



# Medtronic

## HANCOCK® II BIOPROSTHESIS

Results from a Multi-Center Clinical Investigation

Clinical  
Compendium

### THE HANCOCK® II BIOPROSTHESIS

The Hancock® II bioprosthesis is a stented porcine aortic valve xenograft that has been glutaraldehyde-preserved and secured to a flexible stent. Tissue fixation with stabilized glutaraldehyde produces a virtually non-antigenic porcine valve.<sup>1</sup> The bioprosthesis is also treated by a sodium dodecyl sulfate (T6) process.

The acetal homopolymer stent of the Hancock II aortic (Model T505) and the mitral (Model T510) bioprostheses has a lower profile across all valve sizes as compared to the stent of the standard Hancock porcine bioprosthesis.

The inflow edge of the stent of the aortic bioprosthesis is fully scalloped, and the sewing ring is fully flush with the entire inflow edge of the stent. This facilitates implantation in either the Supra-X™ (supra- and extra-annular) or intra-annular position. If the Supra-X position is preferred, the entire bioprosthesis can be seated superior to the annulus, allowing the use of a larger Hancock II aortic valve.

### STUDY BACKGROUND AND PURPOSE

Included in this report is the result of a clinical investigation of the Hancock II bioprosthesis in the United States. The investigation was done to summarize the long-term clinical experience and performance of the Hancock II bioprosthesis.

The clinical investigation was conducted between 1983 and 1992 at 17 hospitals (13 study centers). Data was collected preoperatively, at implantation, within 30 days or prior to discharge, 6 months postoperative, and yearly thereafter. The study centers are listed in Appendix A.



The Hancock® II Bioprosthesis

In 1993, a cohort group consisting of seven study centers from the original Hancock II Clinical Investigation was established to evaluate long-term performance; e.g., valve-related mortality and morbidity of the aortic and mitral Hancock II bioprosthesis. Implants for this cohort took place between 1984 and 1987. Data collection for this long-term cohort is done every other year.

Follow-up data received through August 2000 for this long-term cohort are summarized in this compendium. Follow-up was complete in 94% of the patients.

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## METHODS & PATIENT POPULATIONS

A total of 406 patients had valve replacement: 267 had isolated aortic valve replacement, 102 patients had isolated mitral valve replacement, two patients had isolated tricuspid valve replacement, 27 patients had multiple valve replacement, and eight patients had non-isolated multiple valve replacement. Two-hundred-eighty-six (286) patients (70.4%) were male and 120 (29.6%) were female.

Patient age at implant ranged from 17 to 86 years, with a median of 66 years. The majority of these patients (55.9%) were between 51 and 70 years of age at implant. Of the 267 patients who had isolated aortic valve replacement, (211 men, 56 women), age at implant ranged from 17 to 86 years (median age of 67 years). Of the 102 patients who had isolated mitral valve replacement (53 men, 49 women), age at implant ranged from 26 years to 85 years (median of 65 years).

Survival analyses using the Kaplan-Meier<sup>2</sup> method were used to estimate survival and the freedom from valve-related adverse events. Peto's<sup>3</sup> formula was used for the calculation of the standard errors of these estimates. The reporting of the adverse events followed Edmunds' *Guidelines for Reporting Morbidity and Mortality After Cardiac Valvular Operations*.<sup>4</sup> The statistical methods are outlined in Appendix B.

## PREOPERATIVE DATA

### New York Heart Association (NYHA) Preoperative Functional Class

Three-hundred-twenty-nine (329) patients (81.8%) were categorized in NYHA Functional Class III or IV prior to surgery. The distribution of preoperative NYHA classification are presented in Table 1.

**Table 1: NYHA Functional Class Before Implant**

	AVR	%	MVR	%
I	5	1.9	0	0.0
II	55	20.7	11	11.0
III	169	63.5	71	71.0
IV	37	13.9	18	18.0
Unknown	1		2	

### Primary Etiologies

The most common etiologies reported among aortic valve replacement patients were calcification, rheumatic heart disease, and reoperation for previous replacement. For mitral valve replacement patients, rheumatic heart disease, reoperation for previous replacement, and endocarditis were the most frequent etiologies reported. These data are presented in Table 2.

**Table 2: Etiology for Valve-Replacement Patients**

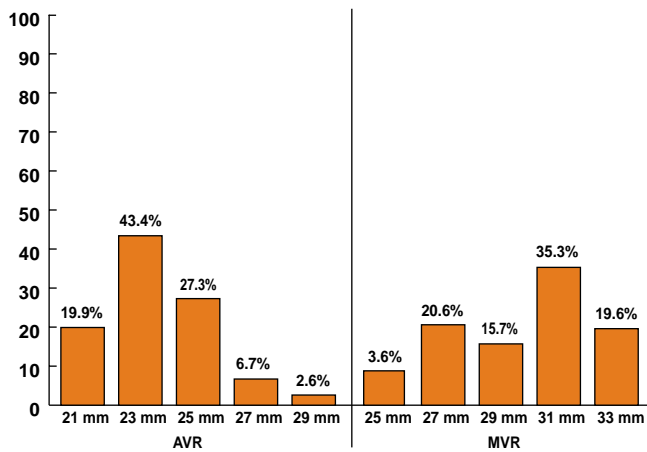
Etiology*	AVR	%	MVR	%
Calcification	175	68.9	1	1.3
Rheumatic Heart Disease	29	11.4	28	35.9
Endocarditis	21	8.3	12	15.4
Congenital	20	7.9	1	1.3
Degenerative	1	0.4	1	1.3
Myxomatous	3	1.2	5	6.4
Reoperation for Previous Repair	3	1.2	4	5.1
Reoperation for Previous Replacement	29	11.4	12	15.4
Papillary Muscle Dysfunction	0	0.0	5	6.4
Rupture Chordae	0	0.0	3	3.8
Other	12	4.7	18	23.1
Unknown	13		24	

\*Patients may have had more than one etiology.

