

Aspire Porcine Bioprosthesis: Ten Years' Experience

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Background and aim of the study: Clinical results of this multicenter study of the Aspire porcine valve were reported previously at eight years; the present report provides an update of valve performance to 10 years postoperatively.

Methods: A total of 749 patients (60% males; mean age 73 ± 7 years) underwent implantation with the Aspire (Tissuemed) porcine bioprosthesis between 1991 and 2002, at three institutions. Follow up was complete for 98% of the cohort. The mean follow up period was 51.6 ± 39.6 months (range: 0-181 months); total follow up was 3,159 patient-years (pt-yr).

Results: There were 617 aortic valve replacements (AVR), 96 mitral valve replacements (MVR) and 32 double valve replacements. There were 62 deaths (8.3%), one of which was valve-related. The late mortality rate was 9.3% per pt-yr (1.2%/pt-yr valve-related). Actuarial freedom from complications at 10 years was: thromboembolism $76 \pm 4\%$ (2.6%/pt-yr); hemor-

rhage $73 \pm 4\%$ (2.8%/pt-yr); structural valve deterioration (SVD) $96 \pm 2\%$ (0.2%/pt-yr); non-structural deterioration $99 \pm 1\%$ (0.1%/pt-yr); prosthetic valve endocarditis $97 \pm 1\%$ (0.3%/pt-yr); and reoperation $97 \pm 1\%$ (0.4%/pt-yr). In patients aged >70 years, the 10-year actuarial freedom from SVD was $98 \pm 2\%$ for AVR and $93 \pm 7\%$ for MVR. Preoperative atrial fibrillation (AF) was a significant predictor of late mortality ($p < 0.001$), thromboembolism ($p = 0.05$) and hemorrhage ($p = 0.01$).

Conclusion: The Aspire porcine bioprostheses is a reliable choice for a tissue valve, for both the aortic and mitral positions, especially in patients aged >70 years. In elderly patients the presence of AF is a significant predictor of early and late mortality and morbidity.

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The Aspire porcine bioprosthesis (Kohler, Swillington, Leeds, UK) - previously known as the Tissuemed bioprosthesis - is a third-generation stented bioprosthesis, which was designed specifically to provide a solution for the premature commissural tears and calcification associated with earlier generations of porcine bioprostheses. This bioprosthesis was first used for implantation in the United Kingdom in 1990, and has been shown to have satisfactory results at five and eight years post implantation (.). More recently, Kumar et al. () reported encouraging results for a 10-year follow up of 139 Aspire bioprostheses implanted in a single center.

The aim of the present study was to report the 10-year clinical performance of the Aspire bioprosthesis from a large multicenter trial.

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Clinical material and methods

Patients

Three tertiary referral cardiothoracic units in the United Kingdom agreed to participate in the present study and implant the Tissuemed (Aspire) porcine bioprostheses; namely, Walsgrave Hospital, Coventry (n = 401 patients), The Glenfield Hospital, Leicester (n = 259), and James Cook University, Middlesbrough (n = 89). For patients admitted to these cardiothoracic surgical units, study information was obtained from patient notes to a set protocol and proforma and entered into a computerized database. In total, seven cardiac surgeons undertook the valve operations, the operative technique being at the discretion of the individual surgeon. Postoperatively, antithrombotic therapy was initiated in all patients as soon as oral intake was possible. After aortic valve replacement (AVR), low-dose aspirin (75 mg daily) was commenced in all patients who were in sinus rhythm, while the remainder received warfarin therapy. The efficacy of warfarin

therapy was monitored by routine measurement of the International Normalized Ratio (INR).

