

# The Mosaic Valve Clinical Performance at Seven Years: Results from a Multicenter Prospective Clinical Trial

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**Background and aim of the study:** The Mosaic valve is a third-generation stented porcine bioprosthesis built upon the historical durability of the Hancock II valve in an attempt to improve hemodynamic performance and durability.

**Methods:** This multicenter trial was prospective and non-randomized in design. Between February 1994 and October 1999, six centers following a common study protocol enrolled 797 patients (mean age 70 years; range: 21-88 years) who underwent aortic valve replacement (AVR), and 232 patients (mean age 68 years; range: 17-84 years) who underwent mitral valve replacement (MVR). The cumulative follow up was 3,442 patient-years (pt-yr) for AVR (mean 4.3 years; maximum 8 years), and 870 pt-yr for MVR (mean 3.7 years; maximum 7 years). Follow up was complete for 95% of AVR patients, and for 97% of MVR patients.

**Results:** The mean gradient and calculated effective

orifice area average across all valve sizes remained stable at one, four and six years. Freedom from valve-related adverse events (mean  $\pm$  SE) at one, four and seven years after AVR were, respectively: Anti-thromboembolic-related hemorrhage (ARH)  $97.0 \pm 0.6$ ,  $95.6 \pm 0.9$ , and  $94.6 \pm 5.1\%$ ; primary hemolysis 100, 100, and 100%; and structural valve deterioration (SVD) 100, 100 and 100%. Freedom at one, four and seven years after MVR were: ARH  $96.9 \pm 1.2$ ,  $95.6 \pm 2.0$ , and  $95.6 \pm 7.6\%$ ; primary hemolysis 100, 100, and 100%; and SVD 100, 100, and 100%.

**Conclusion:** These mid-term results demonstrate the clinical safety and excellent performance of the Mosaic valve. Continued follow up will determine if this new-design, third-generation bioprosthesis will provide increased durability.

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The use of bioprosthetic cardiac valves provides patients with the surgical benefits of correction of their valvular pathology whilst avoiding or minimizing the risk of complications associated with the life-long anti-coagulation necessary with mechanical valves. Unfortunately, bioprostheses have exhibited limited durability because of progressive tissue degeneration and calcification leading to structural valve degeneration (SVD) and suboptimal hemodynamic performances. The Medtronic Mosaic valve is a third-generation stented porcine bioprosthesis built upon the historical durability of the Hancock II valve (1), in an attempt to improve hemodynamic performance and durability

(2,3). The valve design includes predilatation of the porcine aortic root and physiological tissue fixation with glutaraldehyde, with zero net pressure across the leaflets. The tissue is then mounted on a flexible polymer stent and treated with the AOA process, where alpha-amino oleic acid (a naturally occurring long-chain fatty acid) is used and binds to the aldehyde fractions of the glutaraldehyde-preserved porcine tissue. The AOA process has been shown in animal studies to reduce porcine valve mineralization (leaflets and aortic wall) and improve valve gradients (4,5). The Mosaic aortic valve has a low-profile, supra-annular configuration, while the mitral valve has a generous sewing ring.

This report is a review of data obtained from the ongoing post-FDA approval long-term clinical study of the Medtronic Mosaic valve. The primary aim of this study was to document ongoing and long-term efficacy, safety and clinical performance of the Mosaic valve.

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*Table I: Causes of valve-related death after aortic valve replacement (AVR) or mitral valve replacement (MVR) with the Mosaic bioprosthesis.*

Cause of death	AVR (n)	MVR (n)
Endocarditis	7	2
ARH	2	0
CVA	4	0
Myocardial infarction	1	0
CHF due to paravalvular leak	0	1

ARH: Antithromboembolic-related hemorrhage; CHF: Congestive heart failure; CVA: cerebrovascular accident.