## OPERATIVE DATA

The distribution of implanted aortic and mitral valve sizes among patients is reflected in Figure 1.

**Figure 1: Distribution of Aortic and Mitral Valve Size**



## Concomitant Operative Procedures

Coronary artery bypass was the most common concomitant operative procedure. The procedures are summarized in Table 3.

**Table 3: Concomitant Operative Procedures**

Concomitant Procedures*	AVR	%	MVR	%
Coronary Artery Bypass	84	31.5	32	31.4
Mitral Valve Repair	5	1.9	2	2.0
Tricuspid Valve Repair	0	0.0	4	3.9
Congenital Repair	0	0.0	0	0.0
Pacemaker	1	0.4	2	2.0
Aortic Repair	8	3.0	0	0.0
Aortic Annuloplasty	5	1.9	0	0.0
Tricuspid Annuloplasty	0	0.0	1	1.0
Ventricular Septal Defect Closed	1	0.4	0	0.0
Right Coronary Endarterectomy	1	0.4	0	0.0
Intra-aortic Balloon Pump Insertion	1	0.4	3	2.9
Other	3	1.1	3	2.9

\*Patients may have had more than one concomitant operative procedure.

## PATIENT FOLLOW-UP

Among the patients who were implanted with the Hancock® II bioprosthesis, a total of 2942 patient-years of experience had accumulated through August 2000. Cumulative follow-up after isolated aortic valve replacement was 2,204 patient-years with a mean follow-up of 8.3 years per patient (range = 0 years to 16.3 years). Cumulative follow-up after isolated mitral valve replacement was 738 patient-years with a mean follow-up of 7.2 years per patient (range = 0 years to 15.8 years). This is shown in Table 4.

**Table 4: Patient Follow-Up**

Patient-Years	AVR	MVR
Mean	8.3	7.2
Minimum	0.0	0.0
Maximum	16.3	15.8

## SURVIVAL ANALYSES

Linearized rates and estimates of survival for AVR and MVR are found in Tables 5 and 6. Operative mortality following AVR was 4.5% and 12.7% following MVR.

**Table 5: Mortality (AVR)**

	Late Events		Freedom from Event (%)		
	N	%/Pt-Yr	5 Years (SE)	12 Years (SE)	14 Years (SE)
All Deaths	151	(6.9)	72.3 (2.8)	40.9 (3.5)	32.8 (4.1)
Cardiac	44	(2.0)	88.6 (2.2)	73.2 (4.2)	70.7 (5.8)
Non-Cardiac	62	(2.8)	87.9 (2.3)	69.9 (4.3)	64.9 (5.9)
Valve-Related or Unexplained	45	(2.1)	92.9 (1.8)	80.0 (4.0)	71.6 (5.8)
Valve-Related	16	(0.7)	97.8 (1.1)	91.5 (3.0)	90.2 (4.3)

**Table 6: Mortality (MVR)**

	Late Events		Freedom from Event (%)		
	N	%/Pt-Yr	5 Years (SE)	12 Years (SE)	14 Years (SE)
All Deaths	57	(7.7)	67.7 (4.7)	28.3 (5.6)	24.4 (7.5)
Cardiac	23	(3.1)	84.4 (4.1)	54.7 (8.7)	54.7 (13.0)
Non-Cardiac	15	(2.0)	89.3 (3.5)	71.1 (9.0)	71.1 (13.5)
Study Valve-Related or Unexplained	19	(2.6)	89.7 (3.5)	72.8 (8.9)	62.8 (13.5)
Study Valve-Related	5	(0.7)	97.8 (1.8)	88.3 (7.1)	88.3 (10.7)

## FREEDOM FROM VALVE-RELATED DEATH

Valve-related death is defined as any death occurring as the result of a study valve-related adverse event (e.g., structural valve deterioration, nonstructural dysfunction, bioprosthetic thrombosis, thromboembolism, endocarditis, major antithromboembolic-related hemorrhage) or any death that occurs within 30 days of a study valve-related reoperation.

Figure 2 shows freedom from valve-related death following AVR at 14 years is 90.2% ± 4.3%.

**Figure 2: Freedom from Valve-Related Death Following AVR, All Ages**

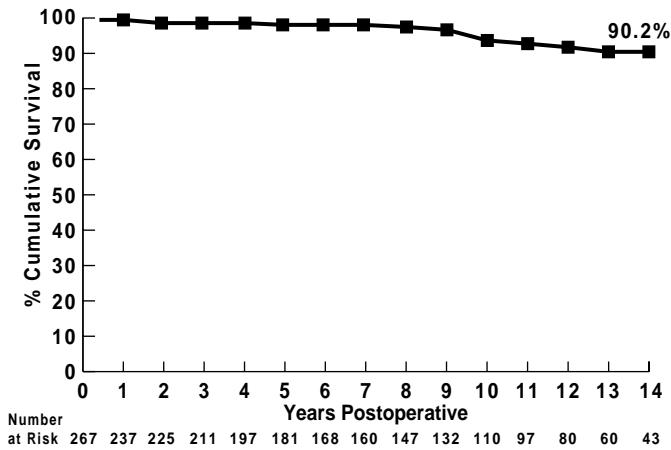
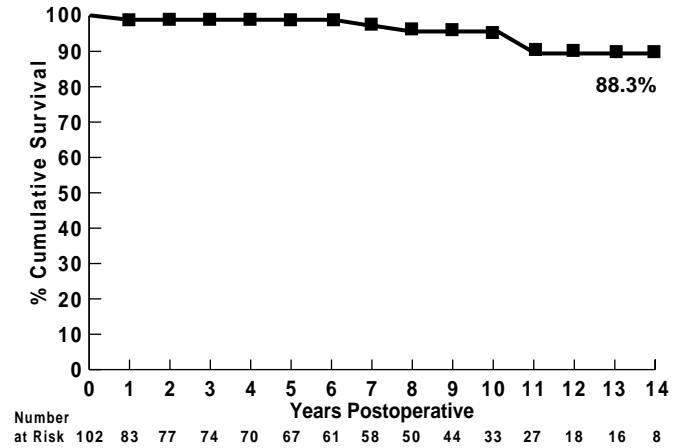


Figure 3 shows freedom from valve-related death following MVR at 14 years is 88.3% ± 10.7%.

