Eight-Year Results of Freestyle Stentless Bioprosthesis in the Aortic Position: A Single-Center Study of 500 Patients

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Background and aim of the study: **Stentless bioprostheses may be the future valve of choice for aortic valve replacement (AVR). The study aim was to investigate mid-term clinical outcome after AVR with the Medtronic Freestyle valve.**
Methods: **Between April 1997 and November 2004, a total of 500 patients (241 females, 259 males) was implanted with a Freestyle bioprosthesis for AVR, without population selection, by a single surgical team at the authors' institutions. Mean patient age was 74.5 ± 9.6 years (range: 26-91 years); 34 patients (7%) were aged <60 years, 121 (24%) were aged >80 years, and 205 (41%) were in NYHA classes III or IV. The surgical procedure used included a modified subcoronary technique in 482 cases and complete root replacement in 18, conducted with mini-extracorporeal circulation. Concomitant procedures included coronary artery bypass grafting in 123 patients (25%), mitral valve repair/replacement in five, and maze in two. Follow up was 98% complete; the mean follow up was 31.3 months (range: 4-95 months).**
Results: **The mean cardiopulmonary bypass time was 98 ± 26 min, and total aortic cross-clamp time 77 ± 19 min. Operative mortality was 5.2% (n = 26), and no patients aged under 60 years died. At eight years, freedom from structural valve deterioration was 100% (0% in the young population), freedom from endocarditis 97.2%, freedom from reoperation 97%, and overall survival 83%. Most of the late deaths (n = 56) were of non-cardiac origin, and occurred in older patients. After one year, the mean aortic echocardiographic gradient was 11.5 ± 1.1 mmHg, and was improved compared to that at discharge. No significant aortic insufficiency occurred.**
Conclusion: **Use of the Freestyle stentless bioprosthesis for AVR resulted in excellent short-term survival in the octogenarian population, and excellent mid-term results in the younger population. In time, experience will indicate whether the Freestyle should be considered as the bioprosthesis of choice for patients of all ages.**

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Stentless porcine aortic valve prostheses have been proposed to improve clinical outcomes following aortic valve replacement (AVR) due to their good hemodynamics and their expected greater durability. Early clinical studies of stentless valves showed hemodynamic function similar to that of homograft valves (1), and better than that of stented valves (2,3). It has been postulated that the superior physiological performance of this valve would lead to enhanced durability due to less mechanical stress on the leaflet tissue (4). Among the stentless porcine bioprostheses available, the Medtronic Freestyle might present technical advantages. First, the tissue fixation method used employs glutaraldehyde solution at zero net differential pressure, and this retains the natural shape and geometry of the porcine root and the collagen of the leaflets. Second, the Freestyle is treated with alpha-amino oleic acid (AOA), which has been shown in animal studies to limit leaflet calcification (5,6). Taken together, these reasons formed the basis of the authors' choice of the Freestyle bioprosthesis.

The study aim was to evaluate the mid-term clinical outcome and durability of the Freestyle prosthesis implanted in patients of a wide age range.

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Clinical material and methods

Patients

Between April 1997 and November 2004, 500 Medtronic Freestyle aortic prostheses were implanted

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in 500 patients by two surgeons working in two institutions. In order to provide realistic clinical results, the Freestyle valve was used immediately after a choice of bioprosthesis had been made, with no selection on age, left ventricular function, or operative risk.

Operative technique

The Freestyle valve was implanted using the modified subcoronary technique (7) in 482 cases, and as a complete root replacement with coronary artery reimplantation in 18 cases. Cardiopulmonary bypass (CPB) was conducted with a mini-extracorporeal circulation circuit (MECC system, Jostra, France), systemic normothermia, and warm antegrade cardioplegia (8). The Freestyle valve could not be implanted in subcoronary fashion, due to technical contraindications, in 30 patients. These included heavy calcification of the native aortic wall itself and calcifications localized beneath the coronary ostia, both of which compromised the upper suture of the stentless valve. Problems were also encountered in re-do aortic operations where the aortotomy could not always be performed at the preferred location. Displaced coronary ostia were not a contraindication to Freestyle implantation, but rather led to the use of a more precise technique.

Clinical assessment

Patients were assessed clinically by a single investigator, using either a standardized interview or telephone questionnaire. This was designed to assess mortality, current cardiac medications, recurrent cardiac events, hospital and outpatient visits, repeat valve operation, and NYHA functional status.

Postoperative transthoracic echocardiography data were obtained from the referring cardiologists. Peak and mean pressure differences were calculated using the modified Bernoulli equation. The effective orifice area (EOA) was calculated using the continuity equation. Aortic insufficiency (AI) was assessed using color-flow Doppler, and graded as 0 = none, 1 = trace, 2 = mild, 3 = moderate, and 4 = severe.

