

Hancock II Bioprosthesis for Aortic Valve Replacement: The Gold Standard of Bioprosthetic Valves Durability?

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Background. This study examined the long-term durability of the Hancock II bioprosthesis (Medtronic, Minneapolis, MN) in the aortic position.

Methods. From 1982 to 2004, 1134 patients underwent aortic valve replacement (AVR) with Hancock II bioprosthesis and were prospectively monitored. Mean patient age was 67 ± 11 years; 202 patients were younger than 60, 402 were 60 to 70, and 526 were older than 70. Median follow-up was 12.2 years and 99.2% complete. Valve function was assessed in 94% of patients. Freedom from adverse events was estimated by the Kaplan-Meier method.

Results. Survival at 20 and 25 years was $19.2\% \pm 2\%$ and $6.7\% \pm 2.8\%$, respectively, with only 34 and 3 patients at risk. Survival at 20 years was $54.9\% \pm 6.4\%$ in patients younger than 60 years, $22.7\% \pm 3.3\%$ in those 60 to 70, and $2.4\% \pm 1.9\%$ in those older than 70 ($p = 0.01$). Structural valve deterioration developed in 67 patients

aged younger than 60, in 18 patients aged 60 to 70, and in 2 patients older than 70. The freedom from structural valve deterioration at 20 years was $63.4\% \pm 4.2\%$ in the entire cohort, $29.2\% \pm 5.7\%$ in patients younger than 60 years, $85.2\% \pm 3.7\%$ in patients aged 60 to 70, and $99.8\% \pm 0.2\%$ in patients older than 70 (truncated at 18 years). Repeat AVR was performed in 104 patients (74 for structural valve failure, 16 for endocarditis, and 14 for other reasons). At 20 years, the overall freedom from AVR was $65.1\% \pm 4\%$ for any reason, $29.8\% \pm 5.4\%$ in patients younger than 60 years, $86.8\% \pm 3.3\%$ in patients 60 to 70, and $98.3\% \pm 0.6\%$ in patients older than 70.

Conclusions: Hancock II bioprosthesis is a very durable valve in patients 60 years and older and is probably the gold standard of bioprosthetic valve durability in this patient population.

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There is a widespread notion that pericardial valves are more durable than porcine valves when used for aortic valve replacement (AVR). This view was likely borne from comparative studies of first-generation porcine aortic valves with currently available pericardial valves and without consideration to patients' ages [1]. Age is undoubtedly the single most important determinant of bioprosthetic valve durability [2–6]. We continue to favor the use of a porcine valve over pericardial valves when valve durability is a factor in the choice of bioprosthetic valve [2].

The Hancock II bioprosthetic heart valve (Medtronic, Minneapolis, MN) is a second-generation porcine aortic valve fixed with a buffered 0.625% glutaraldehyde solution in two stages: an initial stage of low pressure and a late stage of physiologic pressure. It is also chemically treated with sodium dodecyl sulfate to retard calcification [7]. The stent of this bioprosthesis is made of Delrin (DuPont, Wilmington, DE) instead of polypropylene, as in the stent of the original Hancock valve, to prevent creeping.

The Hancock II used for AVR was designed to be implanted in a supraannular position. This valve was introduced in September 1982, and the first implant was in a patient in our institution [8]. Since then we have implanted several hundred of these valves, mostly in the aortic position of older patients. We have monitored these patients prospectively, and this report describes the long-term clinical outcomes of patients who had AVR with this bioprosthetic valve. In the Discussion, we compare the durability of this bioprosthetic valve with others with similarly long-term follow-up.

Patients and Methods

This study was approved by our Institutional Review Ethics Board. Consent for clinical follow-up was obtained at the time of operation.

From September 1982 to December 2004, 1134 consecutive patients had AVR with Hancock II bioprosthesis valve to treat isolated aortic valve disease with or without replacement of the ascending aorta and with or without coronary artery bypass graft. Patients who had concomitant mitral valve operations were excluded. The patients were a mean age of 67 ± 11 years (range, 19 to 94 years) at the time of AVR. They were monitored prospectively

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Table 1. Clinical and Operative Data

Variable	No. (%), ^a or Mean \pm SD (range)
Total patients	1134 (100)
Male	864 (76.2)
Female	270 (23.8)
Age in years	
<60	206 (18.2)
60-70	402 (35.4)
>70	526 (46.4)
Presenting symptoms	
Congestive heart failure	481 (42.5)
Cardiogenic/septic shock	20 (1.7)
Syncope	234 (20.7)
Angina	702 (61.9)
AMI < 30 days	36 (3.1)
Associated diseases:	
Diabetes	165 (14.5)
Hypertension	503 (44.4)
Hyperlipidemia	287 (25.4)
COPD ^b	110 (9.7)
Stroke or TIA	113 (10.0)
Peripheral vascular disease	102 (9.0)
Renal failure, dialysis	19 (1.7)
Previous cardiac operation, any	108 (9.5)
Previous CABG	37 (3.2)
Electrocardiogram on admission	
Sinus rhythm	1010 (89)
Atrial fibrillation	89 (7.8)
Paced beats, heart block	33 (2.9)
Timing of operation	
Elective	880 (88)
Urgent/emergent	118 (18)
Left ventricular ejection fraction	
≥ 0.60	374 (35.5)
0.40-0.59	451 (42.8)
0.20-0.39	188 (17.8)
<0.20%	40 (3.8)
NYHA functional class	
I	47 (4.1)
II	244 (21.6)
III	491 (43.3)
IV	352 (31.0)
Aortic valve lesion	
Normally functioning	3
Stenosis	663 (59.2)
Regurgitation	238 (21.2)
Mixed	216 (19.3)
Coronary artery disease	559 (49.2)
Infective endocarditis	
Active	34 (3.1)
With annular abscess	14 (1.2)
Valve pathology	
Rheumatic	41 (4.1)
Tricuspid calcific	448 (44.5)
Bicuspid	322 (32.6)

Continued

Table 1. Continued

Variable	No. (%), ^a or Mean \pm SD (range)
Other congenital	6 (0.6)
Annuloaortic ectasia	51 (5.1)
Prosthetic dysfunction	65 (6.5)
Aortic dissection	6 (0.6)
Other	49 (4.9)
Body surface area, m ²	1.86 \pm 0.21
Bioprosthetic valve size	
#21	89 (7.8)
#23	324 (28.6)
#25	387 (34.2)
#27	271 (23.9)
#29	61 (5.4)
Patch enlargement of aortic annulus	217 (19.3)
Replacement of ascending aorta	
Supracoronary	90 (7.9)
Composite	58 (5.1)
CABG	572 (50.4)
Cardiopulmonary bypass time, min	106 \pm 39 (32-318)
Aortic clamp time, min	80 \pm 30 (22-218)

^a Numbers may not add to 1134 due to missing data. ^b Chronic obstructive pulmonary disease with forced expiratory volume per second ≤ 1.0 .