**Figure 3: Freedom from Valve-Related Death Following MVR, All Ages**



## VALVE-RELATED COMPLICATION RATES FOLLOWING AVR

Study valve-related morbidity is summarized through 14 years. The reporting of adverse events follows Edmunds' *Guidelines for Reporting Morbidity and Mortality After Cardiac Valvular Operations*.<sup>4</sup> Reasons for study valve-related reoperations and causes of valve-related death are also included.

Tables 7 and 8 present summaries of late events and Kaplan-Meier estimates for adverse events.

**Table 7: Valve-Related Complication Rates Following AVR**

Valve-Related Event	Late Events (% per Patient-year)	% Freedom from Event (SE)		
		At 5 Years	At 12 Years	At 14 Years
Thromboembolism <sup>1</sup>	42 (1.9)	92.9 (1.9)	80.2 (4.3)	77.5 (6.2)
Permanent Neurological Event	21 (1.0)	96.7 (1.3)	89.3 (3.4)	87.9 (4.8)
Transient Neurological Event	18 (0.8)	96.7 (1.3)	91.5 (3.1)	89.9 (4.6)
Primary Valve Thrombosis <sup>2</sup>	3 (0.1)	98.7 (0.8)	98.7 (1.3)	98.7 (1.7)
Structural Valve Deterioration	23 (-)	100.0 (0.0)	90.0 (3.2)	82.9 (5.2)
≤ 60 Years (n=44 patients)	16 (-)	100.0 (0.0)	84.2 (5.9)	68.7 (9.6)
61-70 Years (n=93 patients)	7 (-)	100.0 (0.0)	88.6 (5.6)	88.6 (7.1)
> 70 Years (n=91 patients)	0 (-)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)
Nonstructural Valve Dysfunction <sup>3</sup>	2 (-)	99.1 (0.7)	99.1 (1.0)	99.1 (1.4)
Endocarditis	15 (0.7)	95.8 (1.5)	92.2 (3.0)	88.9 (4.7)
Primary Periprosthetic Leak <sup>4</sup>	6 (0.3)	98.5 (0.9)	96.1 (2.2)	96.1 (3.0)
Major Primary Periprosthetic Leak	0 (0.0)	-	-	-
Major Antithromboembolic-Related				
Hemorrhage	5 (0.2)	99.5 (0.5)	95.9 (2.2)	95.9 (3.1)
Primary Hemolysis <sup>5</sup>	0 (0.0)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)
Reoperation	38 (-)	96.1 (1.4)	84.5 (3.7)	74.3 (5.7)
Explant	37 (-)	96.6 (1.3)	84.9 (3.7)	74.6 (5.7)

1. Three patients had late peripheral arterial emboli.
2. Primary valve thrombosis is a separate sub-category of thromboembolism and identified by clinical investigation (for example) and confirmed at reoperation or autopsy.
3. The term nonstructural valve dysfunction refers to non-structural problems that result in stenosis or regurgitation that are not intrinsic to the valve itself and include entrapment by pannus (tissue over-growth).
4. Periprosthetic leak is defined as a deficit in the attachment of the sewing ring of the heart valve prosthesis and the annular tissue of the native heart valve, as determined by reoperative, autopsy, or clinical investigation (Doppler echocardiography, angiocardiography, auscultation), that caused hemodynamic valve dysfunction. Periprosthetic leaks caused by endocarditis are categorized as secondary events. Periprosthetic leaks that required surgical intervention are considered major periprosthetic leaks and those leaks that did not require surgical intervention are considered minor periprosthetic leaks.
5. Hemolysis is defined as all cases of anemia attributable to the bioprosthesis based on usual clinical criteria that required long-term iron supplement, blood transfusion, or bioprosthesis replacement.

## VALVE-RELATED COMPLICATION RATES FOLLOWING MVR

Study valve-related morbidity is summarized through 14 years. The reporting of adverse events follows Edmunds' *Guidelines for Reporting Morbidity and Mortality After Cardiac Valvular Operations*.<sup>4</sup> Reasons for study valve-related reoperations and causes of valve-related death are also included.

**Table 8: Valve-Related Complication Rates Following MVR**

Valve-Related Event	Late Events (% per Patient-year)	% Freedom from Event (SE)		
		At 5 Years	At 12 Years	At 14 Years
Thromboembolism <sup>1</sup>	23 (3.1)	89.4 (3.7)	66.8 (9.9)	66.8 (14.5)
Permanent Neurological Event	10 (1.4)	95.4 (2.5)	81.5 (8.5)	81.5 (12.4)
Transient Neurological Event	10 (1.4)	95.1 (2.6)	88.3 (7.6)	88.3 (11.4)
Primary Valve Thrombosis <sup>2</sup>	0 (0.0)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)
Structural Valve Deterioration	10 (-)	98.5 (1.5)	78.4 (8.6)	74.1 (13.3)
≤ 60 Years (n=24 patients)	7 (-)	96.6 (3.4)	71.3 (14.4)	61.1 (26.9)
61-70 Years (n=46 patients)	2 (-)	100.0 (0.0)	82.5 (12.2)	82.5 (17.3)
> 70 Years (n=20 patients)	1 (-)	100.0 (0.0)	85.7 (18.7)	85.7 (22.9)
Nonstructural Valve Dysfunction <sup>3</sup>	0 (-)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)
Endocarditis	5 (0.7)	98.8 (1.3)	91.8 (6.4)	91.8 (9.3)
Primary Periprosthetic Leak <sup>4</sup>	1 (0.1)	97.5 (1.9)	97.5 (3.7)	97.5 (5.8)
Major Primary Periprosthetic Leak	0 (0.0)	-	-	-
Major Antithromboembolic-Related				
Hemorrhage	7 (1.0)	95.9 (2.4)	90.1 (6.9)	90.1 (10.7)
Primary Hemolysis <sup>5</sup>	0 (0.0)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)
Reoperation	12 (-)	98.5 (1.5)	72.8 (8.9)	68.7 (13.6)
Explant	12 (-)	98.5 (1.5)	72.8 (8.9)	68.7 (13.6)