## Clinical material and methods

### Patient population

The early clinical performance results of the Mosaic valve from a multicenter international prospective clinical trial involving 17 primary participating centers was reported previously (3). The present prospective clinical trial was completed in the fall of 2000, at which point six centers (see Acknowledgements for details) were selected from the original 17 for the multicenter, prospective, non-randomized post-FDA approval long-term clinical study of the Medtronic Mosaic valve. Factors which contributed to the selection of six centers for the post-approval study included the number of patients enrolled and available for continued follow up, and center study compliance during the initial investigation.

Patients diagnosed with valvular heart disease and requiring isolated replacement of either the aortic or mitral valve were eligible to enter the study.

Concomitant procedures (other than valve replacement) were permitted. Patients with active endocarditis at the time of implant were also permitted to enter the study. A total of 13 patients had active endocarditis (eight AVR, five MVR), and 16 patients had healed endocarditis (eight AVR, eight MVR). Patients requiring a concomitant valve replacement, or who had a pre-existing prosthetic valve in another position, were excluded. Each of the centers involved obtained ethics committee approval, and informed consent was acquired from each patient who entered the study.

### Study design

A total of 1,029 patients was recruited between February 1994 and October 1999 in six centers, following a common study protocol. In total, 797 patients (66% males; mean age 70 years; range: 21 to 88 years) underwent AVR, and 232 patients (48% males; mean age 68 years; range: 17 to 84 years) underwent MVR. Proportionally, 65% of AVR were performed for aortic valve stenosis, 13% for insufficiency, and 22% for mixed lesions. By comparison, 78% of MVR were performed for mitral valve insufficiency, 9% for stenosis, and 13% for mixed lesions. A concomitant coronary artery bypass procedure was performed in 45% of AVR patients, and in 44% of MVR patients. A total of 15% AVR and 23% MVR patients had undergone previous cardiovascular procedures.

### Follow up

Follow up clinical and hemodynamic data were collected at the early evaluation (prior to discharge or within 30 days of implantation), late evaluation (at 3-6 months post implant), at one year, and annually thereafter. Hemodynamic assessments were made using transthoracic echocardiography to assess the structure

*Table II: Valve-related adverse events (late) after aortic valve replacement (AVR) or mitral valve replacement (MVR) with the Mosaic bioprosthesis.*

Event	AVR		MVR	
	No. of patients	%/pt-yr	No. of patients	%/pt-yr
Thromboembolism	45	1.3	12	1.4
Permanent	20	0.6	3	0.4
Transient	24	0.7	8*	0.9
Valve thrombosis	4	0.1	1	0.1
SVD	0	0.0	0	0.0
Endocarditis	24	0.7	5	0.6
Paravalvular leak	10	0.3	6	0.7
Major ARH	26	0.8	6	0.7
Reoperation	21	0.6	5	0.6

ARH: Antithromboembolic-related hemorrhage; SVD: structural valve deterioration  
\*Two early events occurred in one patient after MVR.

Table III: Freedom (%) from valve-related adverse events at seven years after aortic valve replacement (AVR) or mitral valve replacement (MVR) with the Mosaic bioprosthesis.

Event	AVR	MVR
Thromboembolism	90.5 ± 6.6	88.0 ± 12.4
Valve thrombosis	99.6 ± 1.4	99.3 ± 3.1
SVD	100.0	100.0
Endocarditis	96.5 ± 3.9	97.9 ± 5.4
Paravalvular leak	97.9 ± 3.2	95.6 ± 7.6
Major ARH	94.6 ± 5.1	95.6 ± 7.6
Reoperation	97.0 ± 3.7	97.2 ± 6.2

ARH: Antithromboembolic-related hemorrhage; SVD: structural valve deterioration

and function of the Mosaic valve. The mean transvalvular gradient for the aortic bioprosthesis was calculated using the long form of the Bernoulli equation, and effective orifice area (EOA) was calculated using the continuity equation. The valve-related complications, composites of complications and deaths were classified and reported according to the guidelines of the Society of Thoracic Surgeons, of the American Association of Thoracic Surgery and of the European Association of Cardio-Thoracic Surgery (6).