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; NYHA = New York Heart Association; SD = standard deviation; TIA = transient ischemic attack.

by our research personnel at approximately every second year. Communications with patients were through questionnaires. Morbid events were reviewed by contacting patients directly or relatives as well as their family physician or cardiologist. Although few postmortem examinations were performed, medical information on the cause of death was possible in all but 3 patients. Follow-up was a mean duration of 12.4 years (median, 12.2 years; range, 0 to 27 years) and was 99.2% complete. Most patients (94%) had multiple echocardiographic studies to assess valve and heart function.

Table 1 summarizes the clinical and operative data of all patients. The most recent guidelines for reporting mortality and morbidity after cardiac valve interventions were used to define adverse events [9].

Operative Technique

The aortic valve bioprosthesis was secured on a supraannular position by using horizontal mattress sutures of 2-0 polyester with pledgets on the ventricular side of the aortic annulus. Every effort was made to implant the largest possible valve, and patch enlargement of the aortic annulus was performed in 217 patients (19%) to minimize transvalvular gradients [8].

Statistical Analysis

All data analyses were performed with SAS 9.1 software (SAS Institute, Cary, NC). Categorical variables were ex-

pressed as percentages, and continuous variables were expressed as mean ± standard deviation. Univariate analysis included the χ^2 Fisher's exact test for categorical variables and 2-tailed Wilcoxon rank sum test or *t* tests for continuous variables. Stepwise logistic regression analysis method with backward elimination was used to determine independent multivariable predictors of operative deaths.

Long-term survival, freedom from reoperation, and freedom from morbid events were estimated by using the Kaplan-Meier technique, with log-rank tests to compare stratified groups. Linearized rates of certain morbid events were calculated by dividing the total number of events by mean follow-up and expressed as events per 100 patient-years (percent/year). All preoperative variables with a univariate value of *p* < 0.25 or those with known clinical significance but failing to meet this critical α level were submitted to the multivariable model for Cox regression analyses to determine the independent multivariable predictors of late outcomes. Statistical significance was set at *p* ≤ 0.05.

Results

Early and Late Mortality

There were 622 deaths (55%; Table 2). Survival was 96.7% ± 0.5% at 30 days and 93.6% ± 0.7% at 1 year. Survival at 15, 20 and 25 years was 37.4% ± 1.8%, 19.2% ± 2.0%, and 6.7% ± 2.8%, respectively. There were only 3 survivors at 25 years of follow-up. Table 3 reports the independent predictors of patient death after AVR. Figure 1 shows patient survival according to age groups (< 60 years, 60 to 70 years, and > 70 years). The 15- and 20-year survival was 44.2% ± 2.5% and 24.2% ± 2.9% in patients without coronary artery disease and 28.1 ± 2.5% and 11.3 ± 2.6%, respectively, in patients with coronary artery disease (*p* = 0.001).

Table 2. Causes of Deaths

Cause	No. (%)
Total deaths	622 (55)
Operative	45 (4)
Valve -related	75 (6.6)
Stroke	31
Prosthetic valve endocarditis	14 ^a
Structural valve degeneration	18 ^b
Hemorrhage	12
Cardiac	189 (16.6)
Congestive heart failure	83
Coronary artery disease	58
Sudden	46
Dysrhythmias	1
Cardiac tumor	1
Aortic aneurysms	11 (1)
Other causes	302 (26.6)

^a One patient died at the operation. ^b Five patients died at the operation.

Table 3. Independent Predictors of Death of All Causes (Cox regression)

Predictor	HR (95% CI)	<i>p</i> Value
Age (5-year increments)	1.043 (1.032-1.053)	0.0001
Hypertension	1.241 (1.044-1.476)	0.014
COPD	1.579 (1.233-2.023)	0.0006
NYHA class IV	1.316 (1.092-1.585)	0.004
LVEF < 0.40	1.316 (1.092-1.585)	0.016
PVD	1.561 (1.187-2.053)	0.016
Renal failure	2.168 (1.353-3.475)	0.001
Coronary artery disease	1.201 (1.002-1.441)	0.047

CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; LVEF = ejection fraction; NYHA = New York Heart Association; PVD = peripheral vascular disease.

Thromboembolism

During the follow-up, 124 patients sustained thromboembolic complications (89 stroke and 34 transient ischemic attacks), of which 15 patients had two events and 2 patients had three events. Thirty-one patients died as consequence of a stroke.

The linearized rate of thromboembolism was 1.20%/year. Independent predictors of thromboembolism were age older than 60 years, previous stroke, peripheral vascular disease, and preoperative congestive heart failure. The freedom from thromboembolic complication at 10, 15, and 20 years was 88.8 ± 1.2%, 82.1 ± 1.7%, and 77.3 ± 2.3%, respectively. There was no documented case of valve thrombosis.

Prosthetic Valve Endocarditis

There were 41 episodes of prosthetic valve endocarditis: 16 patients were treated surgically, and 1 died; 25 were

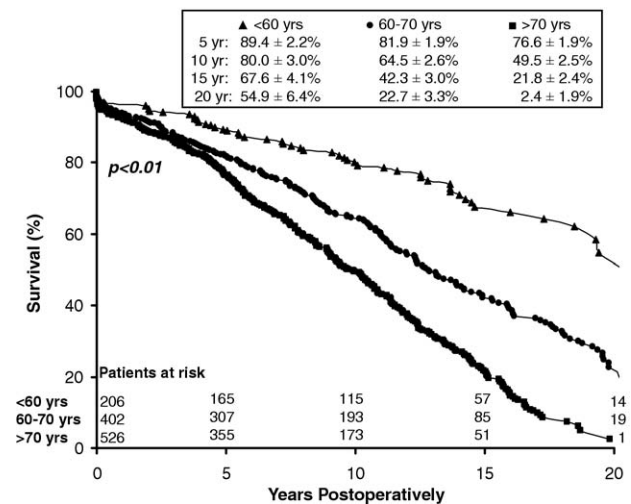


Fig 1. Kaplan-Meier estimates of survival after aortic valve replacement with the Hancock II bioprosthesis according to age < 60 years (triangles), age 60 to 70 years (circles), and age > 70 years (squares).

treated medically, and 13 died during antibiotic treatment. The linearized rate of prosthetic valve endocarditis was 0.39% per year. The freedom from prosthetic valve endocarditis at 1, 5, 10, 15, and 20 years was $99.3\% \pm 0.2\%$, $97.7\% \pm 0.4\%$, $94.5\% \pm 1\%$, $94.5\% \pm 1\%$, and $94.5\% \pm 1\%$, respectively. No variable was identified as predictive of prosthetic valve endocarditis by Cox regression analysis.