1. Three patients had late peripheral arterial emboli.

2. Primary valve thrombosis is a separate sub-category of thromboembolism and identified by clinical investigation (for example) and confirmed at reoperation or autopsy.

3. The term nonstructural valve dysfunction refers to non-structural problems that result in stenosis or regurgitation that are not intrinsic to the valve itself and include entrapment by pannus (tissue over-growth).

4. Periprosthetic leak is defined as a deficit in the attachment of the sewing ring of the heart valve prosthesis and the annular tissue of the native heart valve, as determined by reoperative, autopsy, or clinical investigation (Doppler echocardiography, angiocardiography, auscultation), that caused hemodynamic valve dysfunction. Periprosthetic leaks caused by endocarditis are categorized as secondary events. Periprosthetic leaks that required surgical intervention are considered major periprosthetic leaks and those leaks that did not require surgical intervention are considered minor periprosthetic leaks.

5. Hemolysis is defined as all cases of anemia attributable to the bioprosthesis based on usual clinical criteria that required long-term iron supplement, blood transfusion, or bioprosthesis replacement.

## VALVE-RELATED COMPLICATIONS

### Freedom from Explant Due to Structural Valve Deterioration

Figure 4 shows that freedom from explant due to structural valve deterioration following AVR for all ages at 14 years is  $82.9\% \pm 5.2\%$ .

**Figure 4: Freedom from Explant Due to Structural Valve Deterioration Following AVR**

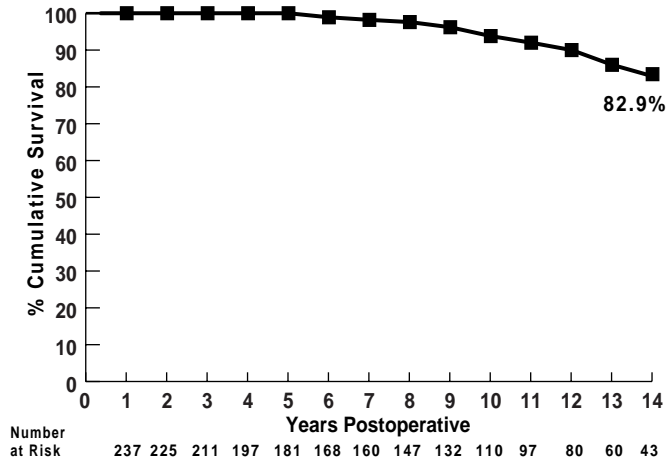
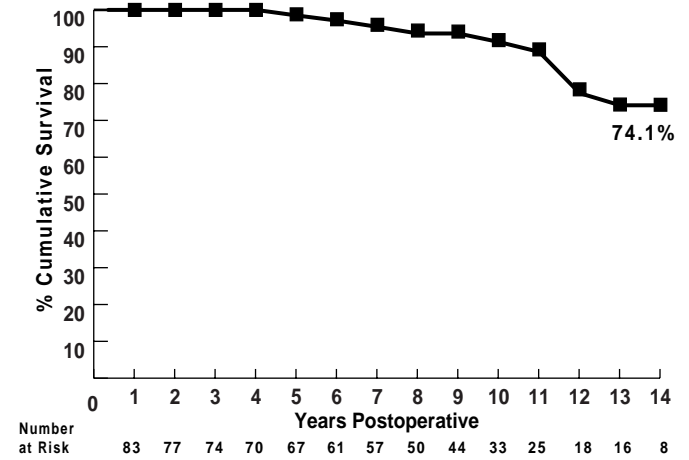


Figure 5 shows that freedom from explant due to structural valve deterioration following MVR for all ages at 14 years is  $74.1\% \pm 13.3\%$ .

**Figure 5: Freedom from Explant Due to Structural Valve Deterioration Following MVR**



## VALVE-RELATED COMPLICATIONS

### Freedom from Explant Due to Structural Valve Deterioration (by Age Groups)

Figure 6: Freedom from Explant Due to Structural Valve Deterioration Following AVR by Age Groups

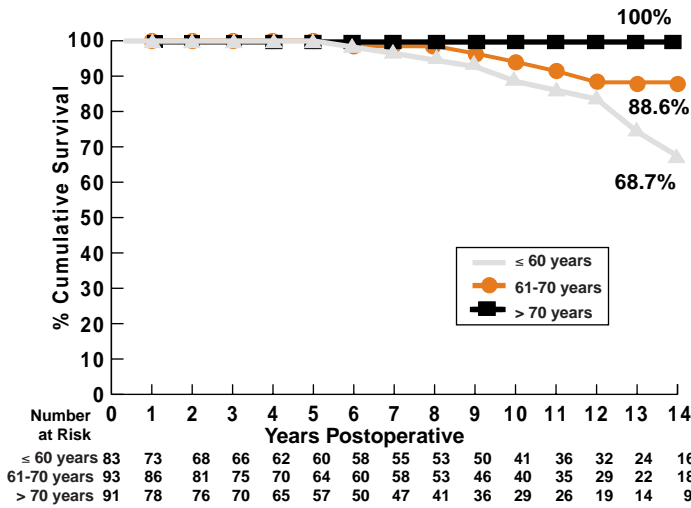


Figure 8: Actual Freedom from Explant Due to Structural Valve Deterioration Following AVR by Age Groups