Follow up was complete for 95% and 97% of AVR and MVR patients, respectively. This provided for a cumulative follow up of 3,442 patient-years (pt-yr) for AVR (mean 4.3 years; maximum 8 years), and 870 pt-yr for MVR (mean 3.7 years; maximum 7 years).

**Statistical analysis**

Statistical analysis was performed using the SAS® statistical software. Descriptive statistics were used to

characterize the patient population data, operative and follow up clinical data. For continuous variables, the number of patients, mean (±SD), minimum and maximum were provided. For categorical variables, the number and percentage of patients were provided.

Early events rate were calculated as the number of patients having the event divided by the total number of patients, expressed as a percentage. Linearized rates (% per pt-yr) were used to summarize late events, and calculated by dividing the number of late events by the sum of the late pt-yr of experience, expressed as a percentage.

Survival analyses using the Kaplan-Meier method were used to estimate survival and the freedom from valve-related adverse events. Peto's formula (7) was used to calculate standard errors of these estimates. Events that occurred during the early and late postoperative periods were included in this analysis.

**Results**

**Early and late deaths**

In the AVR group, the early mortality rate was 2.8%. Among the 22 early deaths, three were valve-related (0.4%), 15 were cardiac (1.9%), three were non-cardiac (0.4%), and one was unexplained (0.1%). The linearized rate for late mortality was 2.2% per pt-yr. Of these 73 deaths, 11 were valve-related (0.3% /pt-yr), 14 were cardiac (0.4% /pt-yr), 41 were non-cardiac (1.2% /pt-yr), and seven were unexplained (0.2% /pt-yr).

In the MVR group, early mortality was 3.0% (n = 7). Of these seven deaths, none was valve-related, four were cardiac (1.7%), and three were non-cardiac (1.3%). The linearized rate for late mortality (23 deaths)

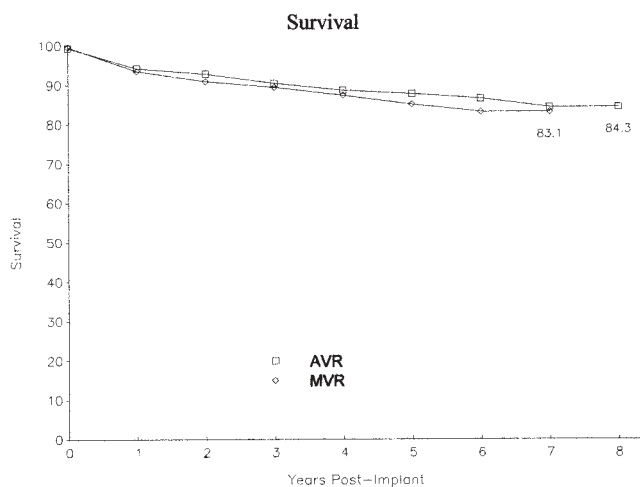


Figure 1: Survival at seven years after Mosaic valve replacement in the aortic (AVR) or mitral (MVR) position.

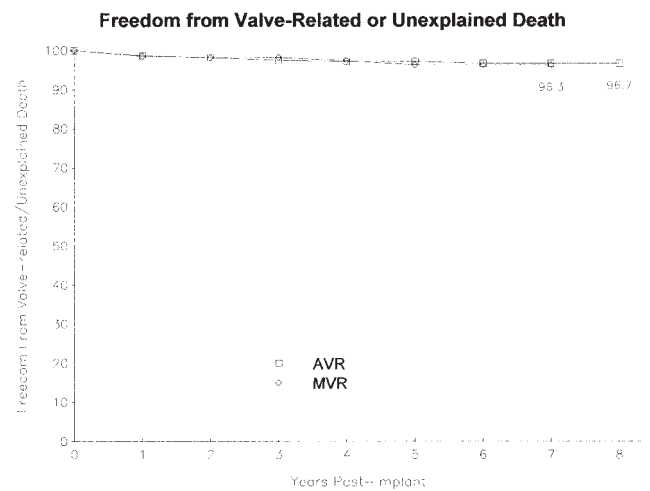


Figure 2: Freedom from valve-related or unexplained death. AVR: Aortic valve replacement; MVR: Mitral valve replacement