Hemorrhagic Complications

A major hemorrhage occurred in 42 patients (39 were taking warfarin sodium and 3 were not). Of these, 12 patients died, 14 required blood transfusion, and 16 were hospitalized for diagnosis and observation. At the last follow-up contact, 90 patients (17%) were taking warfarin sodium because of previous stroke, heart block with a permanent pacemaker, or atrial fibrillation.

Nonstructural Valve Failure

Paravalvular leakage was documented by transthoracic echocardiography in 4 patients; 2 required reoperation. In addition, 1 patient was reoperated on 3 years after implantation for stenosis due to pannus in the inflow of the valve.

Structural Valve Deterioration

Structural valve failure (SVD) was documented in 87 patients by echocardiography or operation, or both. Repeat AVR was performed in 74 patients, and 13 patients were believed to be inoperable (6 in < 60 age group and 7 in ≥ 60 years group). There were only 2 valve failures in patients older than 70 years, 18 in patients aged 60 to 70 years, and 67 in patients younger than 60 years. Age was the only independent predictor of SVD. Freedom of SVD is shown for all patients in Figure 2A and according to age group in Figure 2B. Freedom from reoperation due to SVD is shown in all patients in Figure 3A and by age group Figure 3B. Only 1 patient older than 70 years was at risk at 20 years, making the value unreliable (standard error, 15.1). The freedom from SVD at 15 and at 20 years was, respectively, $80.7\% \pm 2.6\%$ and $66.0\% \pm 3.4\%$ in patients aged younger than 65 and $99.0\% \pm 4.2\%$ and $97.8 \pm 8.2\%$ in patients aged 65 and older. The freedom from SVD at 15 and 20 years was, respectively, $83.6\% \pm 2.5\%$ and $60.9\% \pm 4.9\%$ in patients without coronary artery disease and $91.9\% \pm 2.4\%$ and $66.9\% \pm 8.2\%$ in patients with coronary artery disease ($p = 0.06$), but patients with coronary artery disease were older ($p = 0.01$).

Reoperations on the Aortic Valve

Repeat AVR was performed in 104 patients, including 74 for structural valve failure, 16 for endocarditis, 3 for nonstructural valve failure, 4 for dissection, 3 for ascending aorta/root aneurysm, and 3 normally functioning valves older than 10 years at the time of coronary artery bypass grafting or mitral valve operation. The operative mortality for reoperation was 7% (7 of 104). The freedom from AVR at 20 years was $65.1\% \pm 4\%$ overall; $29.8\% \pm$

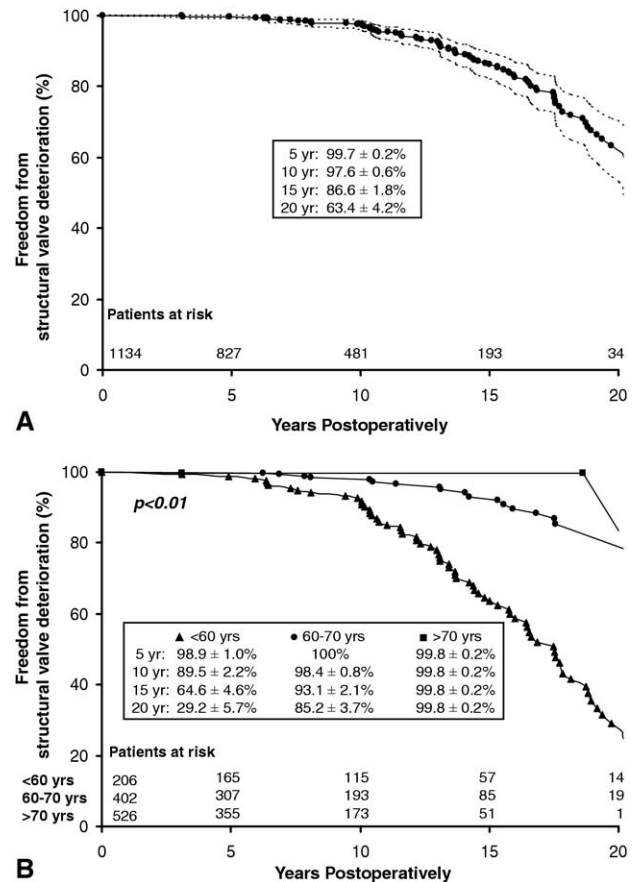


Fig 2. Freedom from structural valve deterioration is shown for (A) all patients (dotted lines on either side of solid line represent upper and lower 95% confidence intervals) and (B) according to age group.

5.4% in patients younger than 60, $86.8\% \pm 3\%$ in patients aged 60 to 70, and $98.3\% \pm 0.6\%$ in patients older than 70 ($p = 0.01$).

Functional Class

At the latest follow-up contact, 56% of patients were in New York Heart Association functional class I, 26% were in class II, and 17% were in class III.

Comment

This report is an accurate account of clinical outcomes of AVR with Hancock II bioprosthesis because our patients have been prospectively followed-up at approximately 2-year intervals, and most of them had echocardiographic assessment of the bioprosthetic valve. Thus, every adverse event from a minor nosebleed to death was recorded. In addition, this large consecutive series of AVR with bioprosthetic valve has complete follow-up in 99.2% of the patients. Overall patient survival at 25 years was low, at 6.7%, but they were a mean age of 67 years at the time of AVR. There were only 3 survivors at 25 years. For this reason we analyzed clinical outcomes up to 20

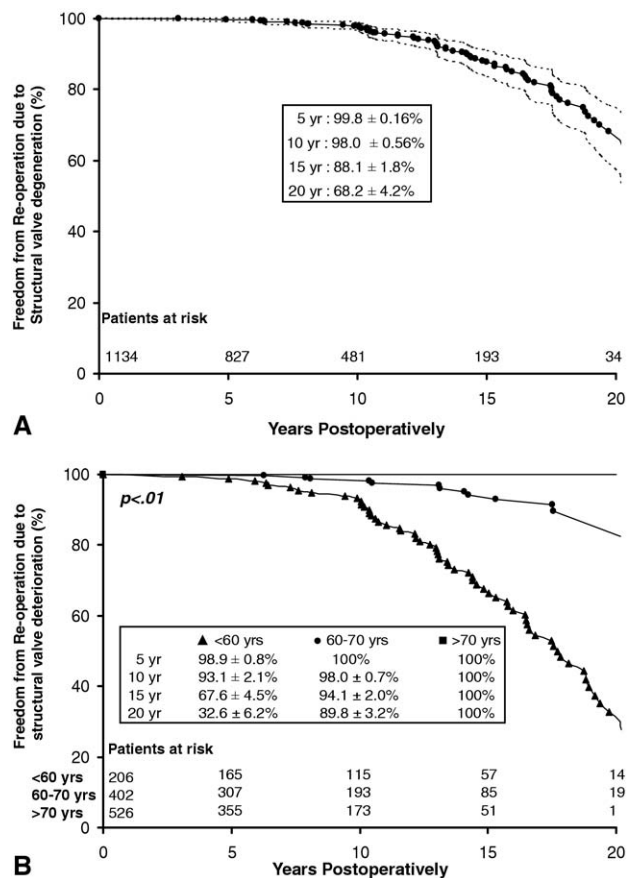


Fig 3. Freedom from reoperation due to structural valve deterioration is shown for (A) all patients (dotted lines on either side of solid line represent upper and lower 95% confidence interval) and (B) according to age group.

years, and for some end points, such as SVD and reoperation rates, patients were divided into three subgroups according to their ages.