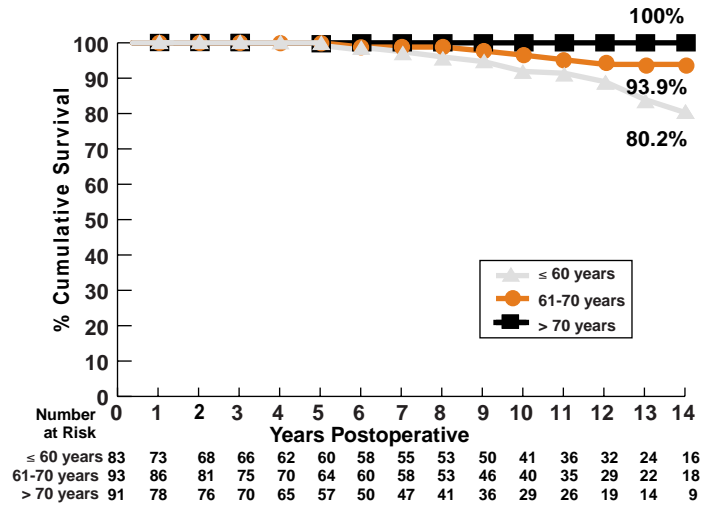


Figure 7: Freedom from Explant Due to Structural Valve Deterioration Following MVR by Age Groups

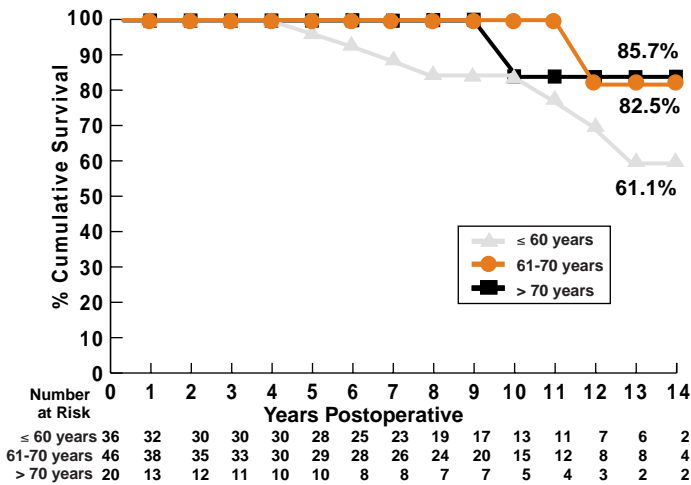
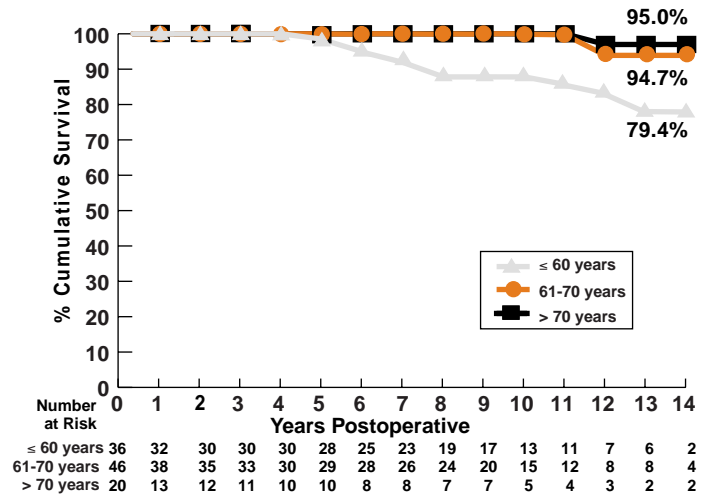


Figure 9: Actual Freedom from Explant Due to Structural Valve Deterioration Following MVR by Age Groups



## VALVE-RELATED COMPLICATIONS

### Freedom from Explant Due to Structural Valve Deterioration for Patients $\geq 65$ Years at Implant

Figure 10 shows that the freedom from explant due to structural valve deterioration is  $92.5\% \pm 5.8\%$  at 14 years for AVR patients

**Figure 10: Freedom from from Explant Due to Structural Valve Deterioration Following AVR Patients  $\geq 65$  Years at Implant**

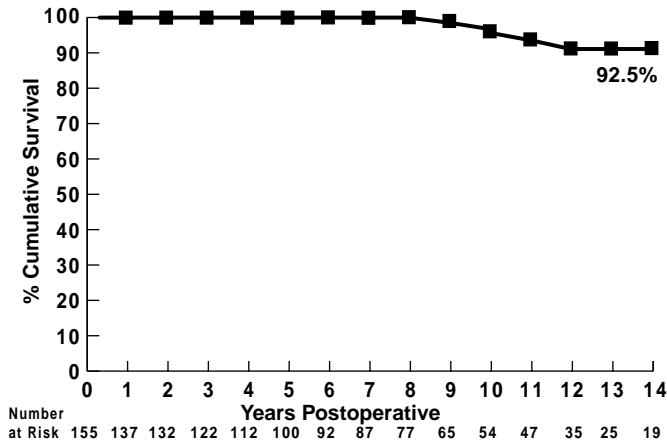
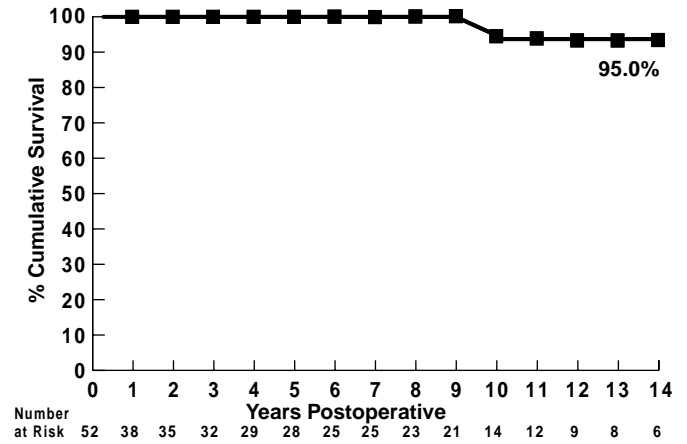