Follow up

Follow up of the patients was conducted by clinical review, postal questionnaire, or direct telephone contact with patients and their general practitioner to a set protocol and proforma. The valve-related events were ascertained, and causes of death determined from the official death register and general practitioner contact and, where possible, by review of post-mortem reports. The performance of the prosthesis was studied according to guidelines for reporting morbidity and mortality after cardiac valvular operations (4). Valve-related complications were defined as thromboembolism, hemorrhage, structural valve deterioration (SVD), non-structural dysfunction, and prosthetic valve endocarditis (PVE). Mortality was defined as death within 30 days of operation or in the same hos-

pital admission as operation, regardless of cause.

Data analysis

Data were expressed as mean \pm SD. Valve-related complications were evaluated in time-related manner with Kaplan-Meier survival curves, and expressed as percent freedom (\pm SE). A log-rank test was used to compare time-related differences. Linearized rates, expressed as percent per patient-year (pt-yr) were calculated by dividing the number of events by the total follow up time in years and multiplied by 100.

Comparison with other studies was accomplished by calculating odd ratios of pooled data. A p-value <0.05 was considered to be statistically significant.

Results

Patient demographics

A total of 763 Tissuemed (Aspire) porcine biopros-

Table I: Demographics of the study population.

Parameter	AVR (n = 617)	MVR (n = 96)	DVR (n = 32)	p-value	Total (n = 749)
Age (years) [†]	73.6 \pm 6.5	71.5 \pm 6.4*	71.1 \pm 9.0*	-	73.2 \pm 6.8
Male gender (%)	62.3	42.7*	65.6	0.001	59.9
Reoperation (%)	3.6	23.9*	12.5*	<0.001	6.6
History of CAD (%)	14.9	34.4*	12.5	<0.001	17.4
History of MI (%)	7.6	29.2*	3.1	<0.001	10.4
Hypertension (%)	16.2	20.8	28.1	0.14	17.4
Diabetes mellitus (%)	5.2	5.2	6.3	0.96	5.2
History of hemorrhage (%)	7.2	13.8	6.5	0.1	8.3
History of TE (%)	11.0	36.8*	12.5	<0.001	14.8
Chronic AF (%)	14.5	52.1*	46.9*	<0.001	20.9
NYHA class (%)					
I	9.9	5.4	12.5	-	9.5
II	29.4	26.9	25.0	0.48	28.7
III	44.9	44.1	46.9	-	44.7
IV	15.7	23.7	15.6	-	17.1
LVF (%)					
1	54.8	57.0	62.1	-	55.6
2	32.9	36.0	17.2	0.17	32.4
3	12.3	7.0	20.7	-	12.0
CPB time (min) [†]	83.7 \pm 34.9	93 \pm 29.6*	121.2 \pm 30.5**	-	86.6 \pm 35.7
Cross-clamp time (min) [†]	56.6 \pm 20.5	61.7 \pm 20.0*	91.0 \pm 25.9**	-	60.0 \pm 22.6
Concomitant CABG (%)	33.6	27.1	9.4**	0.01	31.6
IABP (%)	2.4	13.8*	6.9	<0.001	4.2
Postoperative PPM (%)	4.9	6.3	6.3	0.81	5.1
Tamponade (%)	2.1	3.1	3.1	0.78	2.3
Perioperative CVA (%)	2.4	6.3*	9.4*	0.02	3.2
Perioperative mortality (%)	6.7	17.9*	9.4	0.001	7.6

[†]Values are mean \pm SD.

*p <0.05 versus AVR; **p <0.05 versus AVR and MVR.

AF: Atrial fibrillation; AVR: Aortic valve replacement; CAD: Coronary artery disease; CPB: Cardiopulmonary bypass; CVA: Cerebrovascular accident; DVR: Double valve replacement; IABP: Intra-aortic balloon pump; MI: Myocardial infarction; MVR: Mitral valve replacement; PPM: Permanent pacemaker; TE: Thromboembolism.

theses was implanted in 749 patients between January 1991 and December 2002. AVR was performed in 617 patients (82.4%), mitral valve replacement (MVR) in 96 patients (12.8%), tricuspid valve replacement (TVR) in four patients (0.5%), and double valve replacement (DVR) in 32 patients (4.3%). Among the 745 patients who underwent primary aortic and/or mitral valve surgery, 15 (2%) had a concomitant tricuspid valve procedure (replacement or repair). The incidence of concomitant tricuspid procedures was 11.5% (11/96) in MVR, 6.3% (2/32) in DVR, and 0.3% (2/617) in AVR patients.