Table 3 reports the independent predictors of late death: age by increments of 5 years, hypertension, severe chronic obstructive lung disease (forced expiratory volume in 1 second \leq 1.0), peripheral vascular disease, impaired renal function, left ventricular ejection fraction of less than 0.40, and coronary artery disease. Gender, previous operations, replacement of the ascending aorta at the time of AVR, patch enlargement of the aortic annulus, and size of the valve implanted had no effect on mortality by multivariable analysis.

There were a large number of thromboembolic events, but as reported in Table 1, many patients had had strokes, and an equally large number had peripheral vascular disease preoperatively. Thus, a freedom of thromboembolism of $77.3\% \pm 2.3\%$ at 20 years is not surprisingly low, and in all likelihood, most events were unrelated to the presence of a bioprosthetic aortic valve but rather to patient factors [10].

Patients with prosthetic heart valves have a low but constant risk of endocarditis. The freedom from endocar-

ditis in this cohort was $94.5\% \pm 1\%$ at 20 years. Survival was poor if patients were treated with antibiotics alone. Most patients referred back to our institution had repeat operations, and only 1 of 16 died. During the past 2 decades, we have adopted an aggressive approach in the treatment of prosthetic valve endocarditis, but the outcomes remain largely dependent on the patient's clinical status when the operation occurs [11].

The most important information in this study is SVD, which was documented in 87 patients by echocardiography. Only 74 had reoperation, however; the remaining 13 were deemed inoperable. Thus, "freedom from reoperation for SVD" is not equal to freedom from SVD, yet most studies on durability of bioprosthetic valves have used them interchangeably [3, 5, 6], which underestimates SVD. In this study we calculated the Kaplan-Meier estimates of freedom from SVD as well as the freedom from reoperation due to SVD (Figs 2 and 3). Age was the only predictor of SVD by multivariable analysis. Although we documented fewer cases of SVD among patients with coronary artery disease, this subgroup was older than those without coronary artery disease, and that is probably the reason this variable was not a predictor of SVD. Most patients with coronary artery disease were taking statins, but this therapy had no effect in SVD [12].

As aptly put by Rahimtoola [13], newer-generation bioprosthetic valves have to demonstrate durability beyond 15 years to determine if they are superior to older ones. The Hancock II has been in use since 1981, and its durability in the aortic position is probably the gold standard of bioprosthetic valves. Comparisons are difficult because of different methods of reporting valve failure despite well-defined guidelines [9]. As mentioned before, most investigators use freedom from explant due to SVD as a measurement of valve durability and because the mean age of patients who receive bioprosthetic valves often exceeds 70 years, many will not have a reoperation and there will be too few patients at risk at 20 years. We reviewed the recent literature on this topic and have summarized our results in the following paragraphs.

Yankah and colleagues [6] reported the "durability results up to 21 years" of the Mitroflow pericardial bioprosthesis (Sorin Group Canada Inc, Burnaby, BC, Canada). Those investigators examined the outcomes of 1513 patients with a mean age of 73.2 years and a relatively short mean follow-up of only 4 years. Only 89 patients were younger than 60 years. The freedom from reoperation due to SVD at 20 years was 84.8% in patients aged 70 years and less than 60% in patients younger than 70 (estimated from Fig 2 in their article). From the data in this report it is reasonable to state that the Hancock II is far more durable than the Mitroflow pericardial valve.

We could find no published reports on the durability of the Carpentier-Edwards Perimount (CEP; Edwards Lifesciences, Irvine, CA) pericardial valve at 20 years. Banbury and colleagues [3] reported its durability up to 15 years. They had only 267 patients, who were a mean age of 65 years, but the mean follow-up was 12 years. The freedom from explant due to SVD was 77% at 15 years

and was highly dependent on patient age. These numbers are similar to those reported by Smedira and colleagues [14] from the same institution in a more recent publication comparing homograft with the CEP valve.

In our series of Hancock II valves, patients' mean age was only 2 years older than in the Banbury series, and the freedom from SVD (not explants due to SVD) was 86.6% at 15 years, almost 10% higher. The superior durability of Hancock II at 15 years is also apparent in younger patients when compared with CEP.

Aupart and colleagues [15] reported late outcomes of AVR with CEP in patients with aortic stenosis. It was unclear why those authors chose only patients who had aortic stenosis to include in analysis. They had 1133 patients whose mean age was 72.6 years, and 84 patients were aged younger than 60. The average follow-up was only 5.5 years, but the patients had echocardiographic studies. The freedom from SVD at 18 years was 99% in patients older than 70 years (9 patients at risk), 77% in those aged 60 to 70 (1 patient at risk), and 45% in those younger than 60 (1 patient at risk). Compared with these outcomes, the Hancock II again comes ahead on durability, particularly in patients aged younger than 70 years.

McClure and colleagues [16] recently published the long-term outcomes of 1000 patients who had AVR with the CEP. These patients were a mean age if 74 years, and the mean follow-up was only 6 years. According to Figure 2 in their article, no patients were at risk at 15 years, but they reported a freedom from reoperation due to SVD at 15 years of 34.7% in patients younger than 65 years and 89.4% in patients aged 65 to 75. The freedom from SVD with the Hancock II at 15 years was 80.7% \pm 2.6% for patients younger than 65 and 99.0% \pm 4.2% for patients aged 65 and older.

Mykén [17] reported her 17-year experience with the Biocor porcine bioprosthesis (St. Jude Medical, St. Paul, MN) in 2005, and Mykén and Bech-Hansen [5] reported their "20-year experience" in 2009. This bioprosthesis was implanted in 1518 patients with a mean age of 70.8 years and a mean follow-up of only 6 years. The freedom from reoperation because of SVD was 61.1%, but it is unclear whether any patients were at risk at 20 years. (Fig 2 in their article indicates 9 patients at risk, but the number is placed before the 20-year mark.) The freedom from reoperation due to SVD was 92.1% in patients aged older than 65 years and 44.5% in those 65 or younger. Here, the Figure 3 in their article suggests those values at a time interval between 15 and 20 years. Moreover, the number of patients at risk in Figures 2 and 3 in their article is discordant, making difficult for the reader to know what is correct.