Figure 12 shows that freedom from explant due to endocarditis following AVR is  $88.9\% \pm 4.7\%$  at 14 years.

**Figure 11: Freedom from from Explant Due to Structural Valve Deterioration Following MVR Patients  $\geq 65$  Years at Implant**



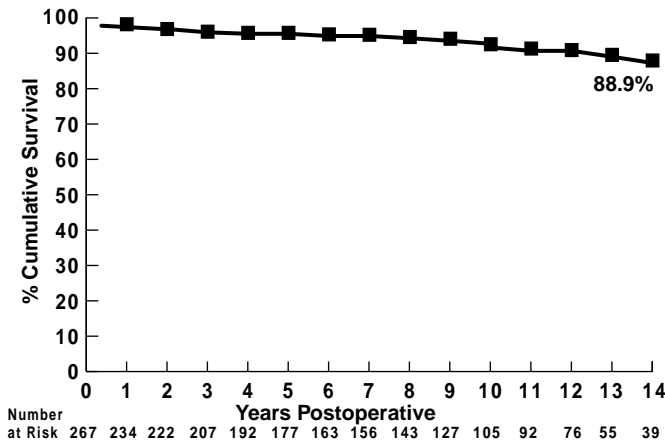
### Freedom from Endocarditis

Endocarditis is defined as documented evidence of infection of the valve based on histopathological evidence of bioprosthetic endocarditis in a surgical or autopsy specimen, or when at least two microbiological blood cultures for the same organism are obtained in a patient with two or more clinical signs or symptoms of endocarditis.

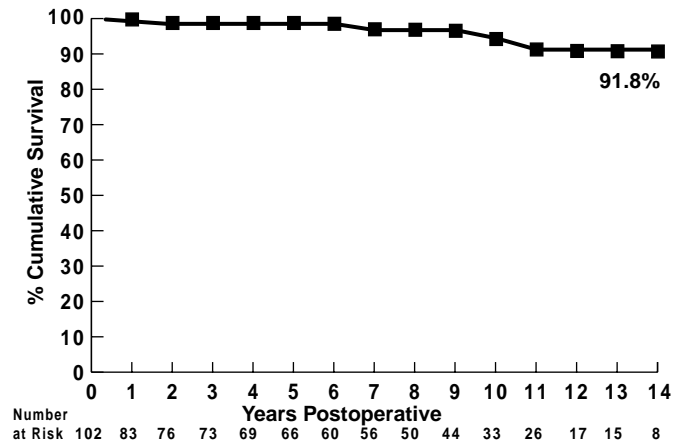
$\geq 65$  years at implant.

Figure 11 shows that the freedom from structural valve deterioration is  $95.0\% \pm 8.7\%$  at 14 years for MVR patients

**Figure 12: Freedom from Endocarditis Following AVR**



**Figure 13: Freedom from Endocarditis Following MVR**



$\geq 65$  years at implant.

## VALVE-RELATED COMPLICATIONS

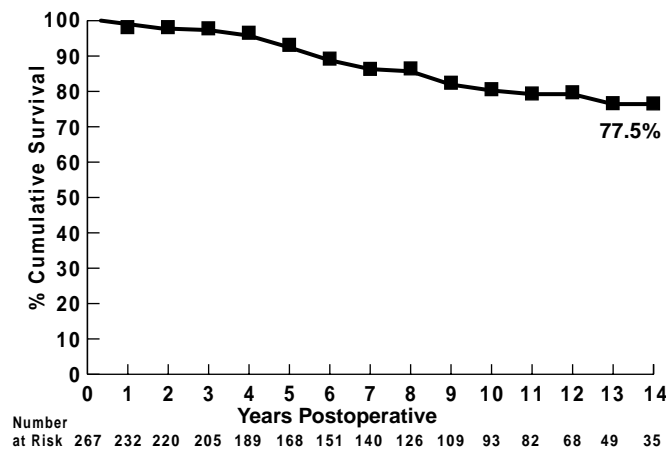
### Freedom from Thromboembolism

Thromboembolism includes all new episodes of focal or global deficits (permanent or transient), peripheral arterial embolization, and myocardial infarction, unless proven to be from other causes.

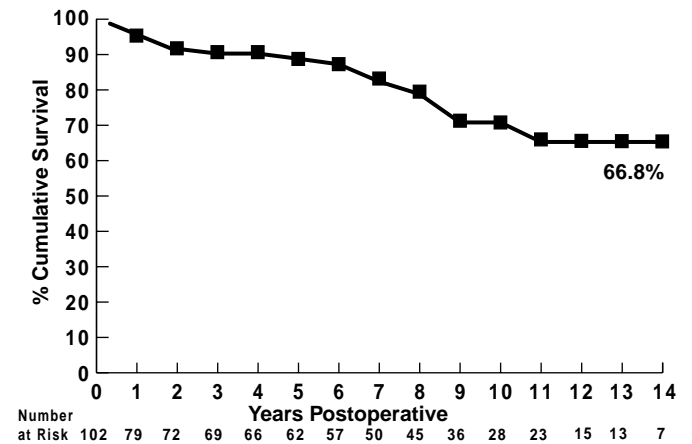
Figure 13 shows that freedom from endocarditis following MVR is  $91.8\% \pm 9.3\%$  at 14 years.

