Survival after stentless and stented xenograft aortic valve replacement: a concurrent, case-match trial

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Key words:
Aorta; Prosthesis; Surgery; Survival; Valves.

Background. **In order to compare the long-term outcome of stented vs stentless aortic xenografts, a non-randomized, concurrent case-match trial was conducted on all consecutive patients operated between January 1992 and April 2000.**

Methods. **Two hundred and ninety-two patients had stented (group 1) and 376 stentless (group 2) xenograft aortic valve replacement (AVR). Group 1 patients were older (75.0 ± 4.1 vs 70.4 ± 6.7 years, p = 0.01), while male gender and aortic stenosis were equally prevalent. NYHA functional class III-IV (85 vs 78%, p = 0.03) and associated procedures (53 vs 41%, p = 0.01) were more common in group 1. The aortic cross-clamping (79.7 ± 27.8 vs 96.1 ± 23.3, p = 0.001) and bypass (91.4 ± 57.5 vs 128.5 ± 34.0, p = 0.002) times were shorter in group 1. A case-match analysis identified 113 identical patient pairs, on the basis of age, gender, diagnosis, NYHA class, associated cardiac disease, and valve size.**

Results. **The early mortality was higher in group 1 (5.3 vs 2.7%, p = 0.3), though not significantly. During follow-up (37 ± 30 vs 43 ± 35 months, p = 0.6), 26 late deaths were recorded (10.3 vs 13.6%, p = 0.4). The 8-year survival was comparable (76 ± 7 vs 75 ± 5%, p = 0.2), but freedom from cardiac (77 ± 7 vs 90 ± 4%, p = 0.02) and from valve-related death (78 ± 7 vs 91 ± 4%, p = 0.02) was higher in group 2. Freedom from structural deterioration (99 ± 1 vs 98 ± 2%, p = 0.7) and from reoperation (99 ± 1 vs 95 ± 3%, p = 0.2) at 8 years was similar. The late functional status was equally satisfactory (NYHA class I-II 92.7 vs 94.7%, p = 0.06).**

Conclusions. **The survival free from cardiac and valve-related mortality when stentless xenografts for AVR are used is superior to that achieved with stented grafts. Stentless AVR has the potential of conferring selective survival advantages late after operation.**

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Introduction

Stentless aortic xenografts have been introduced a decade ago in an attempt to overcome the major shortcomings associated with stented bioprostheses, namely their limited durability and suboptimal hemodynamic behavior[1]. Comparative outcome analysis of stentless and stented xenografts has thus far been carried out almost exclusively by retrospective, non-randomized studies[2-5]. Several reasons explain the paucity of prospective, randomized trials, including: the need of mastering the technique of implantation, the limitations imposed by the aortic root pathology (calcification, dilation, coronary artery anomalies), the necessity of minimizing the grafting time in the presence of left ventricular dysfunction or associated cardiac disease, the variety of stentless valve models put onto the market.

One of the methods recently proposed as a means of mitigating the bias introduced by retrospective studies is case-match analysis. In a work by David et al.[6], stentless aortic xenografts have been associated with a durability similar to that of stented valves, but with a greater survival and freedom from adverse cardiac events. Short of the latter work comparing Toronto SPV with Hancock II bioprostheses, however, no other case-match trial has been reported. An analysis of the outcome after xenograft aortic valve replacement (AVR) in 668 consecutive patients has been undertaken in an attempt to validate these findings and to extend them to other models of stentless valves.

Methods

Patient population. All consecutive patients undergoing AVR with a porcine xenograft at the University of Verona between January 1992 and April 2000 were included in the present non-randomized, concurrent control

trial. The selection criteria for a bioprosthesis during the study interval were: 1) age > 65 years; 2) contraindications to oral anticoagulant therapy; 3) a specific request for a biological valve by the patient. When the decision to replace the aortic valve with a xenograft was reached, the ultimate choice between a stented (group 1) or freehand stentless (group 2) valve was left to the surgeon. The only model of stented porcine bioprosthesis used during the study period was the Hancock II valve (Medtronic, Inc., Minneapolis, MN, USA). Starting in July 1992, five different models of stentless porcine bioprosthesis were used during the study interval. Three models, including the Biocor PSB valve (Biocor Industria e Pesquisa Ltda, Belo Horizonte, MG, Brazil), the Toronto SPV valve (St. Jude Medical, Inc., St. Paul, MN, USA) and the Cryolife-O'Brien valve (Cryolife, Inc., Atlanta, GA, USA), comprised 99% of the stentless bioprostheses employed. The remaining two models (Baxter Prima Plus, Baxter Health Care Inc., Irvine, CA, USA, and Medtronic Freestyle, Medtronic, Inc., Minneapolis, MN, USA) were utilized in a minority of patients. The choice of the type of stentless valve to implant was made by the surgeon in a non-random fashion.