Operative survivors were followed prospectively; 10 patients (2%) were lost to follow up during the closing interval of September 2004 to March 2005. The mean follow up was 31.3 ± 20.4 months (range: 4 to 95 months); total follow up available for analysis was 1,158 patient-years.

Definitions and statistical analysis

Data acquisition was based on the guidelines for reporting morbidity and mortality after cardiac valvular operations (9). Analyses of survival and time-related events were conducted using the method of Kaplan and Meier.

Table I: Preoperative patient characteristics.

Parameter	No. of patients
Age (years)*	74.5 ± 9.6 (26-91)
≥80	121 (24)
60-79	345 (69)
<60	34 (7)
Gender	
Male	259 (52)
Female	241 (48)
NYHA class	
I/II	295 (59)
III/IV	205 (41)
LVEF	
>40%	445 (89)
<40%	55 (11)
CAD	
None	322 (65)
Significant	178 (35)
Aortic valve lesion	
Stenosis	449 (90)
Insufficiency	46 (9)
Endocarditis	5 (1)
Redo aortic valve surgery	4 (1)

*Mean ± SD (range).
Values in parentheses are percentages.
CAD: Coronary artery disease; LVEF: Left ventricular ejection fraction.

Results

Preoperative patient characteristics are presented in Table I.

The overall mean patient age was 74.5 ± 9.6 years, with 34 patients (7%) aged <60 years and 121 (24%) aged ≥80 years. Although the gender distribution was similar (259 males, 241 females), the proportion of males was greater in the younger group (30/34; 88%), whereas the proportion of females was greater in the older group (74/121; 61%).

Patients were highly symptomatic, with 205 (41%) in NYHA class III or IV. Severe left ventricular dysfunction, defined by a left ventricular ejection fraction (LVEF) <40%, was present in 55 patients (11%).

Preoperative aortic valve lesions included aortic stenosis in 449 patients (90%), aortic insufficiency in 46 (9%), and endocarditis in five (1%).

Operative data

The distribution of Freestyle prosthesis sizes is presented in Table II. A total of 242 (48%) small-diameter prostheses (19 or 21 mm) was used: most of these were implanted in the older-female group. The mean CPB time was 98 ± 26 min (88 ± 15 min for AVR alone),

Table II: Distribution of Freestyle valve sizes implanted.

Valve size (mm)	No. of patients
19	82 (16)
21	160 (32)
23	159 (32)
25	78 (15.5)
27	19 (4)
29	2 (0.5)

Values in parentheses are percentages.

while the mean aortic cross-clamp time was 77 ± 19 min (70 ± 13 min for isolated AVR).

Concomitant coronary artery bypass grafting (CABG) was performed in 123 patients (25%). The remaining patients with coronary disease (10%) did not undergo CABG because the target lesions were either distal or secondary. Other concomitant procedures included mitral valve repair or replacement in five patients, and a modified maze (radiofrequency) in two.

Survival

Twenty-six (5.2%) perioperative deaths occurred either during the initial hospitalization or within 30 days after surgery. No deaths occurred in the younger age group (<60 years), but five of those patients aged >80 years died (4%). There were 56 late deaths (12%). Actuarial survival at five and eight years was 84% and 83%, respectively (Fig. 1).

Late death

Valve-related mortality occurred in 11 patients

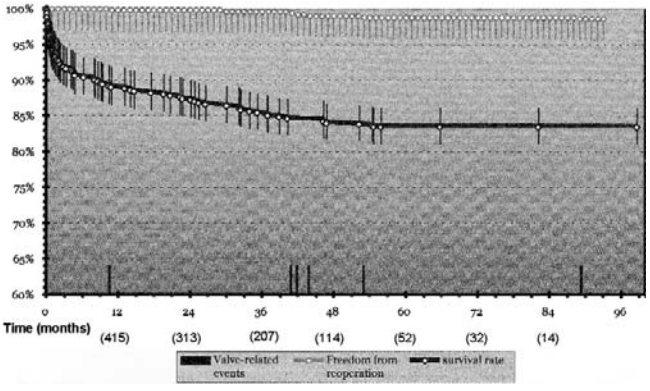

Figure 1: Actuarial survival curve of 500 patients implanted with Freestyle stentless aortic bioprostheses during eight years. Valve-related events are superposed at the bottom of the curve. Numbers of patients at risk are in parentheses. Actuarial freedom from reoperation is shown at the top of the curve.

Table III: Causes of late deaths (n = 56).

Cause of death	No. of patients
Valve-related	
SVD	0 (0)
Thrombosis	0 (0)
Hemorrhage	6 (10.7)
Endocarditis	5 (8.9)
Cardiac-related	
CHF	2 (3.6)
MI	3 (5.4)
Non-cardiac	34 (60.7)
Unknown	6 (10.7)

Values in parentheses are percentages.
CHF: Congestive heart failure; MI: Myocardial infarction; SVD: Structural valve deterioration.