Table IV: Mean gradient at six years after aortic valve replacement (AVR) or mitral valve replacement (MVR) with the Mosaic bioprosthesis.

Valve size (mm)	AVR		MVR	
	Valves (n)	Mean gradient (mmHg)*	Valves (n)	Mean gradient (mmHg)*
19 <sup>+</sup>	0	0	-	-
21	29	14.6 ± 5.9	-	-
23	73	14.3 ± 7.3	-	-
25	47	12.1 ± 5.0	4	4.2 ± 1.3
27	18	9.9 ± 5.1	7	5.8 ± 2.2
29	9	12.1 ± 4.3	11	4.8 ± 2.1
31	-	-	7	4.0 ± 1.5
33	-	-	0	0

\*Values are mean ± SD.

<sup>+</sup>The Mosaic 19 mm valve was not introduced until 1998.

was 2.7% per pt-yr. Of these 23 deaths, three were valve-related (0.4% / pt-yr), five were cardiac (0.6% / pt-yr), 12 were non-cardiac (1.4% / pt-yr), and three were unexplained (0.4% / pt-yr). A summary of the causes of

valve-related deaths for both the AVR and MVR populations is presented in Table I. Survival at seven years was 84.3 ± 7.3% for AVR, and 83.1 ± 12.9% for MVR (Fig. 1). Freedom from valve-related or unexplained

Table V: Indexed effective orifice area (EOA, cm<sup>2</sup>/m<sup>2</sup>) after AVR with the Mosaic bioprosthesis.

Follow up time	Valve size (mm)						
	19	21	23	25	27	29	All sizes
Early							
Valves (n)	7	138	285	204	69	22	725
EOA	0.6±0.1	0.8±0.2	0.9±0.3	1.0±0.3	1.0±0.3	1.0±0.2	0.9±0.3
Late							
Valves (n)	7	134	287	203	69	19	719
EOA	0.7±0.1	0.8±0.2	0.9±0.3	1.0±0.3	1.0±0.3	1.1±0.3	0.9±0.3
1 Year							
Valves (n)	5	131	274	192	67	20	689
EOA	0.7±0.1	0.8±0.2	0.8±0.2	0.9±0.3	1.0±0.3	1.1±0.4	0.9±0.3
2 Years							
Valves (n)	4	129	266	180	62	19	660
EOA	0.7±0.2	0.8±0.2	0.8±0.2	0.9±0.2	1.0±0.3	1.1±0.3	0.9±0.2
4 Years							
Valves (n)	-	94	213	139	48	16	510
EOA	-	0.8±0.2	0.8±0.2	0.9±0.2	1.0±0.3	1.1±0.4	0.9±0.2
6 Years							
Valves (n)	-	27	72	46	18	8	171
EOA	-	0.8±0.2	0.8±0.2	1.0±0.3	1.0±0.3	1.0±0.3	0.9±0.3
8 Years							
Valves (n)	-	-	1	1	-	-	2
EOA	-	-	0.9	0.8	-	-	0.9±0.1

Table VI: Indexed effective orifice area (EOA, cm<sup>2</sup>/m<sup>2</sup>) after MVR with the Mosaic bioprosthesis.