In a study by Jamieson and colleagues [18], the durability of AVR with the Carpentier-Edwards SAV (Edwards Lifesciences) in 1524 patients was compared with the Hancock II bioprosthesis in 670 patients. They found similar rates of SVD at 12 and 15 years, but there was a trend to less SVD by actual analysis for the Hancock II valve in younger patients.

Other studies of the Hancock II bioprosthesis have shown similar excellent long-term durability [19, 20]. A recent study by Valfrè and colleagues [19] found the freedom from reoperation due to SVD was 79.3% at 20 years, was 52.2% in patients aged younger than 60 years, and was 86.8% in patients aged 60 or older. A multicenter study from Italy confirmed this high freedom from SVD [20]. In addition, a comparison using propensity matching analysis between the original Hancock valve and Hancock II showed the latter to be definitely more durable [21].

In summary, the existing data in the literature and our own experience show that the Hancock II bioprosthesis is probably the most durable xenograft valve used for AVR and represents the gold standard on durability against which other valves should be compared.

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The fate of Hancock II porcine valve recipients 25 years after implant[☆]

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Abstract

Objective: The Hancock II (HII) is a second-generation porcine bioprosthesis introduced into clinical use in 1982. This study aimed to evaluate very long-term outcomes for the HII valve in a large patient population. **Methods:** Between May 1983 and November 1993, 517 consecutive patients (pts) (309 male, mean age: 64 ± 9 years) underwent valve replacement (VR) surgery with HII, with 302 (58.4%) in the aortic VR (AVR) and 215 (41.6%) in the mitral VR (MVR) position, respectively. At implant, 106 pts (20.5%) were <60 years of age (G1), while 411 (79.5%) were ≥ 60 years of age (G2). The 25-year follow-up was complete for all pts at a median of 12 years (range: 0–25). **Results:** Long-term death occurred in 208 AVR and in 165 MVR pts. Survival at 15 and 20 years was 39.5% and 23.3% in AVR pts and 39.0% and 15.8% in MVR pts. At 25 years the survival of MVR pts was 13.7% (four pts at risk). Late freedom from re-operation was 85.5% and 79.3% at 15 and 20 years in the AVR pts and 73.3% and 52.8% in the MVR pts, respectively. In the AVR population, 20-year freedom from re-operation was 52.2% in G1 pts and 86.8% in G2 pts ($p < 0.0001$), while in the MVR population it was 41.4% in G1 pts and 61.9% in G2 pts ($p = 0.201$), respectively. **Conclusions:** These results confirm the excellent long-term performance of the HII bioprosthesis.

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Keywords: Bioprosthesis; Hancock valve; Long-term outcome

1. Introduction

Many of the bioprosthetic heart valves that are currently commercially available entered clinical trials in the early 1980s. The majority of these are 'second-generation' devices that were developed to improve upon the limitations of the first-generation valves, namely haemodynamics and durability. Estimates of late durability for these valves, however, are confounded by patient survival, particularly when the majority of patients receiving bioprostheses have been older. Natural death in this population reduces the patient at risk over time presenting challenges for long-term follow-up. Reports of follow-up for these up to 20 years have been rare [1–5].

The Hancock II (HII) bioprosthesis is representative of 'second-generation' bioprosthetic valves. It is the successor of the original Hancock Standard valve which was introduced in 1972. The HII (Medtronic, Inc., Minneapolis, Minnesota, USA) entered clinical use in 1982 featuring a lower implant

profile, an anti-calcification agent (sodium dodecylsulfate or T-6), a minimised right coronary septal muscle-shelf and a two-stage fixation process (low followed by high pressure) [6].

This retrospective multi-centre (Treviso Hospital and Padua University) study reports 25-year results for re-operation and survival with the HII valve.

2. Patients and methods

2.1. Patient population

Between May 1983 and November 1993, 517 patients consecutively received isolated aortic (302) or mitral (215) valve replacement (VR) when indicated for a bioprosthesis. Treviso implanted 365 of the valves and Padua 152. Concomitant tricuspid valve repairs are included in this population. The average age at implant was 64.4 ± 8.5 years (range: 20–90) with 79.5% of patients ≥ 60 years. Male gender represented 59.8% of the population. More specific demographic data may be found in Table 1.

This population represents the patients enrolled in the first 10 years of a larger study published earlier by the authors [7].

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Table 1
Patient preoperative characteristics for AVR and MVR.

	AVR (n = 302 patients) N (%)	MVR (n = 215 patients) N (%)
Male gender	227 (75.2)	82 (38.1)
Mean age	65.7 ± 8.5	62.5 ± 8.2
≥60 years	252 (83.4)	159 (74.0)
Mean BSA	177 ± 15	167 ± 18
Native valve lesion		
- Stenosis	98 (32.5)	29 (13.5)
- Incompetence	91 (30.1)	78 (36.5)
- Mixed	104 (34.4)	93 (43.3)
- Missing	9 (3.0)	15 (7.0)
Failed prosthesis	21 (7.0)	41 (19.5)
Endocarditis (inactive)	10 (3.3)	7 (3.3)
Chronic renal failure	9 (3.0)	5 (2.4)
CAD	64 (21.2)	29 (13.5)
COPD	7 (2.3)	0
Diabetes	11 (3.7)	7 (3.3)
Sinus rhythm	254 (84.4)	60 (28.6)
NYHA class ≥III	225 (75.3)	183 (87.6)

Table 2
Operative data.

	AVR N = (%)	MVR N = (%)
Emergent procedure	14 (4.7)	9 (4.3)
Coronary artery-bypass grafting	56 (18.5)	26 (12.1)
Ascending aorta replacement	24 (8.0)	—
Clamp time (min)	82 ± 27	65 ± 22
CPB time (min)	116 ± 39	101 ± 38

2.2. Surgical technique

Both institutions used the same operative technique. Implantation was done with inverted pledgeted sutures. Coronary artery-bypass grafting (CABG) was concomitantly performed when critical coronary artery lesions were present (70% disease). Other operative data are noted in Table 2.

2.3. Follow-up

After securing approval at the respective hospital ethics committees, patients were followed by telephone or mail interview. Follow-up of this population was 100% complete. Median follow-up was 12.1 years (range: 0–24.7) for aortic VR (AVR) and 11.3 years (range: 0–25.2) for mitral VR (MVR) with 3539 and 2463 patient/years, respectively.

2.4. Statistical analysis

STATASE 9.0 (StataCorp, College Station, Texas, USA) was used for statistical analysis. Survival analysis uses the actuarial Kaplan–Meier method for patient survival and freedom from re-operation. Standard errors for these estimates are calculated with the formula of Peto and colleagues [8]. Survival was defined on a patient basis, so deaths were included as events if they occurred either with or without valve replacement. For the latest patients at risk, linearised event rates were used to represent complications

per 100 patient years. The reverse Kaplan–Meier method was used to estimate the median follow-up time.

