

Fifteen Years of Clinical and Echocardiographic Follow Up with the CarboMedics Heart Valve

Michel Carrier¹, Michel Pellerin¹, Arsène Basmadjian², Denis Bouchard¹, Louis P. Perrault¹, Raymond Cartier¹, Pierre Pagé¹, Philippe Demers¹, Yves Hébert¹

Montreal Heart Institute, ¹Department of Surgery and ²Department of Medicine, Montreal, Quebec, Canada

Background and aim of the study: Mechanical prostheses are used in young patients, the CarboMedics valve having been the mechanical valve of choice of the present authors during the past 15 years. The study aim was to analyze long-term clinical and echocardiographic results obtained with CarboMedics mechanical valves.

Methods: A total of 2,953 patients underwent valve replacement with the CarboMedics valve between 1988 and 2004 at the Montreal Heart Institute. Patients were prospectively followed at the outpatient valve clinic. Subsequently, 1,004 patients underwent echocardiographic examinations during follow up.

Results: In total, 1,597 patients (mean age 57 ± 12 years) underwent isolated aortic valve replacement (AVR), 1,043 patients (mean age 59 ± 10 years) underwent isolated mitral valve replacement (MVR), and 313 patients (mean age 58 ± 11 years) underwent AVR+MVR. The mean five-, 10- and 15-year actuarial survival rates were $83 \pm 1\%$, $70 \pm 2\%$ and $62 \pm 3\%$ in AVR patients, $76 \pm 1\%$, $59 \pm 2\%$ and $40 \pm 14\%$ in MVR

patients, and $68 \pm 3\%$, $51 \pm 4\%$ and $33 \pm 9\%$ in AVR+MVR patients. The mean 15-year freedom from cerebral embolism, hemorrhage and reoperation was $95 \pm 1\%$, $97 \pm 1\%$ and $95 \pm 1\%$ in AVR patients, $92 \pm 1\%$, $97 \pm 1\%$ and $93 \pm 1\%$ in MVR patients, and $94 \pm 2\%$, $93 \pm 2\%$ and $91 \pm 4\%$ in AVR+MVR patients. AVR patients had a mean aortic gradient of 29 ± 14 , 20 ± 8 , 18 ± 7 , 16 ± 7 , 12 ± 5 and 11 ± 5 mmHg with 19, 21, 23, 25, 27 and 29 mm prostheses, respectively ($p = 0.001$). MVR patients had a mean mitral gradient of 5.3 ± 3 , 4.9 ± 2.2 , 4.6 ± 2 , 4.4 ± 2.9 and 4.9 ± 1.8 mmHg with 25, 27, 29, 31 and 33 mm prostheses, respectively ($p = 0.63$).

Conclusion: Patient survival and valve-related complications were satisfactory at 15 years after valve replacement with the CarboMedics valve. Mean aortic gradients were high with the 19-mm aortic prostheses, but all other valve sizes showed good hemodynamic performance, as measured using transthoracic echocardiography.

Mechanical heart valves remain the prostheses of choice for replacement in young patients because of the high failure rate of bioprostheses in this age group (1), the limited availability of homografts, and the technical complexity of the Ross operation. During the past 15 years, the present authors' mechanical prosthesis of choice has been the CarboMedics (CarboMedics, Inc., Austin, TX, USA) heart valve.

The CarboMedics valve was developed in 1986 as a second-generation bileaflet heart valve. The aim was to

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improve the hemodynamic performance and thromboresistance of bileaflet valves at the hinge mechanism. The blood-contacting surfaces on the sewing ring are covered with Biolite® carbon to reduce tissue overgrowth. Moreover, the potential for rotation of the leaflets within the valve mechanism after implantation in order to adapt to the recipient's valvular annulus was one of the most dramatic improvements introduced with this second-generation bileaflet prosthesis (2).

The aim of the present study was to analyze the clinical and echocardiographic follow up of the CarboMedics mechanical valve in a large patient cohort.

Clinical material and methods

Patients

Between 1988 and 2004, a total of 2,953 patients underwent mechanical heart valve replacement with

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Address for correspondence:

Michel Carrier, MD, Department of Surgery, Montreal Heart Institute, 5000 Belanger Street East, Montreal, Quebec H1T 1C8, Canada

e-mail: michel.carrier@icm-mhi.org

the CarboMedics valve at the Montreal Heart Institute. Patients were prospectively followed at the outpatient valve clinic with annual examinations by the responsible physician, or by annual direct contact through the mail. Subsequently, 1,004 patients (34%) underwent echocardiography at the Montreal Heart Institute during the follow up period. In total, 191 patients (6.5%) were lost to follow up during the study period. The mean follow up was 8 ± 5.4 years (range: 1 to 15 years).