Operative technique. Porcine xenograft valve replacement was performed with the aid of moderately hypothermic cardiopulmonary bypass. Prior to 1994, crystalloid cardioplegia was used for myocardial protection. Thereafter, blood cardioplegia was routinely employed. When associated bypass grafting was required, distal coronary anastomoses were completed prior to AVR. In case of an associated mitral operation, this was performed after aortic valve excision and prior to insertion of the xenograft. Aortic root procedures were carried out simultaneously with the implant of the xenograft, whereas ascending aortic repair was performed after valve grafting. The technique of stentless valve implant was freehand, subcoronary grafting using inflow and outflow suture lines for all xenograft models, except for Cryolife-O'Brien valves. The latter were implanted in a subcoronary, supra-annular position with a single suture line. Stented xenografts were anchored to the native aortic annulus by means of interrupted pledget-reinforced sutures.

Case-match. Since the disparity in baseline demographic and operative variables between the two patient groups may have influenced the clinical outcome, a case-match analysis was conducted in order to isolate homogeneous pairs of patients. Pairs were identified on the basis of six criteria: age, gender, diagnosis, associated cardiac disease, NYHA functional class, and size of the porcine bioprosthesis.

Anticoagulant therapy. Oral anticoagulation was adopted for patients undergoing stented AVR during the first 3 postoperative months and discontinued thereafter. No anticoagulation was used in patients having stentless AVR. Routine oral antiplatelet therapy was adopted in patients with associated vascular (i.e. coronary or carotid artery) lesions.

Follow-up methods. Cross-sectional patient follow-up was completed between February and April 2000 by means of in-hospital clinical assessment and telephone interview, carried out by non-blinded medical personnel. Four (0.6%) patients were lost to follow-up investigation.

Statistical analysis. Continuous variables were expressed as means ± SD. Categorical variables were expressed as percentages. Comparison of continuous variables was performed using the two-tailed Student's t-test for paired data and that of discrete variables using the Pearson χ^2 or Fisher exact test, as appropriate. Time-related events were described using the Kaplan-Meier estimate and compared with the log-rank analysis. Linearized rates were used for repeated valve-related complications and were expressed as percent per patient-years. Endpoints of the study included: survival, and survival free from cardiac death, valve-related death, structural valve deterioration, and reoperation on the xenograft. Significance was inferred at a p value < 0.05. Multivariate analysis was performed using the Cox proportional hazards method to identify risk factors for the time-related occurrence of events after AVR, including: overall mortality, cardiac mortality, and valve-related mortality. The variables entered in the analysis were: age, sex, body surface area, diagnosis, prior aortic procedure, associated coronary artery disease, other associated cardiac disease, NYHA functional class, aortic annulus diameter, size of xenograft valve, type of prosthetic device, model of stentless xenograft, aortic cross-clamping time, cardiopulmonary bypass time, and duration of intensive care stay. Definitions of events were established according to previously recommended guidelines[7].

Results

Patient population (Tables I and II). Six hundred and sixty-eight consecutive patients underwent porcine xenograft AVR during the study period: 292 received stented (group 1) and 376 stentless valves (group 2). Comparison of baseline demographic and operative variables in the overall population disclosed significant disparities between the two patient groups. The average age was older and the prevalence of severe cardiac symptoms (NYHA class III or IV) greater in patients receiving stented valves. Prosthetic valve dysfunction as an indication to AVR was more common among patients having stented, while mixed aortic lesions was more prevalent among those having stentless xenografts. Lastly, the duration of aortic cross-clamp and cardiopulmonary bypass was longer among patients receiving stentless xenografts, despite the greater prevalence of associated disease requiring concomitant repair among patients with stented xenografts. Patholo-

Table I. Demographic and operative variables of the entire population.