3. Results

3.1. Survival

Of the patients studied, 373 died – 352 without re-operation and 21 after a re-operation. There were 144 survivors (94 AVR and 50 MVR) at follow-up. In the AVR population, overall survival was $66.2 \pm 2.7\%$, $39.5 \pm 2.9\%$ and $23.3 \pm 3.1\%$ at 10, 15 and 20 years with 18 patients at risk in the 20th year (Fig. 1A and Table 3). Survival favoured younger patients (<60 years) with one at risk at 24 years (Fig. 1B and Table 3). Overall survival in the MVR population was $61.7 \pm 3.3\%$, $39.0 \pm 3.4\%$ and $15.8 \pm 3.0\%$ at 10, 15 and 20 years (Fig. 2A and Table 3), respectively. Again, survival favoured younger patients (<60 years) with four patients alive at 25 years (Fig. 2B and Table 3). The linearised late-mortality rates were 5.88% and 6.70% per patient-year, respectively, for AVR and MVR. The reverse Kaplan–Meier median follow-up was 18.0 years (95% confidence interval (CI): 17.6–18.5) for AVR and 20.0 (95% CI: 18.0–22.0) for MVR.

3.2. Re-operation

Of the AVR cohort, 30 (9.9%) patients required re-operation during the follow-up period. Freedom from re-operation was $94.6 \pm 1.5\%$, $85.5 \pm 2.7\%$ and $79.3 \pm 4.4\%$ at 10, 15 and 20 years (Fig. 3A and Table 3). The linearised rate

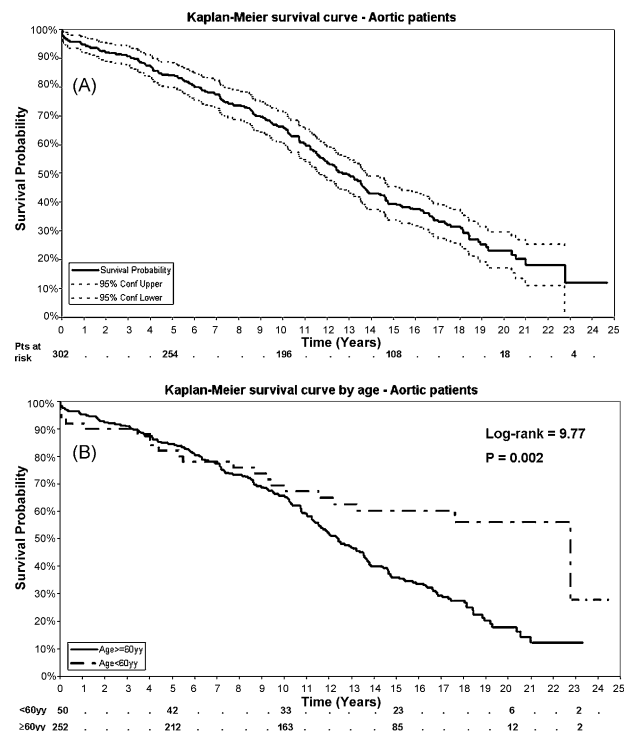


Fig. 1. AVR Kaplan–Meier survival – all ages (panel A) and by age group (panel B).

Table 3
Kaplan–Meier survival and freedom from re-operation.

Patient age at implant	% at 10 years	% at 15 years	% at 20 years
Kaplan–Meier survival			
AVR			
All	66.2 ± 2.7 (196)	39.5 ± 2.9 (108)	23.3 ± 3.1 (18)
<60	69.4 ± 6.6 (33)	60.0 ± 7.2 (23)	56.0 ± 7.8 (6)
≥60	65.6 ± 3.0 (163)	36.0 ± 3.1 (85)	18.0 ± 3.2 (12)
MVR			
All	61.7 ± 3.3 (132)	39.0 ± 3.4 (76)	15.8 ± 3.0 (18)
<60	80.1 ± 5.4 (43)	64.2 ± 6.6 (33)	33.8 ± 7.5 (12)
≥60	55.4 ± 3.9 (89)	30.5 ± 3.7 (43)	9.3 ± 2.9 (6)
Kaplan–Meier freedom from re-operation			
AVR			
All	94.6 ± 1.5 (193)	85.5 ± 2.7 (101)	79.3 ± 4.4 (13)
<60	87.4 ± 5.3 (31)	62.6 ± 8.4 (19)	52.2 ± 9.8 (3)
≥60	96.1 ± 1.4 (162)	90.9 ± 2.5 (82)	86.8 ± 4.7 (10)
MVR			
All	94.8 ± 1.8 (128)	73.3 ± 4.3 (64)	52.8 ± 6.7 (8)
<60	89.1 ± 4.6 (41)	65.6 ± 7.6 (25)	41.4 ± 10.3 (4)
≥60	96.5 ± 1.8 (87)	75.9 ± 5.4 (39)	61.9 ± 8.0 (4)

for AVR re-operation was 0.85% per patient-year. Patients older than 60 years had more favourable outcomes (Fig. 3B and Table 3). Of the MVR population, re-operation was required for 43 (20%) patients. Freedom from re-operation was $94.8 \pm 1.8\%$, $73.3 \pm 4.3\%$ and $52.8 \pm 6.7\%$ at 10, 15 and 20 years. One patient remained at risk at the 25th year (44% free from re-operation). The linearised event rate was 1.75% per patient-year. As with the aortic cohort, older age favoured freedom from re-operation with $61.9 \pm 8.0\%$ for patients ≥ 60 versus $49.7 \pm 8.5\%$ for those <60 at 18 years of

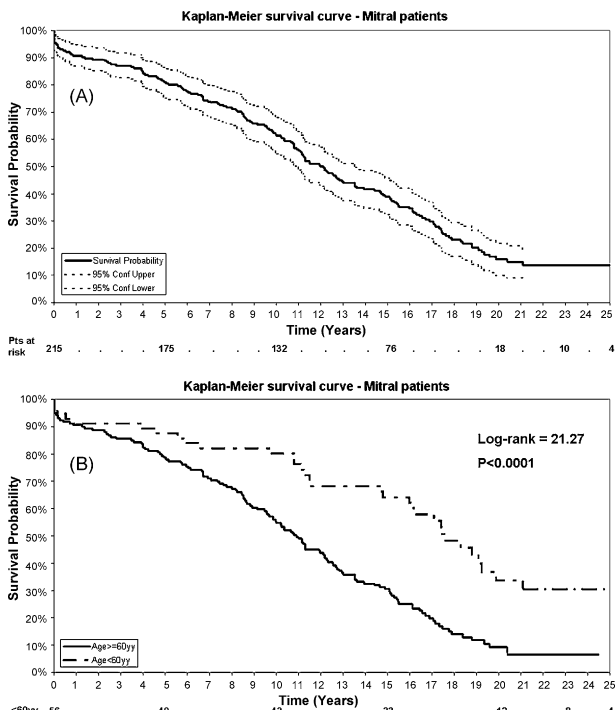


Fig. 2. MVR Kaplan–Meier survival — all ages (panel A) and by age group (panel B).