Figure 14 shows that freedom from thromboembolism following AVR is  $77.5\% \pm 6.2\%$  at 14 years.

**Figure 14: Freedom from Thromboembolism Following AVR**



**Figure 15: Freedom from Thromboembolism Following MVR**

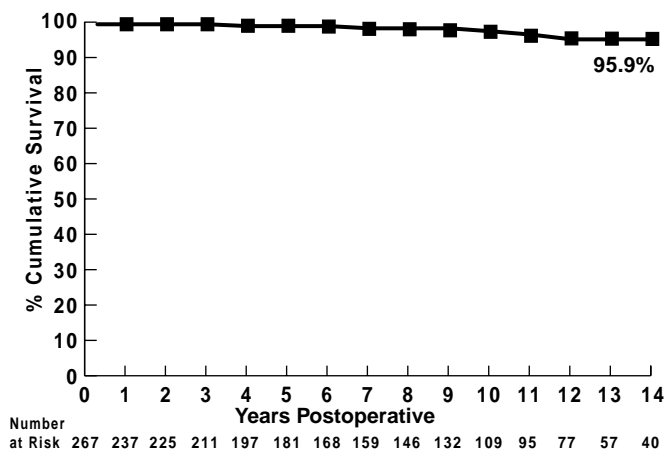


### Freedom from Major Antithromboembolic-related Hemorrhage

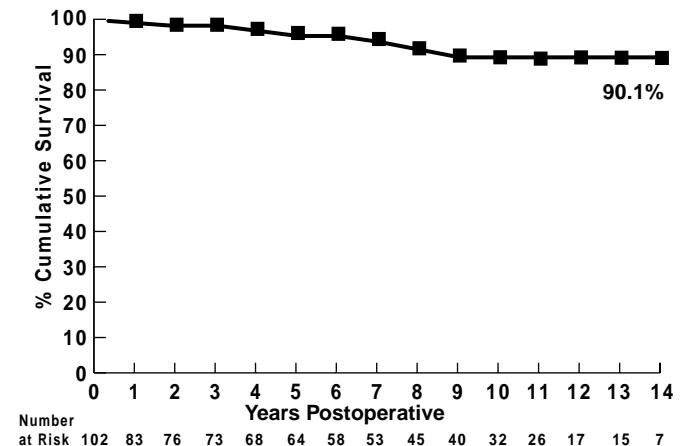
Major hemorrhage related to antithromboembolic therapy includes all episodes of internal or external bleeding that cause death, stroke, operation, hospitalization, or required blood transfusion. It is restricted to patients who were receiving anticoagulant and/or antiplatelet therapy.

Figure 16 shows that freedom from major antithromboembolic-related hemorrhage following AVR is  $95.9\% \pm 3.1\%$  at 14 years.

**Figure 16: Freedom from Major Antithromboembolic-Related Hemorrhage Following AVR**



**Figure 17: Freedom from Major Antithromboembolic-Related Hemorrhage Following MVR**



## VALVE-RELATED COMPLICATIONS

### Freedom from Reoperation

Reoperation is defined as any reoperation that repairs, alters, or replaces the study bioprosthesis.

Figure 18 shows that freedom from reoperation following AVR is  $74.3\% \pm 5.7\%$  at 14 years.

**Figure 18: Freedom from Reoperation Following AVR**

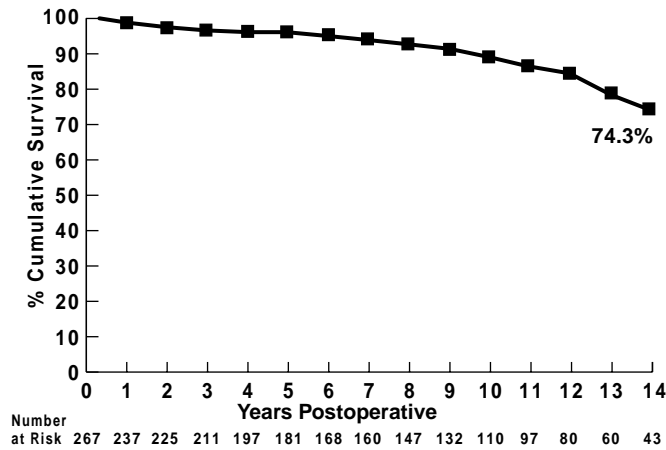
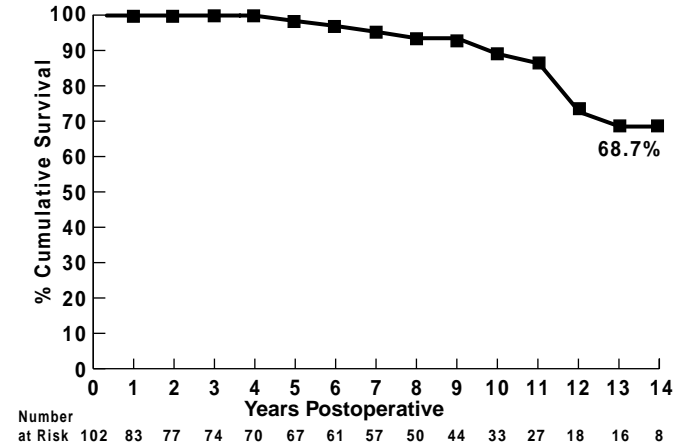


Figure 19 shows that freedom from reoperation following MVR is  $68.7\% \pm 13.6\%$  at 14 years.

