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High Risk of Thromboemboli Early After Bioprosthetic Cardiac Valve Replacement

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Objectives. **We studied the rate of thromboembolism in patients undergoing bioprosthetic replacement of the aortic or mitral valve, or both, at serial intervals after operation and the effects of anticoagulant or antiplatelet treatment and risk factors.**

Background. **Thromboembolism appears to occur early after operation, but the incidence, timing and risk factors for thromboembolism and the role, timing, adequacy, effectiveness, duration and risk of anticoagulation and antiplatelet agents are uncertain.**

Methods. **The rate of thromboembolism was studied at three time intervals after operation (1 to 10, 11 to 90 and >90 days) in 816 patients who underwent bioprosthetic replacement of the aortic or mitral valve, or both, at the Mayo Clinic from January 1975 to December 1982. The effect of antithrombotic therapy (warfarin, aspirin or dipyridamole, alone or in combination) was evaluated.**

Results. **Median follow-up of surviving patients was 8.6 years. The rate of thromboembolism (%/year) decreased significantly ($p < 0.01$) at each time interval after operation (1 to 10, 11 to 90 and >90 days) for mitral valve replacement (55%, 10% and 2.4%/year, respectively) and over the first time interval for aortic valve replacement (41%, 3.6% and 1.9%/year, respectively). During the first 10 days, 52% to 70% of prothrombin time ratios were low (<1.5 × control). Patients with mitral valve replacement who received anticoagulation had a lower rate of thromboembolism for the entire follow-up period (2.5%/year with vs. 3.9%/year without anticoagulation, $p = 0.05$). Of 112 patients with a first thromboembolic episode, permanent disability occurred in 38% and death in 4%. Risk factors for emboli were lack of anticoagulation, mitral valve location, history of thromboembolism and increasing age. Only 10% of aortic, 44% of mitral and 17% of double valve recipients had anticoagulation at the time of an event. Patients with bleeding episodes (2.3%/year) were older and usually underwent anticoagulation. Blood transfusions were required in 60 of 111 patients (1.2%/year), and 13 patients (0.3%/year) died.**

Conclusions. **Thromboembolic risk was especially high for aortic and mitral valve replacement for 90 days after operation, and overall was increased with lack of anticoagulation, mitral valve location, previous thromboembolism and increasing age. Anticoagulation reduced thromboemboli and appears to be indicated in all patients as early as possible for 3 months and thereafter in those with risk factors, but needs prospective testing.**

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Prophylaxis for thromboembolism should be based on pathogenesis and risk. The peak incidence occurs during the first 3 months after valve surgery, probably reflecting the lack of endothelialization of the newly implanted prosthetic and biologic materials (1–3). Although bioprosthetic valves are less thrombogenic than mechanical prostheses, the rate of thromboembolic episodes also varies depending on anticoagulation status and position of the valve (2). Thromboembolic events are less frequent after aortic than mitral valve replacement (4). Unresolved issues include the timing and incidence of thromboembolism, timing and targeting of anticoagulation, the role of antiplatelet agents and the effectiveness and optimal duration of antithrombotic therapy after bioprosthetic valve replacement (3,5).

We studied the rate of thromboembolism in patients who had bioprosthetic replacement of the aortic or mitral valve, or both. This rate was divided into three time intervals after operation: 1 to 10, 11 to 90 and >90 days. The effect of anticoagulant or antiplatelet treatment and risk factors for thromboembolism and major bleeding were also studied.

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Methods

From January 1975 to December 1982, 816 patients underwent replacement of an aortic or mitral valve, or both, with bioprosthetic porcine or bovine pericardial valves at the Mayo Clinic. Aortic valves were replaced in 424 patients, mitral valves in 326 and both valves in 66. Bioprostheses used were Hancock (48%), Carpentier-Edwards (18%) and Ionescu-Shiley (34%).

Anticoagulation and antiplatelet therapy. Patients who had anticoagulation received either intravenous heparin (at least 25,000 U/24 h) or warfarin. Anticoagulation was considered to be adequate when prothrombin time ratios (prothrombin time/control time) were between 1.5 and 2.0 (using rabbit brain thromboplastin), which is equivalent to an international normalized ratio between 3.0 and 4.5.