Patient demographics and operative data are listed in Table I. Patients undergoing MVR were predominantly younger, female, with higher incidences of reoperation, history of coronary disease and myocardial infarction (MI), chronic atrial fibrillation (AF), history of thromboembolic episodes, longer cross-clamp and cardiopulmonary bypass (CPB) times, and a higher incidence of postoperative intra-aortic balloon pump (IABP) and perioperative cerebrovascular accident (CVA) compared to patients undergoing AVR. Patients undergoing DVR were younger, with higher incidences of reoperation and chronic AF, longer cross-clamp and CPB times, and a higher incidence of CVA compared to patients undergoing AVR. There was no difference between these groups in terms of NYHA class and left ventricular ejection fraction (LVEF). The aortic valve pathology in patients who underwent AVR (n = 617) was stenosis in 56%, incompetence in 17.5%, and mixed stenosis and incompetence in 26.5%. The mitral valve pathology in patients who underwent primarily MVR (n = 96) was stenosis in 13.5%, incompetence in 73.0%, and mixed stenosis and incompetence in 13.5%.

Table II: Causes of 30-day mortality.

Cause of death	No. of patients
Cardiac failure	28 (45.2)
Myocardial infarction	11 (17.7)
Septicemia	3 (4.8)
Stroke	4 (6.5)
Respiratory failure	2 (3.2)
Dysrhythmia	2 (3.2)
Hemorrhage/tamponade	3 (4.8)
Multiorgan failure	1 (1.6)
Renal failure	1 (1.6)
SBE	1 (1.6)
Other	6 (9.7)
Total	62

Values in parentheses are percentages.
SBE: Subacute bacterial endocarditis.

Follow up

By the date of census, 733 patients (97.9%) had undergone a follow up examination. The total cumulative follow up was 3,159 pt-yr (2,693 pt-yr for AVR, 327 pt-yr for MVR, and 123 pt-yr for DVR). The mean follow up period was 51.6 ± 39.6 months (range: 0 to 180.8 months).

Early mortality

The 30-day mortality in this elderly cohort of patients, which included 62 deaths, was 8.3% (95% confidence intervals (CI) 6.4-10.1%). The 30-day mortality was 6.7% (95% CI 4.7-8.6%) for AVR patients, 17.9% (95% CI 10.5-25.3%) for MVR patients, and was 9.4% (95% CI 0-18.7%) for DVR patients. Only one death was valve-related, this being due to bacterial endocarditis.

The causes of 30-day mortality are listed in Table II. In patients undergoing isolated AVR the major factors influencing 30-day mortality were: Reoperation (18.2% versus 6.3%, p = 0.05); history of MI (15.2% versus 6.0%, p = 0.03); impaired left ventricular function (4.3%, 10.6% and 18.9% for LVEF >0.5, LVEF 0.3-0.5 and LVEF <0.3, respectively, p = 0.002); and NYHA class (1.9%, 2.5%, 8% and 17.2% for classes I, II, III and IV, respectively, p <0.001). The size of the implanted aortic valve did not influence early mortality (5.1% and 7.7% for valve sizes ≤21 mm and ≥23 mm, respectively, p = 0.20).