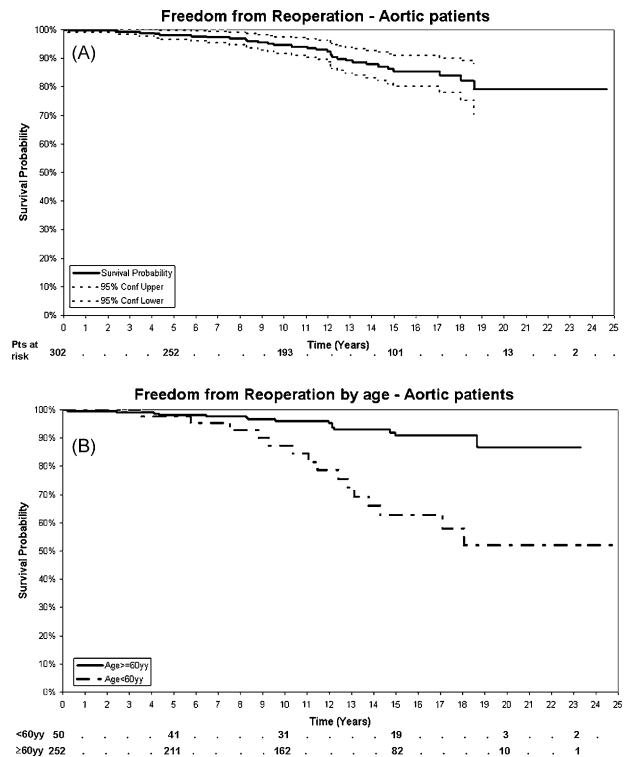


Fig. 3. AVR freedom from re-operation/replacement — all ages (panel A) and by age group (panel B).

follow-up (Fig. 4 and Table 3). The reverse Kaplan–Meier median follow-up was 13.1 years (95% CI: 12.0–14.1) for AVR and 12.3 (95% CI: 10.8–13.8) for MVR patients.

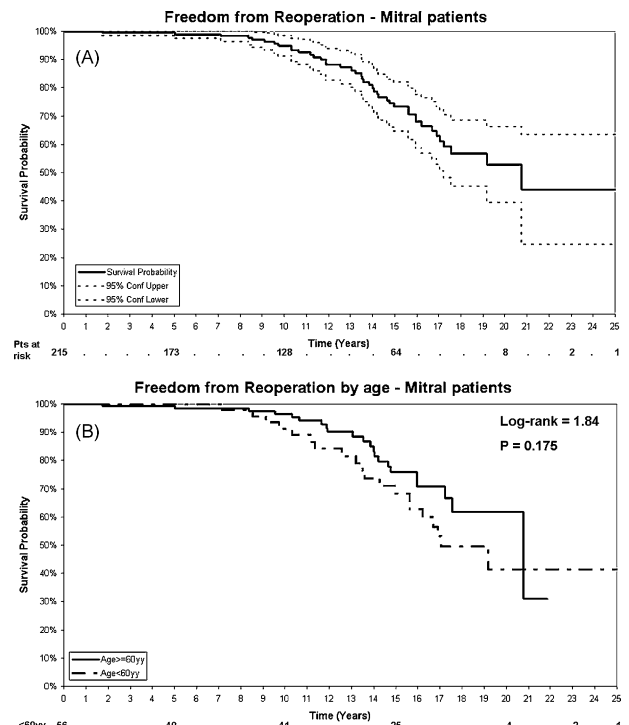


Fig. 4. MVR freedom from re-operation/replacement — all ages (panel A) and by age group (panel B).

4. Discussion

This article reports results up to 25 years experience with the HII bioprostheses. As such, it is the longest follow-up of a second-generation valve reported to date. Overall survival in a population with nearly 80% of the patients over 60 years of age is very satisfactory. Re-operation results in our present experience are particularly gratifying with overall actuarial freedom from events of 79.3% for AVR and 52.8% MVR, respectively, at 20 years. For the patient age group for which bioprostheses are most commonly indicated (≥ 60 years) the results are particularly gratifying with 86.8% and 61.9% freedom from re-operation for AVR and MVR, respectively.

There have been a number of recent reports of '20-year experience' with bioprostheses in the literature. However, time of experience should not be confused with clear results of the experience. That is to say, some papers have few if any patients at risk at 20 years and/or years at which assessments are made are < 20 years. For example, Myken and Bech-Hansen's report on the Biocor valve (St. Jude Medical, St. Paul, MN, USA) covers experience up to 20 years but, clearly, has no follow-up of patients at 20 years as there are no patients at risk at this time point [1]. In the report by Jamieson and colleagues on the Carpentier–Edwards SAV (Edwards Lifesciences, Irvine, California, USA) there are patients at risk at 20 years, but the majority of assessments for outcomes are performed on follow-up to 18 years where numbers of patients at risk are reasonable [2]. This may

provide more accurate assessment but cannot truly suggest expectation for the device's performance at 20 years. Our report, thus, differs in this regard as follow-up is truly at 20 years for the valve cohort. Result comparisons are thus limited by the ability to compare at different time points. Bioprostheses are typically indicated for use in older patients (≥ 60 years of age) for whom natural death diminishes the number of patients surviving at follow-up points [9]. This is especially true when follow-up is up to two decades following implant. When one considers this simply – when the average patient age at implant is 64 years, the average age of survivors at 20 years will be 84 – the impact on late survival can be appreciated. This significantly impacts the number of patients at risk in late follow-up typically resulting in very few patients at risk, perhaps too few to allow for one to assume that the late results are truly representative. This plagues many late follow-up articles including another experience for HII by Borger and colleagues and recent results for the Biocor and Mitroflow valves [1,2,4]. Our outcome results compare well with other late reports. Table 4 compares patients at risk for the latest follow-up point for which freedom from event assessment is made. It should be noted that literature comparisons must be weighed with the understanding that they are confounded by differences in baseline cohort characteristics in addition to the late reporting differences noted above.

In our experience, the Kaplan–Meier late survival for AVR was 23.3% at 20 years and 16.2% for MVR at 19 years. This

Table 4
Comparison of late '20-year' survival and re-operation.