**Figure 19: Freedom from Reoperation Following MVR**



### Freedom from Explant

Explant is defined as study bioprostheses that were removed from the patient at reoperation.

Figure 20 shows that freedom from explant following AVR is  $74.6\% \pm 5.7\%$  at 14 years.

**Figure 20: Freedom from Explant Following AVR**

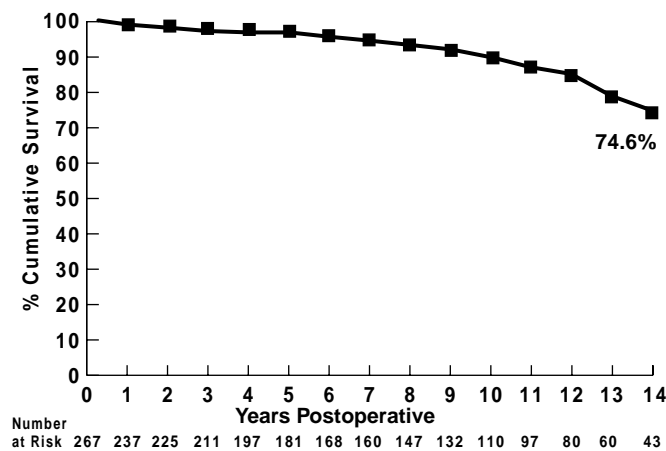
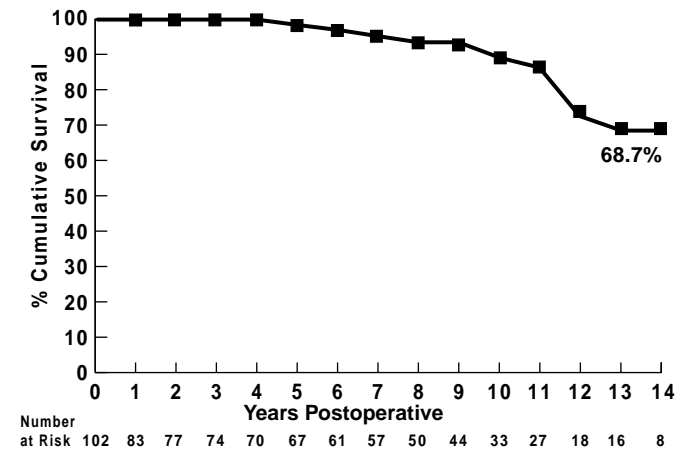


Figure 21 shows that freedom from explant was  $68.7\% \pm 13.6\%$  at 14 years.

**Figure 21: Freedom from Explant Following MVR**



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## SUMMARY

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### Summary of Results

The Hancock® II bioprosthesis continues to demonstrate that it is safe and effective in clinical use, as evidenced by these two major studies. The results are consistent with those reported in the literature for other bioprosthetic heart valves.

In addition, long term postoperative data describing freedom from structural valve deterioration for the aortic and mitral Hancock II bioprosthesis are consistent with statistics for other tissue valves in the published literature.

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## APPENDIX A – HANCOCK® II BIOPROSTHESIS STUDY CENTERS PROVIDING LONG-TERM FOLLOW-UP

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### U.S. Study

Baystate Medical Center	Springfield, Massachusetts, USA
Brigham & Women's Hospital	Boston, Massachusetts, USA
California Pacific Medical Center	San Francisco, California, USA
Columbia Presbyterian Hospital	New York, New York, USA
Harbor UCLA Medical Center	Torrance, California, USA
John L. McClellan VA Hospital	Little Rock, Arkansas, USA
Tallahassee Regional Medical Center	Tallahassee, Florida, USA

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## APPENDIX B – STATISTICAL METHODS

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### Statistical Methods

#### Early Event Rates and Linearized Rates

Early event rates were calculated as the number of patients having the event divided by the total number of patients, expressed as a percentage.

Linearized morbidity rates (percentage per patient-year) were calculated by dividing the number of late morbid events, including multiple events for any one patient, by the sum of the late morbidity patient-years of experience, expressed as a percentage. Linearized morbidity rates are presented for thromboembolism, valve thrombosis, endocarditis, periprosthetic leak, hemolysis, and major antithrombotic-related hemorrhage. Since the likelihood of the event increases over time (increasing hazard function) for prosthetic valve dysfunction, study valve-related reoperation, explant, and death, the linearized rates for these adverse events are not presented.

#### Survival Analysis

Survival analyses using the Kaplan-Meier<sup>2</sup> method were used to estimate survival and the freedom from the first occurrence of the study valve-related adverse event distributions. Peto's formula<sup>3</sup> was used for the calculation of the standard errors of these estimates. Time to first event occurring within both the early and late postoperative periods was included in this analysis.

#### Actual Analysis

Cumulative Incidence (CI) of SVD adjusting for patient deaths was calculated using an algorithm developed by W. Anderson.<sup>5</sup> Actual freedom from SVD is calculated as 1-CI, and is presented as a percentage.

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**Hancock® II Bioprosthesis**

**Indications:** Replacement of impaired native or prosthetic aortic and mitral valves.

**Contraindications:** None known.

**Warnings/Precautions/Adverse Events:** Accelerated deterioration due to calcific degeneration of bioprosthesis may occur in: children, adolescents, young adults, and patients with altered calcium metabolism (e.g., chronic renal failure, hyperparathyroidism). Adverse events can include: angina, cardiac arrhythmia, death, endocarditis, heart failure, hemolysis, hemolytic anemia, hemorrhage, transvalvular or paravalvular leak, myocardial infarction, nonstructural dysfunction, stroke, structural deterioration, thromboembolism, or valve thrombosis.

For additional information, please refer to the Instructions For Use provided with the product.

**CAUTION:** Federal law (USA) restricts this device to sale by or on the order of a physician.



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