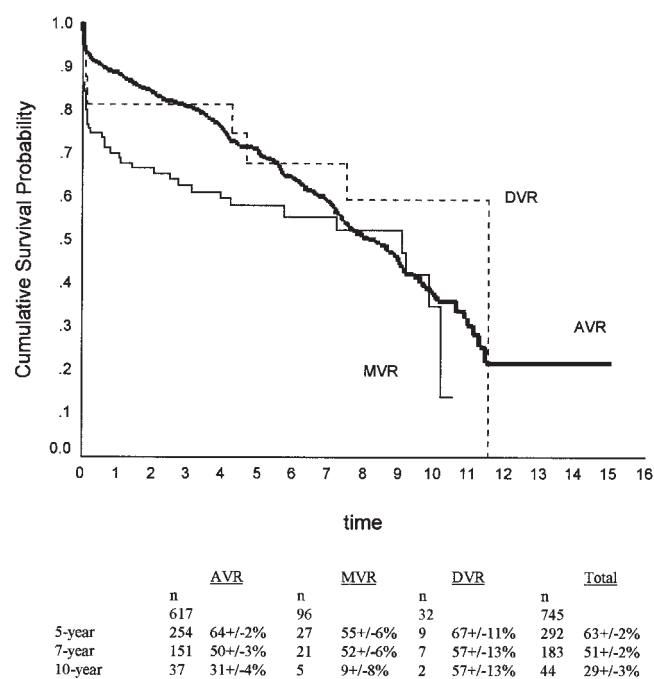


Figure 1: Ten-year survival in patients receiving Aspire valves. AVR: Aortic valve replacement; DVR: Double valve replacement; MVR: Mitral valve replacement.

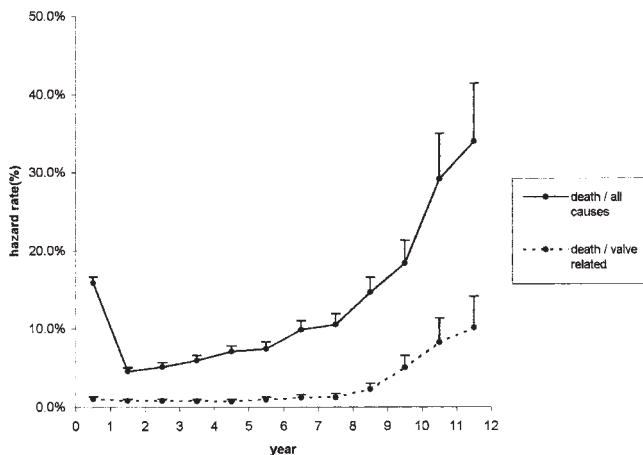


Figure 2: Hazard functions in patients receiving Aspire valves.

Long-term survival

The long-term survival for AVR, MVR and DVR are presented in Figure 1. Patients undergoing MVR had higher rate of late mortality than patients undergoing AVR or DVR (log-rank test, p -value 0.02). Preoperative factors affecting long-term survival in the AVR group were: age >70 years ($p < 0.001$); reoperation ($p = 0.002$); diabetes mellitus ($p = 0.02$); history of MI ($p < 0.001$); chronic AF ($p < 0.001$); NYHA class IV ($p < 0.001$); and LVEF <0.30 ($p < 0.001$). Neither the nature of the aortic disease (in terms of incompetence or stenosis or a combination of both) nor the size of the implanted aortic valve affected long-term survival ($p = 0.17$ and 0.50 , respectively). Preoperative factors affecting long-term survival in the MVR group were a history of MI ($p = 0.02$) and NYHA class ($p = 0.009$). The overall linearized mortality rates were 9.3% per pt-yr (8.8%, 13.7% and 8.2% /pt-yr for AVR, MVR and DVR, respectively).

Valve-related mortality

There were 39 late potentially valve-related deaths. Twenty-one patients died from fatal thromboembolic events, 12 from hemorrhagic complications, five from PVE, and one patient died from prosthetic valve structural failure. The valve-related mortality was 1% per year for the first eight years. After this time, the valve-related mortality accelerated, resulting in an overall freedom from valve-related mortality of $79.6 \pm 5.1\%$ at 10 years (Fig. 2). The 10-year freedom from valve-related mortality was higher in the AVR group than in the MVR group ($83.7 \pm 5.0\%$ versus $46.8 \pm 21.2\%$, $p = 0.03$).