(19.6% of late deaths). Causes of all late deaths are listed in Table III. Valve-related events are superposed on Figure 1.

Thromboembolism

Significant thromboembolic events were not observed during the eight-year follow up period. At the last examination, 19% of patients were taking warfarin only, 40% were taking aspirin only, 5% were taking both (for other medical reasons), and 36% were not receiving any thrombotic or anti-aggregant therapy.

Structural valve deterioration (SVD)

There were no cases of SVD after a maximum follow up of eight years. Notably, no SVD has been identified to date in the younger population, which is screened for valve-related complications.

Endocarditis

Nine patients had bioprosthetic valve endocarditis (three younger patients, five middle-aged, and one octogenarian patient); in three cases this was a recurrence of the initial indication. Two patients died during medical treatment. Among seven patients who were reoperated on, two died perioperatively. One of these patients (aged >80 years) had heavy anatomical lesions and was reoperated on at two months after the initial operation, but died during surgery. The second patient (aged 25 years) was reoperated on at two years after the initial surgery, but died three weeks later from septic multi-organ failure. At eight years, freedom from endocarditis was 97.2%.

Reoperations

Reoperations were performed in 10 patients. At eight years, freedom from reoperation was 97% (Fig. 1).

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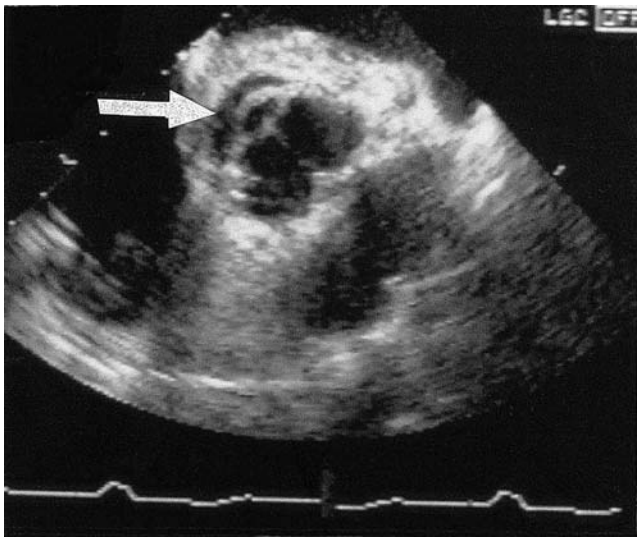

Figure 2: Echocardiographic findings. The arrow indicates the typical clear space introduced between the walls of the native aorta and of the Freestyle valve, when the latter is implanted using the modified subcoronary technique.

Other complications

No patient experienced any significant perivalvular leakage.

Late NYHA class

Among 408 patients contacted at the last follow up, 92% were NYHA classes I or II; there were no patients in class IV.

Echocardiography

Peak and mean systolic gradients across the aortic valve were both significantly decreased at the last examination compared to that at discharge. During the follow up period, and including all living patients, the mean pressure difference across the aortic valve decreased from 15.8 ± 2.2 mmHg to 11.5 ± 1.1 mmHg ($p < 0.03$).

Hemodynamic data according to valve size implanted are presented in Table IV (only subcoronary patients were included in order to obtain homogeneous data). The results provided mean gradients and EOAs at hospital discharge and later, at the final examination. This may help to anticipate an eventual prosthesis-patient mismatch, which occurs when the EOA:body surface area (BSA) ratio is <0.85 cm^2/m^2, when using the Freestyle valve. Typically for stentless bioprostheses, the hemodynamics improve during the first postoperative year and then stabilize.

There were 30 patients with grade 1 aortic insufficiency (AI), and five with grade 2; there were no significant occurrences of AI.

It is important to note that most echocardiographic examinations revealed a clear space in the non-coronary sinus; this was related to the double layer between the native aortic wall and the Freestyle wall when the bioprosthesis is implanted using the modified subcoronary technique. On occasion, this image may be wrongly identified as an abscess, with dramatic consequences for any subsequent treatment (Fig. 2).

Discussion

Despite many investigations having been conducted, the ideal aortic valve substitute remains elusive. The currently used mechanical prostheses are simple to implant and provide good hemodynamics if small-sized valves are avoided, but they continue to require formal anticoagulation with its inherent rules and bleeding risks. Biological prostheses have intrinsically low thrombogenicity but have shorter durability than mechanical prostheses, particularly in patients aged <60 years (4,10). Stented biological prostheses have higher transvalvular gradients when used in smaller sizes (4), as is the case for mechanical valves.