Valve implants

Patients were implanted with either the Standard or Reduced model aortic valve, and the Standard or Optiform mitral CarboMedics valve. Oral anticoagulation was achieved with warfarin in all patients, although the early postoperative anticoagulation protocol was changed during the study period.

Postoperative complications

Valve-related complications were reported according to the Guidelines of the Ad Hoc Liaison Committee of The Society of Thoracic Surgeons and The American Association of Thoracic Surgery (3).

Statistical analysis

The data were presented as mean \pm SD. Differences between groups were analyzed using Student's *t*-test or Fisher's exact test. Analysis of survival was performed using the Kaplan-Meier method and the log-rank test. Proportional hazards regression (Cox) was used to study the influence of covariates (age, gender, associated coronary artery bypass grafting, reoperation, prosthesis size) and the overall mortality after valve replacement. A *p*-value <0.05 was considered to be statistically significant, and rates were presented with 95% confidence limits.

Table I: Distribution of labeled prosthesis size for aortic, mitral and double (aortic + mitral) valve replacement.

Valve size (mm)	Aortic		Mitral	
	Female	Male	Female	Male
18	2	0	0	0
19	112	9	0	0
20	16	7	0	0
21	357	208	0	0
23	167	547	0	0
25	26	306	101	13
27	15	113	400	117
29	3	14	296	208
31	1	6	76	106
33	0	1	7	32

Results

Patient characteristics

In total, 1,597 patients (509 females, 1,088 males; mean age 57 ± 12 years) underwent isolated aortic valve replacement (AVR), 1,043 patients (690 females, 313 males; mean age 59 ± 10 years) underwent isolated mitral valve replacement (MVR), and 313 patients (190 females, 123 males; mean age 58 ± 11 years) underwent combined AVR+MVR.

Associated coronary artery bypass grafting was performed in 449 AVR patients (28%), in 207 MVR patients (20%), and in 41 AVR+MVR patients (13%) ($p = 0.001$). Moreover, the procedure was a reoperation in 344 AVR patients (22%), in 392 MVR patients (38%), and in 154 AVR+MVR patients (49%) ($p = 0.001$). Among AVR patients, 99 underwent enlargement aortoplasty and 82 other patients underwent a Bentall procedure; a Konno procedure was performed in 11 patients. The distribution of labeled prosthesis size is shown in Table I.

The majority of patients (2,045; 69%) who underwent valve replacement were in NYHA functional classes III and IV at the time of surgery.

Patient survival

The mean 30-day operative mortality was 5% ($n = 79$) in AVR patients, 8% ($n = 83$) in MVR patients, and 11% ($n = 34$) in AVR+MVR patients. Overall, 789 patients (27%) died during the follow up period. Causes of valve-related deaths are listed in Table II.

The mean one-, five-, 10- and 15-year actuarial survival rates were $92 \pm 1\%$, $83 \pm 1\%$, $70 \pm 2\%$ and $62 \pm 3\%$ after AVR, $85 \pm 1\%$, $76 \pm 1\%$, $59 \pm 2\%$ and $40 \pm 4\%$ after MVR, and $80 \pm 2\%$, $68 \pm 3\%$, $51 \pm 4\%$ and $33 \pm 9\%$ after AVR+MVR ($p = 0.0001$; Fig. 1).

Long-term complications

Thromboembolism

A total of 81 patients suffered from cerebral embolism (34 strokes, 47 transient ischemic attacks).

Table II: Causes of valve-related deaths.

Cause	AVR	MVR	AVR+MVR
Thromboembolism	11	27	6
Valve thrombosis	2	5	4
Bleeding event	15	22	4
Valve dehiscence	1	3	2
Sudden death	16	17	11
Endocarditis	2	2	5
Reoperation*	31	56	22

*Reoperation included all valve- and non-valve-related cardiac surgery.

AVR: Aortic valve replacement; MVR: Mitral valve replacement.