Improvement in patient symptoms

There was a significant impact on NYHA functional class postoperatively (Fig. 3), with 90% of survivors being in NYHA classes I and II at follow up.

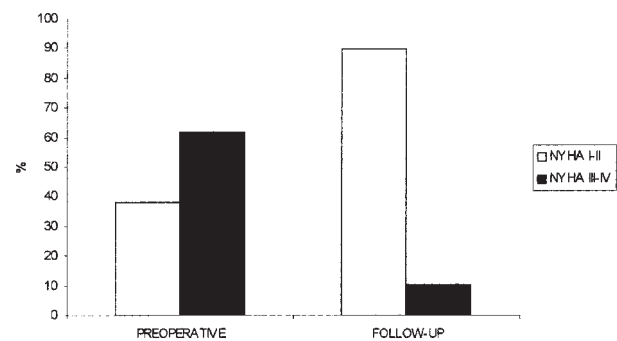


Figure 3: Improvements in NYHA functional class among patients receiving Aspire valves.

Valve-related complications

Valve-related complications included thromboembolism, anticoagulant-related hemorrhage, bacterial endocarditis and valve dysfunction. The linearized occurrence rate for all valve-related complications was 4.7% per pt-yr.

Thromboembolic and bleeding events

Eighty-three patients experienced at least one thromboembolic episode while receiving antithrombotic therapy; of these episodes, 20.5% ($n = 17$) were fatal. Four additional patients who had an initial non-fatal thromboembolic event suffered subsequent fatal events. Among those patients who experienced non-fatal events, approximately 45% had major and 55% minor events. The majority of thromboembolic events were in the brain (96%), and 4% in the lower extremities. Among the total patient cohort the linearized occurrence rate for thromboembolic events was 2.6% per pt-yr. The overall freedom from thromboembolic events at 10 years was $75.6 \pm 4.4\%$, and did not differ among the AVR, MVR and DVR groups ($74.2 \pm 4.8\%$, $80.6 \pm 12.7\%$ and $96.5 \pm 3.4\%$; $p = 0.56$). There were no episodes of either obstructive or non-obstructive valve thrombosis leading to valve failure or fatality.

Eighty-nine patients reported at least one bleeding event after valve replacement, and two of these 13.5% (12 events) were fatal. Among patients who experienced non-fatal events, approximately 65% had major events requiring hospital admission, and 35% had minor events. The majority of hemorrhagic events were gastrointestinal bleedings (56%). There were 22% nasal bleedings, 10% genitourinary, 8% extremity, and 3% central nervous system. Among the total patient cohort, the linearized occurrence rate for all hemorrhagic events was 2.8% per pt-yr. The overall freedom from hemorrhagic events at 10 years was $73.4 \pm 4.2\%$, and did not differ among the AVR, MVR and DVR groups ($73.5 \pm 4.7\%$, $80.5 \pm 6.6\%$ and $57.3 \pm 16.5\%$, respectively; $p = 0.08$).

The presence of atrial fibrillation at the time of surgery had a significant impact on the long-term thromboembolic and bleeding events (Fig. 4).

Prosthetic valve endocarditis

There were nine episodes of PVE, three of which occurred in patients in whom the prosthesis was inserted for infective endocarditis in the first instance. Among the total cohort the linearized occurrence rate for all PVE events was 0.3% per pt-yr. The overall freedom from PVE at 10 years was $97.1 \pm 1.3\%$, and did not differ among the AVR, MVR and DVR groups ($97.7 \pm 1.2\%$, $94.3 \pm 5.5\%$ and $90.9 \pm 8.7\%$; $p = 0.58$).