Valve	# Patients	Mean age	Mean follow-up (years)	CABG (%)	NHYA \geq III (%)	Actuarial survival (years/patients @ risk)	Linearised rate (%/patient-year)	Longest follow-up (n @ risk)
Comparison of late '20-year' survival								
AVR								
Present study	302	65.7	11.6	18.5	75.3	20.3 (20/13)	5.73	24 (1)
Biocor ¹	1518	70.8	6.2	42	64	17.1 (19/12)	6.12 [†]	19 [†] (12)
CE SAV ²	1847	68.9	7.82	42.7	NR	6.8 (20/4)	6.3	20 (4)
Mitroflow ³	1512	73.2	4.07	50.2	55.7	6.1 (7)	9.97	20 (7)
HII ⁴	1010	67	7.4	46	77	19 (20/6)	NR	20 (6)
MVR								
Present study	215	62.5	10.95	12.1	85.1	16.2 (19/14)	6.43	25 (1)
Biocor ¹	194	64.9	6.2	34	88	16.4 (19/4)	7.78 [†]	19 [†] (4)

Valve	# Patients	Mean age	Mean follow-up	Actuarial freedom from re-operation (years/patients @ risk)	Linearised rate (%/patient-year)	# Re-operations
Comparison of late '20-year' re-operation						
AVR						
Present study	302	65.7	11.6	79.3 (20/13)	0.85	30
Biocor ¹	1518	70.8	6.2	61.1 [‡] (19/10)	1.3 [‡]	≤ 92
CE SAV ²	1847	68.9	7.82	64 (18/34)	1.11 [‡]	161
Mitroflow ³	1512	73.2	4.07	84.5 ^Δ	1.4	86
HII ⁴	1010	67	7.4	53 (20/6)	NR	72
CEP ¹⁰	716	72.6	5.5	62 (18/15)	0.45	28
MVR						
Present study	215	62.5	10.95	52.8 (19/14)	1.83	43
Biocor ¹	194	64.9	6.2	79.3 [‡] (19/4)	2.01	24

NR: neither rate nor cumulative patient years reported.

¹ Myken late follow-up time is unclear it appears > 18 , but clearly < 20 years.

² Freedom from re-operation for structural valve deterioration.

³ Linearised rate generated from reported patient years and events.

^Δ Actual freedom from re-operation.

compares favourably with values reported in the literature. It must be acknowledged that survival can be highly variable due to different factors such as health-care systems and baseline patient characteristics. Myken and Bech-Hansen reported actuarial survival with Biocor as 17.7% for AVR and 16.4% for MVR [1]. The Biocor aortic population is older than ours (70.8 vs 65.7 years); however, preoperatively, our patients' disease was more advanced with 75.3% in the New York Heart Association (NYHA) class \geq III versus 64% with Biocor. The mitral cohorts, on the other hand, were similar in age and preoperative disease. Concomitant CABG was more common in the Biocor population. Jamieson and colleagues report an AVR survival of only 6.8% at 20 years for the Carpentier–Edwards S.A.V. [2]. Mean age differs slightly between our cohort and Jamieson's, but the percentage of patients $>$ 60 years is similar at 83% and 80%, respectively. Yankah and colleagues report actuarial survival at 20 years for the Mitroflow aortic valve (Sorin, Turin, Italy) [3]. Comparison at 15 years (12.7%) may be more robust as there are 58 patients at risk [3]. Our 15-year event freedom was 38.5%, with 101 patients at risk. The latest follow-up in the literature for the Carpentier–Edwards pericardial valve is that of Aupart and colleagues [10]. They report their 18-year experience with actuarial survival of 22.4%. Comparison is particularly confounded by the fact that patients with native aortic insufficiency were not enrolled. Details regarding the compared populations are presented in Table 4.

We acknowledge that conventional reporting for re-operation focusses on the most common cause, structural valve deterioration (SVD) [1–5]. However, the cause of re-operation is of little consequence to the patient, health-care system, etc., as it is the re-operation itself that is the most significant impact to these groups. Of greater importance is the rate and timing of re-operation. Of course, the cause of failure may impact the surgeon in terms of therapy, timing of surgery, etc., but we would argue that comparing SVD is problematic given different definitions for reporting. For example, explant for SVD may under-report events while SVD, according to Edmunds and colleagues, *Guidelines for Reporting Morbidity and Mortality after Cardiac Valvular Operations*, may over-report intrinsic device failure [11,12]. The Edmunds guidelines specifically exclude re-operation for thromboembolism, prosthesis-patient mismatch, pannus, impingement, prosthetic valve endocarditis, etc., as SVD; however, these are not uncommon causes for re-operation. We thus opted for all-cause re-operation as a comparable follow-up outcome. Our HII results for re-operation, with a low number of re-operations over a long follow-up period, compare very favourably with other reports for overall age (Table 4). Comparison by age group is not possible as this level of detail is typically reserved for the smaller re-operation subset of SVD.

In conclusion, the results we report demonstrate good late survival and excellent freedom from re-operation when compared to late experience with other bioprosthetic valves.

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Appendix A. Conference discussion

Dr F. Mohr (Leipzig, Germany): I think this is a very important message and one could even speculate whether we could lower the age even further.

Dr P. Tesar (Milton, Australia): That was an outstanding paper from my perspective; I think it is amazing to get data out to 25 years. The highlight for me, and it is important, is the competing aspect of death to patients when they are followed in perpetuity, and you saw that roughly 78% of your patients died despite a median follow-up of about 12 years, and I think that is what we are going to see with all long long-term follow-up studies, because death is inexorable, for all of us.

The question I have for you is what are the lessons that you see from this paper? There has been a generational change in prostheses since you implanted these. What prosthesis do you now implant, bioprosthesis, in the aortic and mitral position, and have you changed the age criteria for when you implant the bioprosthesis in patients with or without coronary artery disease as well?

Dr Valfrè: I didn't hear the last question, but the message that I have is that personally I followed the fate of the Hancock family of valves since 1969. Next month I will celebrate the first implant of a Hancock formaldehyde-treated valve, and, as you just realized from my presentation, our group now celebrates 25 years of the Hancock II valve. We compared during the ongoing

continuing experience the Hancock valve with the other biological valves, tissue valves, used in different ages. Of course in our study, patients below 60 represent one-fourth of the cases, while older patients are in the majority. We have seen that you can safely implant the Hancock valve at different age decades, even below 60, because we saw a very clear relationship between durability of the valve and age of the patient at implant. So from age 60 you can always safely implant a Hancock because of the durability, but even for a patient at 50 years of age, you have a high chance, 85%, of having a still-functioning valve at 15 years. So I think this is a very important message.

The previous presentation was about stentless versus stented valves and Dr Mohr knows perfectly that we did follow quite the same experience. In effect, the quality of life with the stentless valve could temporarily give a little better result. But you have to focus on the kind of pathology. Our experience just presented considers the decade between '83 and '93, during which we had patients referred by cardiologists that were affected in prevalence by a pure valvular pathology; it means that very small associated pathologies were present. In a few words, we have been able to consider almost only valvular disease. In conclusion, basing on the results in terms of durability, the Hancock II represents the gold standard.