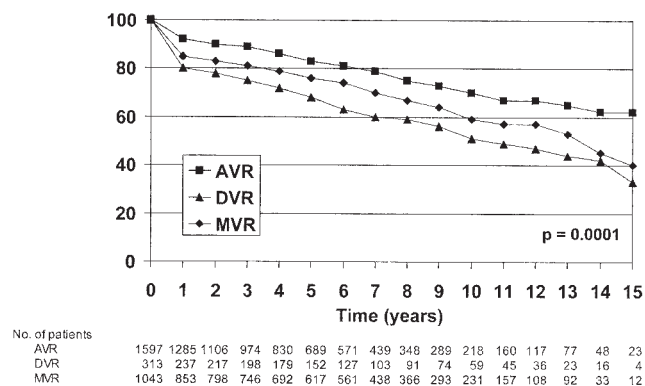


Figure 1: Actuarial survival 15 years after valve replacement.

The mean freedom from cerebral embolism was $95 \pm 1\%$, $92 \pm 1\%$ and $94 \pm 2\%$ at 15 years after AVR, MVR and AVR+MVR, respectively. The incidence of cerebral embolism was 0.4% per patient-year (pt-yr) after AVR, 0.6% per pt-yr after MVR, and 0.65% per pt-yr after AVR+MVR. Ten patients suffered from peripheral embolism (one patient after AVR, six patients after MVR, and three after AVR+MVR).

The mean freedom from thromboembolism was $95 \pm 1\%$, $89 \pm 2\%$ and $93 \pm 2\%$ at 15 years after AVR, MVR and AVR+MVR, respectively (Fig. 2; $p = 0.048$). The incidence of thromboembolism was 0.4% per pt-yr after AVR, 0.7% per pt-yr after MVR, and 0.7% per pt-yr after AVR+MVR.

Valve thrombosis

Prosthetic thrombosis occurred in 39 patients during the follow up period: in two patients after AVR (0.1%), in 30 after MVR (2.8%), and in seven after AVR+MVR (2.2%). Reoperation was required in 30 patients, while valve thrombosis was the main cause of death in 11 patients. Thrombotic events occurred within 30 days of surgery in eight of these patients (21%). The incidence of valve thrombosis was 0.02% per pt-yr after AVR, 0.47% per pt-yr after MVR, and 0.42% per pt-yr after AVR+MVR.

Anticoagulant-related hemorrhage

Eighty-seven patients developed anticoagulant-related hemorrhage during the follow up. The incidence of hemorrhage was 0.4% per pt-yr after AVR, 0.7% per pt-yr after MVR, and 0.5% per pt-yr after AVR+MVR ($p = 0.03$). The mean freedom from anticoagulant-related hemorrhage was $95 \pm 1\%$, $95 \pm 2\%$ and $89 \pm 3\%$ at 15 years after AVR, MVR and AVR+MVR, respectively (Fig. 3; $p = 0.03$).

Prosthetic valve endocarditis

Fifty-four patients suffered from prosthetic valve endocarditis (PVE) during the follow up. The inci-

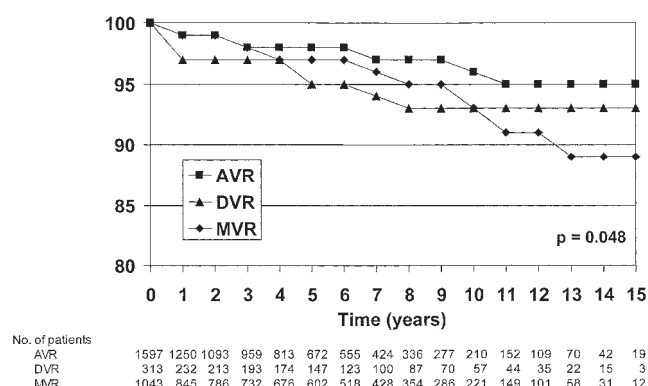


Figure 2: Actuarial freedom rate from thromboembolism.

dence of PVE was 0.3% per pt-yr after AVR, 0.3% per pt-yr after MVR, and 0.7% per pt-yr after AVR+MVR ($p = 0.02$). The mean freedom from PVE was $97 \pm 1\%$, $97 \pm 1\%$ and $93 \pm 2\%$ at 15 years after AVR, MVR and AVR+MVR, respectively (Fig. 4; $p = 0.02$).

Reoperation

A total of 117 patients underwent valve reoperation for a specific valve-related problem with replacement or repair of the prosthesis during follow up. The mean freedom from reoperation was $94 \pm 1\%$, $91 \pm 1\%$ and $85 \pm 4\%$ at 15 years after AVR, MVR and AVR+MVR, respectively (Fig. 5; $p = 0.001$). There was no structural failure during the follow up period. Causes of reoperation included valve thrombosis in 30 patients, PVE in 26, paravalvular leak in 48 (17 AVR, 22 MVR, nine AVR+MVR), and various non-prosthesis-related problems in 12.

