deterioration is leaflet tears, possibly due to the shorter follow-up time in our cohort [4].

PATIENT-PROSTHESIS MISMATCH

The present study also assessed the incidence of severe PPM in Freestyle patients. Patients were stratified according to their indexed aortic valve area on the discharge echocardiogram. In the current cohort, the incidence of severe mismatch (indexed aortic valve area < 0.65 cm^2/m^2) was 6.0%, lower than previous reports [4,17]. In our cohort, predictors of significant PPM were low ejection fraction before surgery, large body surface area, and younger age but not female gender or small prosthesis size. These findings are similar to other studies analyzing the predictors of PPM [18]. The incidence of ≥ mild PPM at discharge varies between 20% and 70% in the literature [17,19] and may be as high as 91% in patients with a small aortic annulus [20]. However, the incidence of ≥ mild PPM was 20% and that of severe mismatch only 6.0% in the present study. The presence of severe PPM is known to be associated with lesser improvement in functional capacity [21], lesser regression of left ventricular hypertrophy [22], and lower survival after aortic valve replacement [17,23]. To minimize the incidence of PPM it is imperative to calculate the minimal effective orifice of the prosthesis to be inserted before the procedure [24,25], to compare it to normal reference tables of effective areas for aortic valve prostheses (projected effective orifice area), and to use one of several solutions, such as aortic root enlargement or choosing a prosthesis model with optimal hemodynamic performance. We show that the Freestyle stentless aortic bioprosthesis indeed provides such optimal hemodynamic performance [9]

LIMITATIONS

Although our study showed that PPM did not adversely impact long-term outcome in patients with Freestyle valves, certain limitations need to be discussed. The small number of patients with severe mismatch was underpowered to show minor although possibly significant differences in outcome between patients with or without severe PPM. Furthermore, it has been suggested that PPM adversely impacts the clinical outcome in young patients, patients with large body surface area or patients with significant left ventricular dysfunction, who constituted a minority among our patients. We believe that further studies addressing the impact of PPM in patients implanted with a stentless valve are required.

The study is observational without a control group and lacks randomization of treatment, limiting the strength of our conclusions. However, the acquisition of wide clinical, as well as echocardiographic data with up to 15 years of follow-up after surgery is a significant strength of our study.

CONCLUSIONS

Aortic valve replacement with the Freestyle bioprosthesis provides good long-term clinical outcomes, even in octogenarians without significant comorbidities, with a low prevalence of patient prosthesis mismatch, excellent post-surgical gradients, and a low rate of reoperation and structural valve deterioration.

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References

1. Pibarot P, Dumesnil JG, Jobin J, Cartier P, Honos G, Durand LG. Hemodynamic and physical performance during maximal exercise in patients with an aortic bioprosthetic valve: comparison of stentless versus stented bioprostheses. *J Am Coll Cardiol* 1999; 34 (5): 1609-17.
2. Doty DB, Cafferty A, Cartier P, et al. Aortic valve replacement with Medtronic Freestyle bioprosthesis: 5-year results. *Semin Thorac Cardiovasc Surg* 1999; 11 (4 Suppl 1): 35-41.
3. Cohen G, Zagorski B, Christakis GT, et al. Are stentless valves hemodynamically superior to stented valves? Long-term follow-up of a randomized trial comparing Carpentier-Edwards pericardial valve with the Toronto Stentless Porcine Valve. *J Thorac Cardiovasc Surg* 2010; 139 (4): 848-59.
4. Mohammadi S, Tchana-Sato V, Kalavrouziotis D, et al. Long-term clinical and echocardiographic follow-up of the freestyle stentless aortic bioprosthesis. *Circulation* 2012; 126 (11 Suppl 1): S198-204.