Follow up time	Valve size (mm)					
	25	27	29	31	33	All sizes
<i>Early</i>						
Valves (n)	35	74	68	22	4	203
EOA	1.0±0.3	1.0±0.3	1.0±0.3	0.9±0.3	0.8±0.2	0.9±0.3
<i>Late</i>						
Valves (n)	34	73	62	22	4	195
EOA	0.9±0.3	0.9±0.3	1.0±0.3	1.1±0.4	0.9±0.1	1.0±0.3
<i>1 Year</i>						
Valves (n)	33	71	67	20	4	195
EOA	1.0±0.3	1.0±0.3	0.9±0.3	1.0±0.3	1.0±0.4	1.0±0.3
<i>2 Years</i>						
Valves (n)	30	66	60	21	3	180
EOA	1.0±0.2	0.9±0.3	0.9±0.3	1.1±0.5	1.1±0.4	1.0±0.3
<i>4 Years</i>						
Valves (n)	14	37	32	15	2	100
EOA	0.9±0.3	1.0±0.3	1.0±0.3	1.0±0.4	1.8±0.4	1.0±0.3
<i>6 Years</i>						
Valves (n)	4	5	9	7	-	25
EOA	1.1±0.3	0.9±0.2	1.0±0.3	0.9±0.4	-	1.0±0.3

death was 96.7 ± 3.9% (SE) for the AVR group, and 96.3 ± 7.0% for the MVR group (Fig. 2).

#### NYHA classification

Following AVR, 739 patients had their NYHA class recorded at or after their one-year follow up evaluation. Of these 739 patients, 32 (4.3%) were in NYHA class III or IV at their last follow up evaluation. In only two of the 32 AVR patients was the high NYHA class considered to be valve-related, and both patients had moderate aortic insufficiency. After MVR, 210 patients had their NYHA class recorded at or after their one-year follow up evaluation. Of these patients, 12 (5.7%) were in NYHA class III or IV at their last follow up evaluation. All of these 12 patients had non-valve-related reasons for their NYHA status of III or IV. The most common reasons were chronic obstructive pulmonary disease, cancer and arthritis.

#### Antithromboembolic therapy

Protocols varied among centers. In the AVR group, 13.2% of patients were receiving warfarin, 68.4% antiplatelet therapy, and 18.4% had no therapy at seven years' follow up. In the MVR group, 30% of patients were receiving warfarin, 30% antiplatelet therapy, and 40% no therapy at seven years' follow up. At seven years, 5.3% (2/38) of the AVR patients, and 30%

(3/10) of the MVR patients, were in atrial fibrillation or flutter.

#### Valve-related adverse events

Late valve-related adverse events are summarized in Table II. Freedom from valve-related adverse events at seven years are summarized in Table III. There was no incidence of SVD in either group. Causes of reoperation for the AVR group included valve thrombosis (n = 3), endocarditis (n = 12), paravalvular leak (n = 5) and non-structural valve dysfunction (n = 1). In the MVR group, the causes included valve thrombosis (n = 1), endocarditis (n = 2) and paravalvular leak (n = 2). Of the 29 patients who underwent valve replacement for endocarditis (16 AVR, 13 MVR), only two developed endocarditis postoperatively (both after AVR). Both of these patients had their valves explanted, and recovered.

#### Hemodynamic evaluation

Mean gradients are summarized in Table IV, while indexed EOA are presented for AVR and MVR in Tables V and VI, respectively. Changes in indexed left ventricular mass across time for AVR patients, with data available at the early, one- and six-year echocardiographic examinations, are summarized in Table VII. In the AVR group, valvular regurgitation at six years

Table VII: Summary statistics for indexed left ventricular mass (LVM) after AVR with the Mosaic bioprosthesis.