Echocardiographic data

In AVR patients the mean aortic gradient was 29 ± 14 , 20 ± 8 , 18 ± 7 , 16 ± 7 , 12 ± 5 and 11 ± 5 mmHg with 19, 21, 23, 25, 27 and 29 mm labeled valve sizes, respectively ($p = 0.001$). These examinations were performed

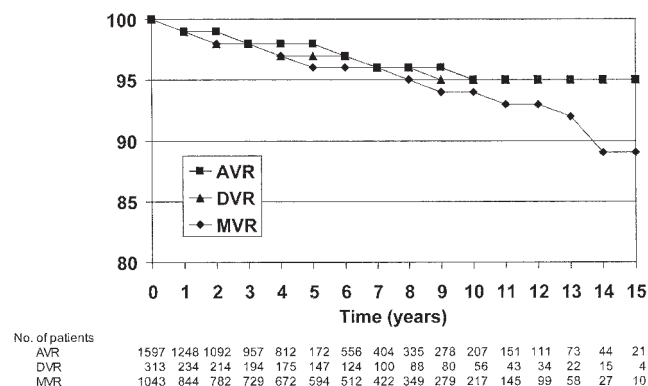


Figure 3: Actuarial freedom rate from hemorrhage.

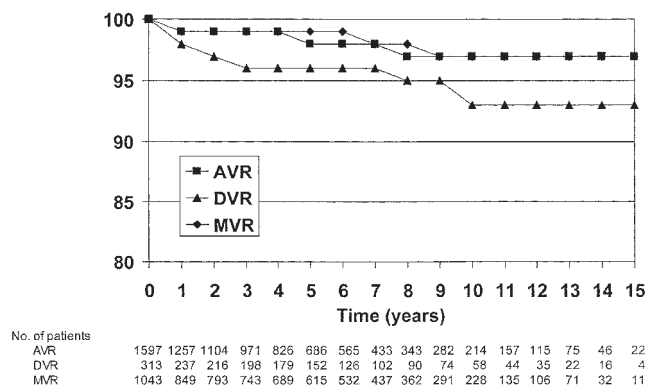


Figure 4: Actuarial freedom rate from endocarditis.

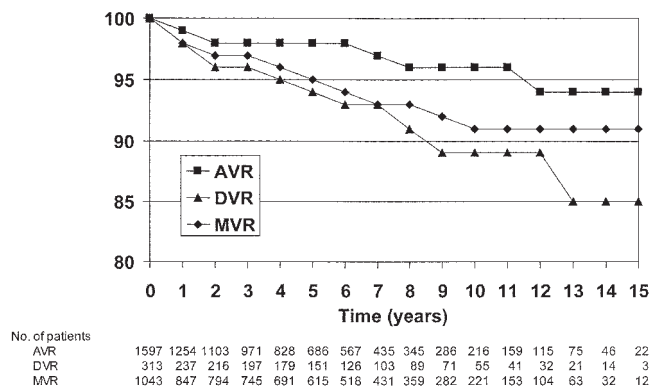


Figure 5: Actuarial freedom rate from reoperation.

at a mean period of 4.7 ± 3.7 years after valve replacement. In MVR patients the mean mitral gradient was 5.3 ± 3 , 4.9 ± 2.2 , 4.6 ± 2 , 4.4 ± 2.9 and 4.9 ± 1.8 mmHg for 25, 27, 29, 31 and 33 mm labeled valve sizes, respectively ($p = 0.63$). On average, these examinations were performed at 6.1 ± 3.9 years after valve replacement.

Effect of prosthesis size on survival

The mean 10-year actuarial survival of patients who underwent AVR with 19, 21, 23, 25 and 27 mm prostheses was $47 \pm 8\%$, $68 \pm 4\%$, $73 \pm 3\%$, $75 \pm 3\%$ and $69 \pm 6\%$, respectively (significant difference between groups, $p = 0.004$, log-rank test). The mean 10-year survival of patients who underwent MVR with 25, 27, 29, 31 and 33 mm prostheses was $51 \pm 6\%$, $56 \pm 3\%$, $60 \pm 13\%$, $65 \pm 5\%$ and $58 \pm 13\%$, respectively (significant difference between groups, $p = 0.01$, log-rank test). Age, associated coronary artery bypass grafting and reoperation (all $p < 0.01$) were related with the risk of death at long-term follow up after isolated AVR and MVR, but prosthesis size was not a significant factor in either AVR or MVR patients.