5. Rahimtoola SH. The problem of valve prosthesis-patient mismatch. *Circulation* 1978; 58 (1): 20-4.
6. Pibarot P, Dumesnil JG. Prosthetic heart valves: selection of the optimal prosthesis and long-term management. *Circulation* 2009; 119 (7): 1034-48.
7. Tasca G, Mhagna Z, Perotti S, et al. Impact of prosthesis-patient mismatch on cardiac events and midterm mortality after aortic valve replacement in patients with pure aortic stenosis. *Circulation* 2006; 113 (4): 570-6.
8. Bleiziffer S, Eichinger WB, Hettich I, et al. Impact of patient-prosthesis mismatch on exercise capacity in patients after bioprosthetic aortic valve replacement. *Heart* 2008; 94 (5): 637-41.
9. Kunadian B, Vijayalakshmi K, Thornley AR, et al. Meta-analysis of valve hemodynamics and left ventricular mass regression for stentless versus stented aortic valves. *Ann Thorac Surg* 2007l; 84 (1): 73-8.
10. Doty DB, Cafferty A, Kon ND, Huysmans HA, Krause AH Jr, Westaby S. Medtronic Freestyle aortic root bioprosthesis: implant techniques. *J Cardiac Surg* 1998; 13 (5): 369-75.
11. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994; 47 (11): 1245-51.
12. Bridgewater B, Kinsman R, Walton P, Gummert J, Kappetein AP. The 4th European Association for Cardio-Thoracic Surgery: adult cardiac surgery database report. *Interact Cardiovasc Thorac Surg* 2011; 12 (1): 4-5.
13. Westaby S, Horton M, Jin XY, et al. Survival advantage of stentless aortic bioprostheses. *Ann Thorac Surg* 2000; 70 (3): 785-90, discussion 90-1.
14. Bach DS. Choice of prosthetic heart valves: update for the next generation. *J Am Coll Cardiol* 2003; 42 (10): 1717-19.
15. Dahm M, Husmann M, Eckhard M, Prufer D, Groh E, Oelert H. Relevance of immunologic reactions for tissue failure of bioprosthetic heart valves. *Ann Thorac Surg* 1995; 60 (2 Suppl): S348-52.
16. Flameng W, Ozaki S, Meuris B, et al. Antimineralization treatments in stentless porcine bioprostheses: an experimental study. *J Heart Valve Dis* 2001; 10 (4): 489-94.
17. Blais C, Dumesnil JG, Baillot R, Simard S, Doyle D, Pibarot P. Impact of valve prosthesis-patient mismatch on short-term mortality after aortic valve replacement. *Circulation* 2003; 108 (8): 983-8.
18. Dumesnil JG, Pibarot P. Prosthesis-patient mismatch: an update. *Curr Cardiol Rep* 2011; 13 (3): 250-7.
19. Ruel M, Al-Faleh H, Kulik A, Chan KL, Mesana TG, Burwash IG. Prosthesis-patient mismatch after aortic valve replacement predominantly affects patients with preexisting left ventricular dysfunction: effect on survival, freedom from heart failure, and left ventricular mass regression. *J Thorac Cardiovasc Surg* 2006; 131 (5): 1036-44.
20. Lopez S, Mathieu P, Pibarot P, et al. Does the use of stentless aortic valves in a subcoronary position prevent patient-prosthesis mismatch for small aortic annulus? *J Cardiac Surg* 2008; 23 (4): 331-5.
21. Pibarot P, Dumesnil JG, Lemieux M, Cartier P, Metras J, Durand LG. Impact of prosthesis-patient mismatch on hemodynamic and symptomatic status, morbidity and mortality after aortic valve replacement with a bioprosthetic heart valve. *J Heart Valve Dis* 1998; 7 (2): 211-18.
22. Tasca G, Brunelli F, Cirillo M, et al. Impact of valve prosthesis-patient mismatch on left ventricular mass regression following aortic valve replacement. *Ann Thorac Surg* 2005; 79 (2): 505-10.
23. Pibarot P, Dumesnil JG. Prosthesis-patient mismatch: definition, clinical impact, and prevention. *Heart* 2006; 92 (8): 1022-9.
24. Bleiziffer S, Eichinger WB, Hettich I, et al. Prediction of valve prosthesis-patient mismatch prior to aortic valve replacement: which is the best method? *Heart* 2007; 93 (5): 615-20.
25. Pibarot P, Dumesnil JG. Hemodynamic and clinical impact of prosthesis-patient mismatch in the aortic valve position and its prevention. *J Am Coll Cardiol* 2000; 36 (4): 1131-41.

Capsule

Cyclic GMP-AMP synthase is an innate immune sensor of HIV and other retroviruses

Retroviruses, including HIV, can activate innate immune responses, but the host sensors for retroviruses are largely unknown. Gao et al. show that HIV infection activates cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) synthase (cGAS) to produce cGAMP, which binds to and activates the adaptor protein STING to induce type I interferons and other cytokines. Inhibitors of HIV reverse transcriptase, but not integrase, abrogated interferon-β induction by the virus, suggesting that the reverse-transcribed HIV DNA triggers the innate immune response. Knockout or knockdown of cGAS in mouse or human cell lines blocked cytokine induction by HIV, murine leukemia virus, and simian immunodeficiency virus. These results indicate that cGAS is an innate immune sensor of HIV and other retroviruses.

Science 2013; 341: 903

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Capsule

Notch2-dependent classical dendritic cells orchestrate intestinal immunity to attaching-and-effacing bacterial pathogens

Defense against attaching-and-effacing bacteria requires the sequential generation of interleukin 23 (IL-23) and IL-22 to induce protective mucosal responses. Although CD4+ and NKp46+ innate lymphoid cells (ILCs) are the critical source of IL-22 during infection, the precise source of IL-23 is unclear. Satpathy et al. used genetic techniques to deplete mice of specific subsets of classical dendritic cells (cDCs) and analyzed immunity to the attaching-and-effacing pathogen *Citrobacter rodentium*. The authors found that the signaling receptor Notch2 controlled the terminal stage of cDC differentiation. Notch2-dependent intestinal CD11b+ cDCs were an obligate source of IL-23 required for survival after infection with *C. rodentium*, but CD103+ cDCs dependent on the transcription factor Batf3 were not. These results demonstrate a non-redundant function for CD11b+ cDCs in the response to pathogens in vivo.

Nature Immunol 2013; 14: 937

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