Follow up/ Indexed LVM	Valve size (mm)					
	21	23	25	27	29	All sizes
<i>Early</i>						
Valves (n)	20	58	36	14	6	134
Mean ± SD	126.9±42.1	135.1±38.8	156.9±48.9	160.2±48.7	161.4±55.2	143.5±45.1
Median	111.4	130.9	149.6	167.4	153.8	138.2
Minimum	53.1	74.6	70.4	98.1	101.1	53.1
Maximum	210.2	247.0	251.7	238.1	253.4	253.4
<i>1 Year</i>						
Valves (n)	20	58	36	14	6	134
Mean ± SD	101.7±19.4	109.4±28.4	123.3±41.8	130.3±33.7	146.8±52.3	115.8±34.6
Median	104.3	105.7	113.8	128.1	139.3	109.6
Minimum	57.6	55.1	69.5	74.5	91.6	55.1
Maximum	141.1	179.4	254.6	205.5	219.1	254.6
<i>6 Years</i>						
Valves (n)	20	58	36	14	6	134
Mean ± SD	97.6±23.4	107.4±26.9	122.6±37.5	121.0±24.5	122.5±32.2	112.1±30.7
Median	97.9	110.2	124.0	123.9	119.8	110.7
Minimum	49.5	56.5	62.1	64.0	81.7	49.5
Maximum	159.8	175.7	207.6	160.7	180.1	207.6

was absent in 74% of patients, trivial in 17%, mild in 7%, and moderate in 2%. There were no cases of moderate to severe or severe aortic insufficiency in this cohort at six years' follow up. In the MVR group, there was also zero incidence of moderate or severe mitral regurgitation at six years; indeed, 80% of patients had no mitral regurgitation, 3% had trivial, and 17% mild.

## Discussion

The benefit of a bioprosthetic implant over a mechanical implant - mainly the lower incidence of antithromboembolic-related hemorrhage events - has historically been achieved at the cost of an increased rate of SVD and of limited longevity (8). Important technological innovations were incorporated into the design of the Mosaic third-generation bioprosthesis, with the hope of improving hemodynamic performance and longevity. The ongoing follow up of the present cohort is unique in that a large patient population has been subjected to prospective serial standardized echocardiographic follow up, allowing frequent and consistent assessment of functionality. Studies of this type are not generally available to support the performance of earlier-generation bioprostheses.

This intermediate seven-year report of results from the ongoing post-FDA approval long-term clinical study provided data which validated the excellent clinical and hemodynamic performances of this new valve, when implanted both in the aortic and mitral

positions. Indeed, at seven years there was still no incidence of SVD in either position in this particular cohort of patients, in addition to a low incidence of valve-related adverse events comparable to that seen elsewhere for both porcine and pericardial bioprostheses (1,9-12).

The hemodynamic data presented herein were excellent, and compared favorably with those obtained for other frequently implanted tissue valves (including the porcine Carpentier-Edwards S.A.V. and Carpentier-Edwards pericardial Perimount), where echocardiography was also used for hemodynamic assessment (13-16). The present hemodynamic data at six years (gradients and indexed EOA) were also comparable with data obtained in earlier Mosaic series which reported on one- to four-year echocardiography findings (2,3,14,17-19). It is believed that these low transvalvular gradients are a direct benefit of this new valve design and tissue processing, where the normal architecture of the leaflets is preserved (20), thereby allowing for a load-stress relationship in vitro which is close to that of a normal leaflet (21). In the AVR group, these low transvalvular gradients were indeed associated with a significant indexed left ventricular mass reduction at one year, with the reduction remaining stable for more than six years after implantation. The dilatation of the aortic root at the time of preservation also allows normal plane closure of the leaflets, without restriction. This was in contrast to the situation in the previous Intact Medtronic valve, where fixation in a

non-dilated root was unfortunately associated with overcrowding of the leaflets. Nonetheless, the Intact valve has been associated with a low incidence of SVD at 10-year follow up in the aortic position (freedom from SVD  $92 \pm 8\%$ ) among patients aged over 40 years (22). With the improved tissue fixation, the addition of a beneficial anticalcification treatment (23-25), and the current hemodynamic performance of the Mosaic valve, it is expected that this valve will provide patients with longer durability than current standard bioprostheses, and may indeed be suitable for implantation in a younger population.