Structural valve deterioration

There were seven episodes of SVD. Among the total patient cohort the linearized occurrence rate for all SVD events for 10 years after implantation was 0.2% per pt-yr (0.15%, 0.61% and 0.81%/pt-yr for AVR, MVR and DVR, respectively). Overall freedom from SVD at 10 years was $96.0 \pm 2.0\%$, and did not differ among the AVR, MVR and DVR groups ($96.9 \pm 2.0\%$, $94.3 \pm 5.5\%$ and $84.6 \pm 14.1\%$; $p = 0.16$). Among patients aged >70 years the 10-year freedom from SVD was $98 \pm 1.8\%$ and $93 \pm 6.6\%$ for AVR and MVR, respectively.

Non-structural dysfunction

There were four episodes of non-structural dysfunction, two of which manifested as paravalvular leaks (one aortic valve, one mitral valve) and one as valve dehiscence (one mitral valve). A fourth episode occurred at the tricuspid site, and essentially manifested as tricuspid stenosis caused by impairment of mobility of the valve leaflets because of the retained subvalvular apparatus of the native tricuspid valve. The overall freedom from non-structural dysfunction

at 10 years was $99.3 \pm 0.4\%$. The non-structural dysfunction rate was 0.13% per pt-yr.

Reoperation

A total of 14 patients underwent reoperation. The reason for reoperation was PVE in five cases (two aortic valves, two mitral valves, one simultaneous aortic and mitral valve), SVD in four cases (three aortic valves, one mitral valve), paravalvular leak in three cases (one aortic valve, two mitral valves) and one valvular stenosis (one tricuspid valve). In one case the reason for valve replacement remained unclear (one aortic valve). Among the total patient cohort the linearized occurrence rate for reoperation at 10 years after implantation was 0.4% per pt-yr. The overall freedom from reoperation at 10 years was $97.2 \pm 1.3\%$.

Discussion

The present study represents the largest multicenter study assessment of the Aspire porcine bioprosthesis. The Aspire porcine bioprosthesis was associated with an excellent freedom from SVD at 10 years, comparable to that of other porcine and pericardial bioprostheses in elderly patients (Table III). This explains the high freedom from reoperation (97%) compared to values of 48% to 77% reported in other studies, in which the bioprostheses were used in relatively younger patients. Unlike other studies which involved porcine biological valves (5), in the present study there was no difference in the incidence of SVD between the aortic and mitral positions, reflecting an excellent longevity and resistance to mechanical forces of the Aspire valve. Notably, only one patient died because of prosthetic valve failure. Furthermore, functional improvement of the patients was very satisfactory, as 90% were either

Table III: Freedom from structural valve deterioration (SVD) at 10 years: Comparison between newer bioprostheses.

Valve position/ type	Patient age (years)	Freedom from SVD at 10 years (%)
Aortic		
Aspire porcine	>70	98
C-E supra-annular porcine	>70	98
C-E pericardial	>65	97
Medtronic Intact porcine	>60	100
Mitroflow pericardial	>70	97
Mitral		
Aspire porcine	>70	93
C-E porcine	>70	81
C-E pericardial	>70	100

C-E: Carpentier-Edwards.

asymptomatic or mildly symptomatic at the time of follow up.

In patients undergoing isolated AVR, the 30-day mortality (6.7%) was not significantly higher than the range of 4.3% to 5.8% reported for other biological prostheses in much younger patients (odds ratio 1.32, 95% CI 0.81-2.16, $p > 0.05$) (6,7). The 10-year survival in the present study did not differ from that reported by Dellgren et al. (8) in a similar cohort with a mean age of 71.3 years. Patients who underwent MVR, however, had a significantly higher perioperative mortality (18%) and lower long-term survival (8.5% after 10 years) compared to results in other studies, where the corresponding values were 5.8-9.6% and 49.7-62.7% (9-11). The reason for this discrepancy was unclear. Most studies with biological prostheses fail to mention subgroup characteristics and, therefore, comparisons of comorbid conditions are not straightforward. Marchand et al. (12) reported a 10-year survival of 56.8% after MVR with a bioprosthesis. Although the comorbidity of this cohort was similar to that of the present series (CABG 25.5% versus 27.1%, AF 48.8% versus 52.1%, reoperation 26.5% versus 23.9%), the average age was 60.7 ± 11.6 years and the mitral pathology was mostly rheumatic, whereas in the present study the mean age was 71.5 ± 6.4 years and the pathology was infrequently rheumatic. It might be assumed that older age, and a mitral valve pathology other than rheumatic (myxomatous degeneration or ischemic), may carry a remarkably higher early and late mortality.