	Group 1	Group 2	p
No. patients	292	376	
Age (years)	75.0 ± 4.1	70.4 ± 6.7	0.01
Male gender	146 (50%)	195 (52%)	0.6
NYHA class III-IV	248 (85%)	294 (78%)	0.03
Aortic stenosis	203	241	0.1
Aortic regurgitation	54	75	0.5
Mixed lesions	21	55	0.003
Prosthetic valve dysfunction	14	5	0.005
Type of xenograft valve	Hancock II, 292	Toronto SPV, 164 Biocor PSB, 106 Cryolife-O'Brien, 101 Other, 5	
Average valve size (mm)	23.2 ± 1.4	24.9 ± 2.9	0.6
Aortic cross-clamping time (min)	79.7 ± 27.8	96.1 ± 23.3	0.001
Cardiopulmonary bypass time (min)	91.4 ± 57.5	128.5 ± 34.0	0.002
Associated procedure:	154 (53%)	153 (41%)	0.01
CABG	86	100	0.4
MVR/repair	35	32	0.1
Aortic operation	49	20	0.001
Other	4	6	0.9

CABG = coronary artery bypass graft; MVR = mitral valve replacement.

Table II. Demographic and operative variables of the case-matched population.

	Group 1	Group 2	p
No. patients	113	113	
Age (years)	73.7 ± 4.1	73.1 ± 4.9	0.3
Male gender	54 (48%)	54 (48%)	1
NYHA class III-IV	89 (79%)	89 (79%)	1
Aortic stenosis	85	85	1
Aortic regurgitation	9	9	1
Mixed lesions	19	19	1
Type of xenograft valve	Hancock II, 113	Biocor PSB, 46 Toronto SPV, 37 Cryolife-O'Brien, 28 Other, 2	
Average valve size (mm)	23.8 ± 1.4	23.8 ± 1.4	1
Aortic cross-clamping time (min)	79.9 ± 30.4	94.9 ± 22.2	0.001
Cardiopulmonary bypass time (min)	114.0 ± 40.3	125.8 ± 27.7	0.03
Associated procedure:	50 (44%)	50 (44%)	1
CABG	38	38	1
MVR/repair	9	9	1
Aortic operation	2	2	1
Carotid endarterectomy	1	1	1

CABG = coronary artery bypass graft; MVR = mitral valve replacement.

gy of the aortic root and ascending aorta was primarily responsible for the higher prevalence of associated procedures. Having identified 113 homogeneous patient pairs, comparison of demographic and operative variables showed significant differences only for the duration of aortic cross-clamp and cardiopulmonary bypass. Therefore, as the prevalence and type of associated cardiac disease was one of the case-match parameters identical in the two groups, the longer grafting time for stentless aortic xenografts resulted in a longer duration of myocardial ischemia and extracorporeal perfusion.

Survival. The in-hospital mortality in the 226 patients identified by case-match analysis was 4.0% (9/226). The in-hospital mortality among patients having stented AVR was 2-fold greater than in patients having stentless valves (6/113, 5.3% vs 3/113, 2.7%), but the estimate did not reach significance due to the smaller number of events (p = 0.3). The average follow-up in the two groups was comparable (37 ± 30 vs 43 ± 35 months, p = 0.6). There were 26 late deaths (11.9%): no difference was observed between the two patient groups (11/107, 10.3% vs 15/110, 13.6%, p = 0.4). The overall mortality was

nearly identical in the two case-matched groups (17/113, 15.0% vs 18/113, 15.9%, p = 0.9): cardiac death was the leading cause of overall mortality and significantly more prevalent among patients with stented xenografts (15/113, 13.3% vs 6/113, 8.8%, p = 0.04). Therefore, the actuarial survival at 1, 5 and 8 years was similar in the two groups (91 ± 3, 82 ± 5, 76 ± 7 vs 97 ± 2, 87 ± 3, 75 ± 5%, p = 0.2) (Fig. 1). However, freedom from cardiac death (92 ± 3, 85 ± 4, 77 ± 7 vs 97 ± 2, 94 ± 3, 90 ± 4%, p = 0.02) at the same time intervals, was significantly higher among patients having stentless xenografts (Fig. 2). Freedom from valve-related death was also higher among recipients of stentless valves (93 ± 3, 86 ± 4, 78 ± 7 vs 97 ± 2, 96 ± 2, 91 ± 4%, p = 0.02) (Fig. 3).