Discussion

The present series constitutes the largest single-center, long-term experience with the CarboMedics heart valve. The results suggest that the CarboMedics heart valve offers overall good clinical results in an unselected patient population, with a high incidence of associated procedures and valve reoperations. The rate of valve-related complications, thromboembolic events, reoperation and PVE were similar to the results reported by Emery et al. (4) in the report studying the St. Jude Medical (SJM) prosthesis at 25 years of follow up.

The mean transprosthetic gradient was higher for the 19 mm aortic prosthesis than for other valve sizes, and was also associated with a lower 10-year survival. Although effective orifice area and patient-prosthesis mismatch were not measured in the present study (5), the elevated transvalvular gradient for the 19-mm aortic valve appeared to have affected both immediate and long-term survival.

The transprosthetic gradients were similar among the different sizes of mitral prostheses, although the 10-year survival rate was lower in patients with the 25-

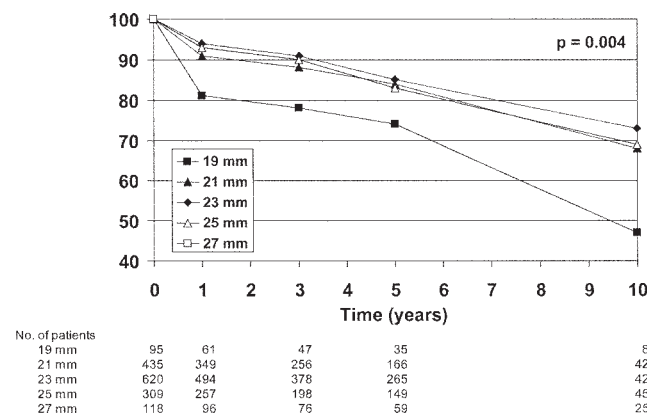


Figure 6: Ten-year actuarial survival according to aortic prosthesis size.

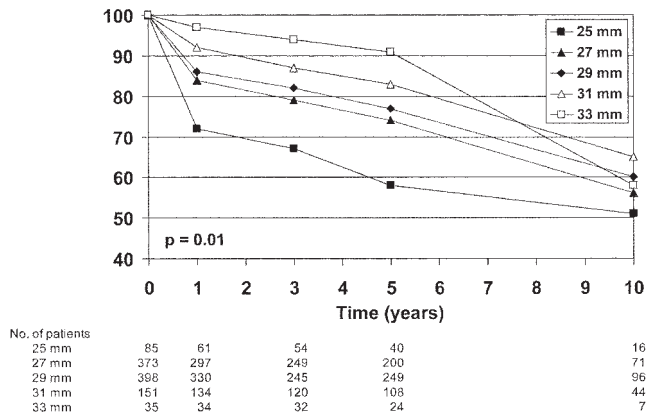


Figure 7: Ten-year actuarial survival according to mitral prosthesis size.

mm mitral prosthesis. Patient-prosthesis mismatch might explain this effect on long-term patient survival (6).

Medalion et al. (7), showed that smaller aortic prosthesis sizes were associated with a greater risk of death, but this was accounted for by differences in patient characteristics before AVR. In the present analysis, although patients with 19 mm aortic and 25 mm mitral valves had the lowest survival rates, multivariate analyses suggested that other covariates were responsible for the higher rate of death at long-term follow up with these small prostheses. Blackstone et al. (8), while studying survival in 13,258 AVR patients, concluded that there was no relationship between a small prosthesis size and intermediate or long-term survival. The authors recognized that there was a small increase in early mortality among patients who received prostheses with small valve orifices, and emphasized that there was much to learn about factors affecting mortality after AVR, including the efficiency of a valve, and its size.

Although the mean incidence of mitral valve thrombosis was 0.47% per pt-yr in the present study compared to 0.18% per pt-yr with the SJM valve (4), the incidence of bleeding events was lower (0.7% versus 2.7% per pt-yr). Tominaga et al. (9), also reported an incidence of 0.25% per pt-yr for mitral valve thrombosis with the CarboMedics prosthesis. Khan et al. (10), in comparing tissue valves to the SJM prosthesis, showed a rate of 0.2% per pt-yr for mitral valve thrombosis and a rate of 5.6% per pt-yr for all-valve complications. Anticoagulation with oral warfarin and low-dose aspirin is recommended for mechanical valve prostheses, particularly when implanted in the mitral position (11,12). Aspirin was not used during the earlier phases of the present study, and the lower intensity of anticoagulation might explain the higher rate of mitral valve thrombosis observed in the present patients. In analyzing the overall problem of prosthetic valve thrombosis, it has been reported previously that an inadequate level of anticoagulation is the most important factor involved in the pathogenesis of this complication (13).