In patients undergoing AVR, both the perioperative mortality and long-term survival rates were influenced by advanced NYHA status, reduced LVEF, reoperation and a history of MI. Advanced age, diabetes mellitus and the presence of AF at the time of surgery also influenced long-term survival. Previous studies have shown that advanced age, male sex, reduced LVEF and advanced NYHA functional class are independent predictors of mortality among patients with AVR (13). The influence of AF on long-term mortality in the present series is worth emphasizing. A number of recent studies have suggested that AF might be associated with increased late morbidity and mortality (14-17). This raises the question of whether radiofrequency ablation (either epicardial or endocardial) might have a therapeutic place in elderly patients with AF undergoing AVR (18,19). Also, in the present study neither the nature of the aortic pathology nor the size of the aortic prosthesis influenced perioperative mortality (20).

In the present study the incidence of thromboembolism and hemorrhage was higher than in other series (5-10). In patients undergoing AVR, the 10-year freedom from thromboembolism was 74%, whilst in other series it ranged from 82% to 92%. Similarly, the 10-year freedom from hemorrhage was 73.5%, but ranged from

90% to 99% in other series. The most likely reason for these differences is the much older age of patients in the present study. Unfortunately, most studies with biological prostheses do not refer to rates of bleeding and thromboembolic events in age subgroups, and therefore direct comparisons are not feasible. Nevertheless, Cannegieter et al. (21) have reported a 5.6% per pt-yr bleeding rate for patients aged ≥ 70 years when treated with anticoagulants after mechanical valve implantation, which was significantly higher than the value of 3.1% per pt-yr found in the present study. Among elderly patients, the incidence of AF - a well-known cause of thromboembolism - is higher. Notably, patients with AF preoperatively had a higher incidence of late thromboembolic and hemorrhagic events (Fig. 4). There is also accumulating significant evidence that advanced age is closely associated with atherosclerosis of the ascending aorta, and that this condition is a strong independent factor for stroke and other peripheral embolic events (22,23). It is worth noting that, to date, the thromboembolic events in patients with a prosthetic valve are attributed arbitrarily to the valve and/or the associated AF. This raises the question of whether the aortic atherosclerotic burden of patients with prosthetic valves should be taken into account in future studies, especially when evaluating thromboembolic events.

Study limitations

The major limitation of the present study was that the population was significantly older (average age 73 years) than in most other reports on biological prostheses, in which the average age ranged from 57 to 67 years (5-7,9-12,24,25). This may reflect the tendency of British centers to use biological valves predominantly in patients aged >70 years. In elderly patients, SVD and reoperations appear more successful as many patients may die before developing structural valve problems requiring reoperation. In contrast, the thromboembolic and hemorrhagic complications may appear worse, as it is well established that these have a high incidence in elderly patients. For this reason, comparisons made in the present study focused on the subgroup of patients aged >70 years.

In conclusion, the Aspire porcine bioprosthesis provides excellent freedom from SVD at 10 years, comparable to that seen with other new-generation porcine and pericardial bioprostheses. The relatively higher incidence of hemorrhagic and thromboembolic events in the present study was most likely to be due to the greater age of the patients. It may be necessary to conduct further studies in order to shed light on the performance of the Aspire valve in younger populations. In elderly patients undergoing AVR, atrial fibrillation -

a potentially curable condition - is associated with a higher mortality and morbidity.

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