Xenograft deterioration and reoperation. Structural valve deterioration at 1, 5, and 8 years was comparable in the two case-matched groups (100, 99 ± 1, 99 ± 1 vs 100, 100, 98 ± 2%, p = 0.7). Reoperation on the xenograft was necessary in 1 (endocarditis) group 1 and in 4 (3 non-structural deterioration, 1 structural deterioration) group 2 patients. Thus, freedom from reoperation on the valve at 1, 5 and 8 years was lower in group 1 patients, although not significantly (100, 99 ± 1, 99 ± 1 vs 98 ± 1, 97 ± 2, 95 ± 3%, p = 0.2). Cases of non-structural deterioration were all clustered among recipients of one stentless valve model (Cryolife-O'Brien). All patients but one, who was submitted to emergent reoperation for a failed stentless valve at a near-by hospital, survived replacement of the dysfunctional xenograft.

Other valve-related adverse events. The linearized rates of hemorrhage (0.3 vs 0.2%/patient-years, p = 0.9) and endocarditis (0.4 vs 0%/patient-years, p = 0.2) were not significantly different, while that of embolism

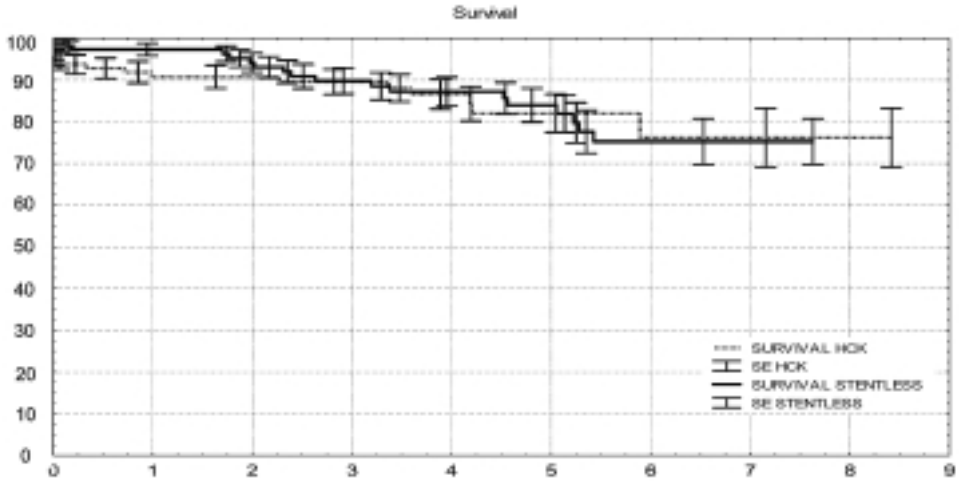

Figure 1. *Survival of 226 patients undergoing xenograft aortic valve replacement at the University of Verona between January 1992 and April 2000. The* solid line *indicates the survival of 113 patients receiving stented xenografts. The* broken line *indicates the survival of 113 patients receiving stentless xenografts. Error bars depict the standard error (SE) of the mean. Patients at risk are reported on the x-axis (p = 0.2).*