Definitions of thromboembolic and bleeding events. *Thromboembolism to the brain or retina* was defined as a temporary or permanent neurologic deficit of sudden onset with focal motor weakness or visual deficit, unexplained by other findings. It was coded as *minor or transient* when the deficit lasted <24 h and there was a full recovery, and *major or permanent* when the neurologic deficit was persistent (>24 h) or the patient died. Neurologic deficits within the first 24 h after operation were excluded because they may have been caused by an air or cholesterol embolism. A *peripheral embolism* was diagnosed when there was a sudden onset of arterial occlusion in the extremities. A *coronary embolism* was defined as an acute myocardial infarction in a young patient (<40 years old) with documented normal coronary arteries and no risk factors. In general, a computed tomographic scan confirmed the diagnosis of cerebral infarction, and peripheral emboli were confirmed at angiography or operation. Cerebral thromboembolism was not considered of cardiac origin in the presence of severe atherosclerotic carotid disease, with abnormal carotid ultrasound or oculoplethysmography or with arteriographic evidence of severe carotid stenosis (>75%).

Bleeding events requiring admission to the hospital were recorded regardless of the patient's anticoagulation status.

Follow-up. After hospital discharge, patients were followed up by their physicians who determined treatment and performed all the routine evaluations. Questionnaires were sent to the patients and their primary physicians in 1983 and again in 1988. The questionnaires included a functional evaluation of the patient, current medication and drugs discontinued since operation, occurrence of strokes or other thromboembolic events, bleeding complications and hospital admission for cardiac problems. All prothrombin times were requested from physicians for those patients taking anticoagulant agents. If a patient was admitted to another hospital, details of that admission were obtained with the patient's consent. If questionnaires were returned unclaimed or incomplete, patients were contacted by telephone; when patients could not be reached or the information remained incomplete, the treating physician was contacted. Therefore, all questions were answered by either the patient or the treating physician, or both.

Only prothrombin times sent by the treating physician were recorded; 15,604 prothrombin times were obtained, or an average of one every 6 weeks of follow-up for patients receiving anticoagulation. Prothrombin times were obtained at least once in 83% of all patients taking anticoagulant agents.

Statistical methods. The primary end points considered were thromboembolic and bleeding events; patients were censored at death or at their last available follow-up date (6). Time-dependent Cox proportional hazards models were used to identify potential risk factors associated with thromboembolic and bleeding events. According to these models, the instantaneous risk of an event at any time is proportional to an underlying function of time, with the proportionality factor depending on the current treatment status (anticoagulant agents, aspirin and dipyridamole) as well as other non–time-dependent covariates.

Multivariate Cox models were developed with a forward stepwise procedure. The location of valve replacement (aortic or mitral, or both) was always included in the model. Patients were coded as either receiving or not receiving treatment for each day they were at risk; all other covariates remained fixed as the values at time of operation. The covariates assessed in the model for thromboembolism were treatment status, preoperative and postoperative atrial fibrillation, preoperative thromboembolic event, year of operation, type of valve, age, gender, New York Heart Association functional class, left atrial size and coronary artery disease (values of the last two variables were not available for all patients). Treatment status, age, gender and year of operation were evaluated as risk factors for bleeding events.

Differences in the rates of thromboembolic and bleeding events between time periods (0 to 10, 11 to 90, and >90 days) were tested separately for each valve location, using an approximate test for Poisson random variables. The rate of events that occurred during anticoagulation versus the rate in the absence of anticoagulation was tested using a Mantel-Haenszel test stratified by time periods.

The log-rank test was used to assess differences between the Kaplan-Meier curves for valve location with respect to the end points of thromboembolic and bleeding events, death and cardiac death.

Results

Results are reported according to the guidelines of McGoon (7). Follow-up information was obtained for 99.9% of the patients. Median follow-up of surviving patients was 8.6 years; mean [±SD] follow-up was 8.3 ± 2.4 years (range 1.7 to 13.2, median 7.9), 9.5 ± 2.4 years (range 1.7 to 13.2, median 9.9) and 8.1 ± 2.7 years (range 0.03 to 13.3, median 7.7) for patients undergoing aortic or mitral valve replacement, or both, respectively.

Clinical variables before and after operation are presented in Table 1. Fifty-nine percent of patients were between 60 and 80 years old, and 5.5% were >80 years. Patients with aortic prostheses were older and had a higher incidence of coronary