Two solutions have been proposed in an attempt to overcome these problems. First, significant efforts have been made to optimize hemodynamics with the new diameter-enhanced prostheses such as the St. Jude Medical HP for mechanical prostheses, or the

*Table IV: Hemodynamic data. Echocardiographic gradient (mmHg) and effective orifice area (EOA; cm^2) according to valve size.**

Valve size (mm)	At discharge		At check-point	
	Gradient	EOA	Gradient	EOA
19	20.4 ± 7.1	1.11 ± 0.23	14.8 ± 6.5	1.16 ± 0.24
21	16.2 ± 5.9	1.48 ± 0.29	12.6 ± 4.6	1.57 ± 0.38
23	14.3 ± 5.3	1.59 ± 0.36	11.2 ± 4.2	2.10 ± 0.40
25	12.6 ± 4.5	1.81 ± 0.61	9.6 ± 5.1	2.01 ± 0.43
27	10.5 ± 3.2	2.51 ± 0.42	8.3 ± 2.9	2.39 ± 0.10

*Only subcoronary implants were considered (n = 482), in order to obtain homogeneous data.

Mitroflow for pericardial bioprostheses. Second, stentless aortic valves have been developed which take advantage of the physiological nature of homograft valves, with a more standardized method of implantation. Clinical studies have shown residual transvalvular gradients to be similar to those of native valves and more favorable than for stented valves, particularly under exercise conditions (1,3,11). The Toronto stentless porcine valve was introduced in 1988 (12), and long-term results are now available (13,14). Clinical results were excellent for early and mid-term follow up, and hemodynamic data were as good as expected (15). Nevertheless, a significant increase in hazard for SVD occurred in late follow up (14).

The Medtronic Freestyle was introduced in 1992, with certain technical specificities leading to a higher durability. During production, the Freestyle valve is crosslinked in dilute glutaraldehyde solution using a zero-pressure tissue fixation method (low-pressure fixation causes significant loss of transversal cuspal ridges and collagen crimping) (5). In addition, the Freestyle is treated with AOA, which has been shown in animal studies to mitigate porcine leaflet calcification (6). The intended consequence of this process to achieve better results than with the Toronto stentless valve (16).

The results of these studies have confirmed good outcomes for the Freestyle bioprosthesis, although the follow up is generally recognized as being too short (7,17). In this respect, the results of the present study were encouraging with regard to clinical or hemodynamic data over an eight-year follow up. The strength of this series was related to the absence of any selection of patients; all patients requiring a bioprosthesis have been implanted with a Freestyle valve since 1997, unless this was contraindicated due to technical difficulties. The modified subcoronary technique was mainly preferred as the Freestyle was used as an alternative to a stented bioprosthesis, while the surgery had to be comparable in order to be accepted. Root replacement was impractical for most cases, particularly among the older population, and was reserved for classical indications and for younger patients with a small annulus size in order to offer them an optimal EOA. In the present series, echocardiographic measurements confirmed the excellent hemodynamic results of the Freestyle valve at follow up examination, with high in-vivo values of EOA, even for small-sized valves. The early mortality among the octogenarian group (4%) was excellent, though this was most likely related not only to the very low proportion of patient-prosthesis mismatch (PPM), but also to the good hemodynamic profile of the stentless valve in this population, in which many small-sized valves were implanted. PPM has been shown to be a strong factor for mortality (18-21), and the hemodynamic benefits of the Freestyle valve have in most cases eliminated PPM as a risk factor (22). With regard to those patients aged >75 years in the present series, PPM evaluation based on an EOA measured in vivo confirmed the small proportion of patients involved, even among the 19- and 21-mm valve group. In this small group, early mortality was significantly greater than in the overall population, thereby confirming that PPM should be considered as a factor for mortality. Unfortunately, patient numbers in the present study were too low to be statistically relevant and to develop this topic further.

One further point for consideration is that of younger patients, aged <60 years. All studies with stented bioprostheses have shown early significant rates of SVD at this age (4,10,15), though Freestyle valves would be expected to offer better results in terms of their technical specificities. The Freestyle valve may represent an alternative to a homograft in young patients, though to date only one study has reported encouraging results in this respect (23). In the present series, although no patient aged <60 years experienced SVD, the longest available follow up was only eight years. When young patients request a bioprosthesis to be implanted, the Freestyle valve should be considered, since the risk for eventual reoperation is known to be similar to that for primary AVR (24). In this young (and often very active) population, a full root replacement might be the better option when the annulus size is <23 mm, in order to ensure optimal hemodynamics in these physically demanding patients (25).

In conclusion, an analysis of 500 non-selected patients implanted with a Freestyle aortic stentless bioprosthesis during the past eight years showed very encouraging results for patients of all ages. The prolonged surgical implantation time did not compromise early mortality among octogenarians; rather, the results obtained were some of the best reported to date. However, confirmation of the Freestyle as a justifiable alternative to a homograft in young patients will require a further five years of follow up.

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