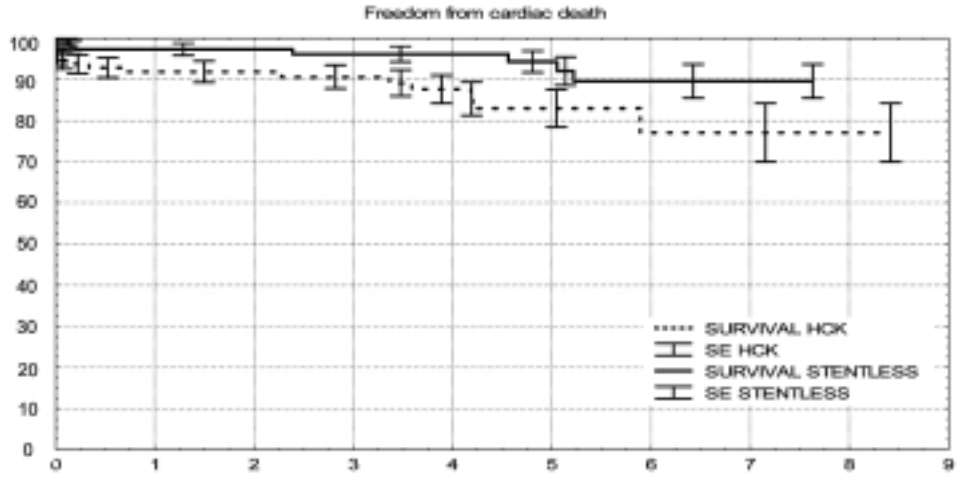

Figure 2. *Freedom from cardiac death of 226 patients undergoing xenograft aortic valve replacement at the University of Verona between January 1992 and April 2000. The* solid line *indicates the survival of 113 patients receiving stented xenografts. The* broken line *indicates the survival of 113 patients receiving stentless xenografts. Error bars depict the standard error (SE) of the mean. Patients at risk are reported on the x-axis (p = 0.02).*

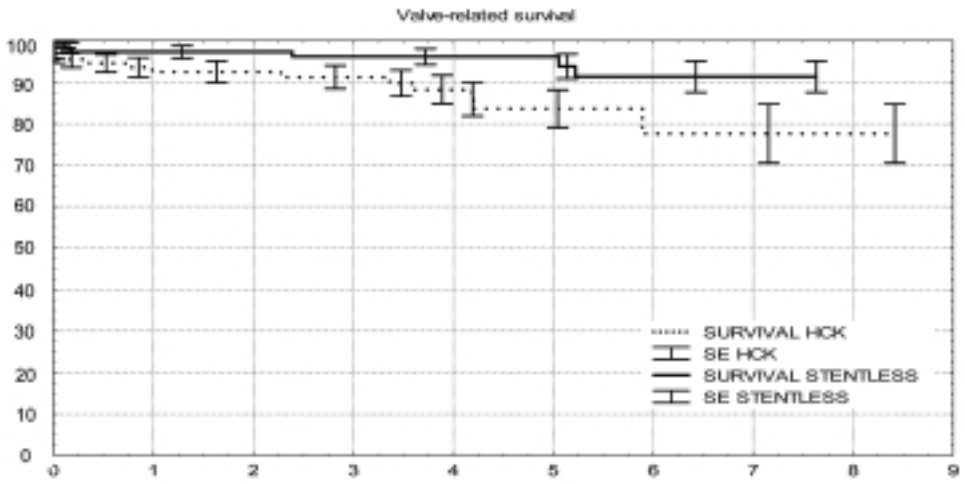

Figure 3. *Freedom from valve-related death of 226 patients undergoing xenograft aortic valve replacement at the University of Verona between January 1992 and April 2000. The* solid line *indicates the survival of 113 patients receiving stented xenografts. The* broken line *indicates the survival of 113 patients receiving stentless xenografts. Error bars depict the standard error (SE) of the mean. Patients at risk are reported on the x-axis (p = 0.02).*

was lower in recipients of stentless valves (0.7 vs 0%/patient-years, p = 0.06).

Functional outcome. At follow-up, the clinical conditions of long-term survivors were equally rewarding with 89 (92.7%) of group 1 and 90 (94.7%) of group 2 patients in NYHA class I or II (p = 0.06).

Discussion

Since the durability of stentless valves has not proved to be longer than that of stented prostheses[6], the late survival after operation has become the primary focus of clinical research[3-5]. With regard to the timing and extent of regression of left ventricular hypertrophy early after AVR, an enormity of data has shown distinct hemodynamic advantages of stentless xenografts[8-10]. Although uncertainty remains about the possibility that such changes be maintained over time, great effort has been devoted to the demonstration that a more physiologic behavior of the valve would translate into enhanced survival[2-6]. To date, however, conclusive evidence on the survival advantages of stentless xenografts over stented is not available due to the lack of long-term prospective, randomized trials. Explanations for the paucity of prospective studies include: the technical demands of stentless valve surgery, the restrictions imposed by pathology of the aortic root (dilation, calcification, anomalies of the coronary ostia), the concern regarding the longer grafting time, particularly in the presence of a failing left ventricle, and the great variety of stentless valve models.