Lim et al. reported a prospective randomized comparison of CarboMedics and SJM valves in 485 patients, all of whom had a target International Normalized Ratio (INR) of 3 to 4.5 (14). There was no case of valve thrombosis and no difference in the rate of valve-related events after five years of follow up.

Study limitations

With regard to limitations, the echocardiographic data were incomplete due to the longitudinal long-term clinical follow up of the patients, although the prospective collection of data was complete in most

patients with long-term follow up.

In conclusion, 15 years of experience with the CarboMedics heart valve shows that this prosthesis offers good overall clinical results. It is suggested that the use of smaller-sized prostheses (19 mm aortic and 25 mm mitral) might be associated with lower patient survival related to prosthesis-patient mismatch and other comorbidities. Anticoagulation should be optimized according to published guidelines, especially when prostheses are implanted in the mitral position.

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Meeting discussion

DR. W. R. ERIC JAMIESON (Vancouver, Canada): We presented in Vancouver four or five years ago a comparative study between St. Jude Medical and CarboMedics and showed a sort of trend towards thrombosis of the mitral prosthesis. We could not prove for either total thromboembolism, major or minor thrombosis that we could incriminate the mitral valve, although there was a trend. It was probably clinically irrelevant, but if we had had enough patients we may well have seen some positive findings. Do you have any special approach to managing these patients - how high should their INR-values be, and should they be receiving concomitant antiplatelet therapy?

DR. MICHEL CARRIER (Montreal, Canada): We published details of a series on valve thrombosis about two to three years ago, and there were some significant changes in warfarin levels. At the time, we felt that there were clear causes for these thromboses. Now, we follow the guidelines very closely - all patients in the past seven to eight years have received warfarin plus aspirin after mitral valve replacement, obviously to try to avoid these types of complications. This does not apply to the aortic valve, however.

DR. JAMIESON: Has your thrombosis rate decreased in recent years?

DR. CARRIER: Yes.

DR. SUNDAR RAMANATHAN (Coimbatore, India): With regard to your survival data, there is a remarkable difference between a 19 mm valve in the aortic position compared to a 25 mm valve. Did you find out - especially for the 19-mm aortic valve - how many patient-prosthesis mismatches there were, by definition?

DR. CARRIER: We did not examine that point because the study dated back to 1988, and these types of data were not recorded at that time. Certainly most deaths occurred soon after surgery, and if we were to perform a prospective multivariate analysis the patient might well be the main factor for death. We no longer use 19-mm prostheses in the aortic position. If we face that problem, we enlarge the annulus using conventional techniques. So I can't answer the question about prosthesis-patient mismatch, but it seems that these patients died soon after surgery. Certainly we now stay away from the 19 mm prosthesis in general.

DR. RAMANATHAN: Does the same thing hold true for a 25 mm mitral prosthesis?

DR. CARRIER: Yes.

DR. RAMANATHAN: You no longer use a 25 mm mitral prosthesis?

DR. CARRIER: Correct.

MR. JOHN R. PEPPER (London, UK): In any explanted valves, or in any patients who died and were subjected to autopsy, what was the incidence of pannus?

DR. CARRIER: That point was not examined. In patients reoperated on for valve thrombosis, only 10 to 15% had significant pannus that might cause problems. The remainder of the patients had fresh thrombus related to anticoagulation.

MR. PEPPER: Was pannus seen more often in the mitral position than in the aortic position?

DR. CARRIER: In the mitral position.

DR. HORMOZ AZAR (Norfolk, Virginia, USA): Did you determine which valve size was more prone to thrombosis, and whether the presence of atrial fibrillation was a risk factor, or not?

DR. CARRIER: We have published these findings previously, and we could not specify one size as being problematic. On the subject of atrial fibrillation, half of the patients were in fibrillation, but not all were compliant and the INR was very suboptimal. The physicians were also modifying the INR to prepare patients for other types of general surgical procedures. There were four or five patients in whom attempts were made to implant pacemakers, and they developed thrombus of the prosthesis. So, atrial fibrillation might be a factor, although these series were very small. There was certainly no relationship between thrombosis and valve size in the mitral position, but again the study was limited to only 39 patients.