Table 1. Preoperative and Postoperative Clinical Variables

	Valve Replacement		
	Aortic (n = 424)	Mitral (n = 326)	Aortic and Mitral (n = 66)
Age (yr)			
<20–40	45 (11%)	30 (9%)	6 (9%)
40–60	83 (19%)	101 (31%)	23 (35%)
60–80	262 (62%)	187 (57%)	34 (51%)
≥80	34 (8%)	8 (3%)	3 (5%)
Mean ± SD	64 ± 16	61 ± 14	61 ± 13
Gender			
Male	333 (79%)	125 (38%)	30 (45%)
Female	91 (21%)	201 (62%)	36 (55%)
Left atrial size (mm)			
<40	103 (24%)	17 (5%)	4 (6%)
40–45	72 (17%)	34 (11%)	7 (11%)
45–54	91 (21%)	89 (27%)	16 (24%)
≥55	24 (6%)	108 (33%)	24 (36%)
Atrial fibrillation			
Preoperative	35 (8%)	178 (55%)	35 (53%)
Postoperative	50 (12%)	161 (49%)	34 (53%)
Either	59 (14%)	202 (62%)	40 (61%)
Thromboembolism			
Preoperative	25 (6%)	59 (18%)	11 (17%)
Unknown	4 (1%)	1 (0.3%)	
Coronary artery disease			
None	166 (39%)	164 (51%)	32 (48%)
One vessel	65 (15%)	20 (6%)	2 (3%)
Two vessels	46 (11%)	33 (10%)	3 (5%)
Three vessels	35 (8%)	14 (4%)	1 (2%)
No coronary angiography	112 (27%)	95 (29%)	28 (42%)
NYHA functional class			
I	16 (4%)	8 (2%)	2 (3%)
II	82 (19%)	44 (14%)	5 (8%)
III	225 (53%)	173 (53%)	28 (42%)
IV	101 (24%)	101 (31%)	31 (47%)
Time of surgery			
1975–1977	116 (27%)	132 (41%)	20 (30%)
1978–1980	121 (29%)	112 (34%)	18 (27%)
1981–1982	187 (44%)	82 (25%)	28 (43%)
Type of prosthesis			
Hancock	177 (42%)*	182 (56%)	35† (53%)
Carpentier-Edwards	56 (13%)	90 (28%)	3 (5%)
Ionescu-Shiley	191 (45%)	54 (16%)	28 (42%)
Treatment			
Aspirin‡	105 (25%)	40 (12%)	11 (17%)
Dipyridamole‡	108 (25%)	76 (23%)	18 (27%)
Sulfinpyazone	1 (0.2%)	2 (0.6%)	0
Warfarin started in hospital	144 (34%)	258 (79%)	46 (70%)
Digoxin started in hospital	248 (58%)	251 (77%)	54 (82%)
Pts with anticoagulation (% of PT <1.3 and <1.5 × control)§			
At 0–10 days postop	32% (63 and 70)	78% (40 and 52)	70% (49 and 62)
At 11–90 days postop	35% (36 and 52)	86% (21 and 35)	74% (26 and 42)
At >90 days postop	37% (48 and 61)	86% (28 and 42)	82% (27 and 45)

*Two patients (Pts) had a Hancock valve with a conduit from left ventricle to descending aorta, †All but one patient had the same type of prosthesis implanted in both positions (mitral and aortic). ‡Ever taking aspirin or dipyridamole before event. §Treated during or before (≥1 day), but not in response to, thromboembolic event. Data presented are number (%) of patients, unless otherwise indicated. NYHA = New York Heart Association; postop = after operation.

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Table 2. Postoperative Events

	Valve Replacement		
	Aortic (n = 424)	Mitral (n = 326)	Aortic and Mitral (n = 66)
Thromboembolism			
First	51 (12%)	55 (17%)	6 (9%)
Second	10 (2%)	13 (4%)	1 (2%)
Bleeding events			
First	59 (14%)	41 (13%)	11 (17%)
Second	13 (3%)	6 (2%)	2 (3%)
Total deaths	184 (43%)	165 (51%)	36 (55%)
Cardiac*	87 (21%)	92 (28%)	19 (29%)
Noncardiac	71 (17%)	41 (13%)	11 (17%)
Operative†	9 (2%)	11 (3%)	4 (6%)
Cerebral infarction	5 (1%)	4 (1%)	1 (2%)
Cerebral hemorrhage	4 (1%)	6 (2%)	1 (2%)
Systemic emboli	2 (0.5%)	4 (1%)	0
Hemorrhage	6 (1%)	6 (2%)	0
Unknown	0	1 (0.2%)	0
Reoperation	68 (16%)	54 (17%)	17 (26%)

*38% arrhythmic, 17% ischemic, 43% heart failure, 2% endocarditis. †Within 30 days of operation. Data presented are number (%) of patients.

artery disease. Those with mitral or double valve replacement were predominantly female, presented with larger left atria (95% abnormal), had a greater prevalence of atrial fibrillation before and after operation and had a higher prevalence of previous thromboembolic episodes (18%). Almost 67% of patients with mitral valve replacement compared with 33% of those with aortic valve replacement were discharged with anticoagulation. Aspirin was usually instituted when warfarin was discontinued; the median times to starting aspirin were 134, 253 and 433 days for aortic, mitral and double valve replacement, respectively. Dipyridamole was given with warfarin in 101 patients, with aspirin in 85 and alone in another 14.