Several retrospective clinical observations comparing stentless xenografts with stented ones have shown a superior survival and freedom from valve-related adverse events with the former[2-5]. The results of a simple retrospective comparison performed at our institution and reported elsewhere[11] are in line with previous studies. Similar to a prior work[2], however, bias in the selection of patients assigned to the two valve substitutes is highlighted by the different profile of the two populations. Patients receiving stented xenografts are older and more commonly present with advanced cardiac failure and associated disease than those having stentless valves. To reduce the impact of such disparities on survival, David et al.[6] have proposed a case-match study in which they identified homogeneous patient pairs on the basis of age, NYHA class, the left ventricular ejection fraction, and the presence of coronary artery disease. These variables have all been recognized as influencing the long-term survival after AVR with stented bioprostheses[12]. Since elderly individuals with senile aortic stenosis represent the vast majority of patients in the series herein, the use of left ventricular ejection fraction as a parameter for the description of the severity of cardiac disease would have been inadequate[13]. Consequently, homogeneous pairs of patients in the present study have been isolated by matching age, gender, diagnosis, NYHA class, presence and type of associated cardiac disease, and size of bioprosthesis.

In the work by David et al.[6], a superior overall survival, freedom from cardiac death and valve-related morbidity have been shown among survivors of Toronto SPV stentless valve placement compared with those observed following Hancock II stented valve insertion. The findings in the current study partly agree with these observations, as the survival free from cardiac and from valve-related death was greater among recipients of stentless valves, but the overall survival was similar in the two patient groups. Reasons which may account for this difference include the higher prevalence of associated cardiac disease (32 vs 44% of patients), the inclusion of patients with associated mitral, aortic and carotid artery disease, the inclusion of the in-hospital mortality, and the older average age (62 vs 73 years) in

the present series. The latter factor has relevant implications, as Del Rizzo et al.[3] have shown that the survival advantage of stentless bioprostheses is most prominent in younger patients (< 60 years) and diminishes with advancing age.

The present is the first case-match trial supporting the observations by David et al.[6] on the Toronto SPV stentless xenografts and extending these findings to older patients and to other models of stentless valves (Biocor PSB, Cryolife-O'Brien). These results lend support to the comparative analysis of the mid-term outcome with the three xenograft models previously carried out at our institution[14]. A prior work by Del Rizzo et al.[8] has shown the hemodynamic advantages of the Toronto SPV valve. A similar behavior has been documented after AVR using the Biocor PSB[4] and the Cryolife-O'Brien valves[15]. Common to most stentless xenograft models is the property of enhancing the regression of left ventricular hypertrophy to a greater extent than stented bioprostheses, as two recent prospective, randomized trials have proved[9,10]. The larger effective orifice area of stentless valves, when compared to stented ones of the same external diameter (i. e. a lower incidence of prosthesis-patient mismatch)[16], may account for the more thorough regression of left ventricular hypertrophy after operation[17]. As ventricular hypertrophy has since been associated with an increased cardiac mortality[18], the most credited hypothesis is that the unique hemodynamic properties of stentless xenografts are responsible for the observed greater survival free from cardiac death. Additional reasons, however, explain the selective survival advantage of stentless valves in the current study. In fact, a sizable proportion of cardiac casualties have been caused by valve-related events. In particular, as previously found by others[4,5], the rate of embolic complications, including lethal ones, has proved to be higher among recipients of stented xenografts. Whether the lower thrombogenicity of stentless valves or, simply, the unsatisfactory control of blood anticoagulation in patients with stented valves is responsible for this result awaits verification. On the basis of the current findings, the survival advantage conferred by stentless xenografts is due not only to the more favorable impact of the valve on left ventricular function and remodeling, but also to the lower morbidity related to the prosthetic device *per se*.