In addition to continued excellent clinical and hemodynamic performance, a major benefit of choosing a bioprosthesis rather than a mechanical valve is the low incidence of thromboembolism and major antithromboembolic-related hemorrhage associated with tissue valves. In the present study, late thromboembolism rate of 1.3% per pt-yr was seen in the AVR group, and 1.4% per pt-yr in the MVR group. A comparable low rate of major antithromboembolic-related hemorrhage was also reported for both groups, with 0.6% per pt-yr after AVR and 0.7% per pt-yr after MVR. These rates were comparable with those reported in previous Mosaic valve studies (2,3,18,26), and also with rates for several other bioprostheses, including the stented Carpentier-Edward porcine prosthesis (27-30), the Carpentier-Edward pericardial prosthesis (9,10,31,32), the stentless Biocor (33,34), and Medtronic Freestyle (35-38).

*In conclusion*, the mid-term performance of the Mosaic valve is encouraging, as this third-generation porcine bioprosthesis continues to provide excellent hemodynamics, a minimal incidence of valve-related adverse events, and an encouraging freedom from SVD. Continued clinical follow up and monitoring of this patient population should demonstrate if indeed this valve will provide patients with increased durability and low morbidity, when compared with bioprosthetic valves of an earlier design and generation.

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## Meeting discussion

**DR. ENDRE BODNAR** (United Kingdom): Has this study been given financial support by Medtronic? You know how our arrangement is, that it should be declared at the beginning of the presentation.

**DR. GUY FRADET** (Vancouver, British Columbia, Canada): Medtronic provided funding for the centers for the clinical trial and the gathering of data.

**DR. BODNAR**: Thank you very much.

**DR. BLASE CARABELLO** (USA): I found it very troubling that most of your patients, for AVR and MVR, were initially in NYHA classes III and IV. Was that

because the physicians referring the patients to you had waited so long, or that the patients had waited so long?

**DR. FRADET:** I cannot really answer that - probably both reasons were valid.

**DR. CARABELLO:** It is bothersome that even in this day and age patients are not reaching the operating room until they have NYHA class III and IV symptoms. We as a society should try to promote earlier surgery than that.

**DR. FRADET:** I could not agree more, but the ACC guidelines are quite conservative.

**DR. CARABELLO:** No, they are not, actually.

**DR. FRADET:** In my mind they are.

**DR. CARABELLO:** Having been one of the writers of the guidelines, we suggest that it is a recommendation for even class II symptoms in every valve disease. I personally think 1.2 is probably about the right class.

**DR. FRADET:** I couldn't agree more.

**DR. ALAIN CARPENTIER (France):** You gave us so much information that it was difficult to see the message, except that this valve is great at seven years. The important point with this valve was the surprisingly high incidence of thromboembolic complications found by Dr. Jamieson. Did you find the same problem?

**DR. FRADET:** We did not find a similar problem. But Dr. Jamieson conducted much of his follow up by telephone, whereas our patients were followed up in the clinic. The different centers had different anticoagulation protocols. I know that at seven years, 30% of the MVR population was in atrial fibrillation and anticoagulated, but 44% of them were not receiving aspirin or anticoagulants.

**DR. CARPENTIER:** That is perhaps why you had a higher incidence of hemorrhage than Dr. Jamieson?

**DR. W. R. ERIC JAMIESON (Canada):** I will try to put some consensus to this - and perhaps also make a comment. In the aortic position, you report an overall of class of 1.3, while the Canadian study had 1.8, and the cohort in Vancouver had 2.0. So these are not appreciably different. In the mitral position, you had class 1.4 overall, the Canadian cohort was 1.7, and in Vancouver we reported 2.6. So, if you consider the late major event rates, they are not grossly different.

**DR. FRADET:** I agree with that, but in light of your message I think it was important to point out that it may not be that high when you look at all the centers together.