The expectation of a durability longer than that of stented bioprostheses has thus far been dissatisfied. Similar to the observations by David et al.[6], the present case-match trial confirms that structural deterioration affects all xenografts, whether stentless or stented, at the same rate, albeit still low 8 years after implant. A series of explanations may account for this finding, including: an incorrect hypothesis underlying the causes of degeneration of bioprostheses; the instability of the anatomic substrate where stentless valves are grafted; the detrimental impact of technical factors related to stentless valve surgery; the substantial improvement in durability of second-generation stented bioprostheses. The original observation that freehand-sewn aortic homografts have proved less prone to structural deterioration than stent-mounted ones has led to the anticipation that freehand stentless xenografts would outlast stented bioprostheses[1]. The hypothesis entertained was that the greater resemblance to the native aortic valve anatomy and physiology would minimize shear stress on the leaflets, a factor recognized among the primary causes of tissue valve degeneration[19]. It is possible that this hypothesis may not be correct and that other factors, such as an immune response to the xenograft (therefore irrespective of valve design), play a predominant role. Moreover, the functional properties of stentless valves are strictly dependent on the integrity of the aortic valve-root complex, as the prosthesis is anchored to the native aortic root. Jin and Westaby[20] have shown how progressive dilation of the sinotubular junction, which frequently occurs with aging, causes progressive prosthetic valve insufficiency due to reduced leaflet coaptation. Dysfunction of the stentless valve may, in turn, be associated with an increased shear stress and premature xenograft deterioration. A prior work from our institution has shown that, contrary to what occurs with stented bioprostheses, deterioration of stentless valves manifests with progressive stiffening and rupture, often abrupt, of the leaflets at the commissures, in the absence of calcification[21]. In addition, the modality and rate of degeneration are identical with the three different valve models: Toronto SPV, Biocor PSB and Cryolife-O'Brien[21]. Therefore, there may be a single mechanism leading to failure, common to most stentless xenografts, which reflects the prosthetic valve design. This would be suggested by the morphologic findings of degenerated xenografts. As a corollary, it follows that even minor mishaps with the implant technique, often undetected at the time of operation, may translate into relevant valve dysfunction with time[22]. This finding is again specific for stentless xenografts and will obviously not affect stent-mounted bioprostheses. Lastly, a growing body of evidence has shown that the durability of second-generation stented xenografts has dramatically improved, possibly due to low-pressure fixation and antimineralization treatment of the leaflets[12,23]. When considered as a whole, and added to the observation that non-structural deterioration may be more commonly due to the greater complexity of surgery[13,24,25], it is not surprising that freedom from valve failure with stentless valves has not proved more satisfactory than with stented ones.

Survival free from reoperation on the valve is not a valid endpoint to compare the durability of stentless and stented xenografts. Given the slowly progressing nature of transprosthetic obstruction in deteriorated stented bioprostheses, the decision to intervene may often be deferred. On the contrary, degeneration of stentless valves is less predictable and the volume overload consequent to prosthetic valve regurgitation is poorly

tolerated by a non-compliant left ventricle, such as is found in senile aortic stenosis. Therefore, at the time of diagnosis replacement of a failing stentless valve must be promptly scheduled. The importance of elective planning is evident from the current and prior work[21], showing a significantly higher mortality for emergent procedures. The influence of clinical experience is also apparent, as the operative risk may be significantly less at centers where aortic root surgery has been performed for a long time.

Similar to the findings on freedom from structural valve failure and reoperation, the functional status late after implant does not allow one to distinguish between stentless and stented xenografts. Both types of prostheses are associated with satisfactory clinical conditions, even in case of an elderly population commonly affected by associated cardiac disease, such as the one herein. This result confirms those of previous studies on stentless and stented valves[2,4,5,12,23]. However, it seems at odds with the superior hemodynamic behavior demonstrated for stentless xenografts[9,10,16], which could in theory be associated with an improved clinical status. Restrictions inherent to the NYHA functional classification, particularly its subjective nature, and the advanced patient age may conceivably account for this divergence.

Limitations. The present study has several limitations. In spite of the case-matching, the aortic cross-clamping and cardiopulmonary bypass times were longer among patients with stentless valves. Since implant of the latter is more demanding, matching patients according to the perfusion variables would have implied a higher prevalence of associated disease requiring treatment among recipients of stented bioprostheses. On the basis of previous evidence[12], it was decided that associated cardiac disease would more profoundly influence survival than the duration of myocardial ischemia or extracorporeal perfusion. A second limitation is that three stentless valve models are simultaneously compared to one stented valve model. This, associated to the small sample size could weaken the conclusions of the study. However, the possibility of extending the observations on the Toronto SPV valve to other prostheses may at the same time constitute the originality of the current analysis. On the basis of the premise that the functional behavior is similar with different stentless valve models, the present work confirms that the clinical outcome may also be equally favorable. Lastly and most notably, the study herein only partly overcomes the limitations inherent with simple retrospective comparison. In theory, only prospective, randomized long-term trials will provide rigorous information on comparative clinical outcomes.

In conclusion, the present case-match trial demonstrates that stentless aortic xenografts may confer selective advantages in terms of survival free from cardiac and from valve-related mortality when compared with stented ones. Since the freedom from valve deterioration is similar, extension of stentless AVR to any patient without anatomic contraindications deserves further consideration.

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