There was a strong correlation between year of operation and the type of valve implanted. In the first 4 years of the study period, all bioprosthetic valves implanted were Hancock, and in the last 2 years the majority (86%) were Ionescu-Shiley. Table 2 lists the postoperative thromboembolic and bleeding episodes, reoperations and causes of death. During follow-up, 385 patients (47%) died. Kaplan-Meier survival curves to all causes of death for each valve location are shown in Figure 1 (top); survival curves to cardiac death are shown in Figure 1 (bottom). Patients with mitral or double valve replacement had a greater incidence of cardiac death ($p = 0.03$) than those with aortic valve replacement.

Thromboembolic episodes. One hundred twelve patients (2.3%/year) had one thromboembolic episode, and 24 (6.1%/year after the first episode) had two episodes (Tables 2 and 3). Two patients had a neurologic deficit within 24 h of operation but are not included as having a thromboembolic episode. Table 3 lists the sites of thromboembolism, linearized rates, resultant degree of disability and treatment status. Ninety-three percent of the emboli went to the brain and retina and 7% were peripheral. Fifty-eight percent of patients fully recovered; 38% had a permanent neurologic deficit; and 4% died. Only 10%, 44% and 17% of aortic, mitral and double valve recipients, respectively, had anticoagulation at the time of the event.

Figure 1. Kaplan-Meier survival curves for death **(top)** and cardiac death **(bottom)** after valve replacement.

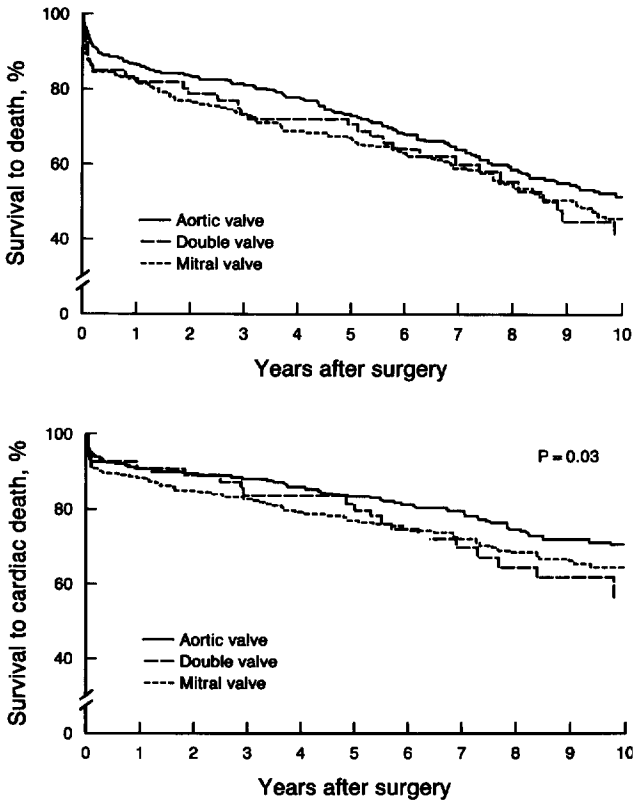

Table 3. Site, Outcome and Therapy at Time of First and Second Thromboembolic Events

	Valve Replacement					
	Aortic		Mitral		Aortic and Mitral	
	First	Second	First	Second	First	Second
No. of events (%/yr)	51 (2.2)	10 (4.6)	55 (3.1)	13 (5.8)	6 (1.7)	1 (3.7)
Total linearized rate (%/yr)	2.2	4.6	3.1	5.8	1.7	3.7
Site (% of total events)						
Cerebral	96%	100%	89%	85%	6/6*	1/1*
Coronary	0	0	0	15%	0	0
Peripheral	4%	0	11%	0	0	0
Outcome of cerebral events						
Full recovery	47%	50%	69%	54%	3/6*	0
Permanent defect	53%	40%	24%	38%	2/6*	1/1*
Death	0	10%	7%	8%	1/6*	0
Therapy at event (% of total)						
Warfarin	8%	30%	44%	62%	1/6	0
Aspirin	25%	20%	13%	15%	0	0
Dipyridamole	25%	40%	13%	23%	0	1/1*
None	41%	10%	30%	0	5/6*	0

*Expressed as fraction of total patients.

Figure 2 shows the rates of thromboembolic episodes, with and without anticoagulant agents, at the three different intervals for each valve location. The rate of thromboembolic episodes in aortic valve recipients during the first 10 days after operation was extremely high in those patients without anticoagulation and was significantly higher than that rate at 11 to 90 days (3.6%/year) and >90 days (1.9%/year) ($p < 0.001$). In mitral valve recipients, the rate during the first 10 days (55%/year) was significantly higher than that at 11 to 90 days (10%/year) ($p < 0.007$), and the latter was significantly higher than the rate after 90 days (2.4%/year) ($p = 0.006$). By multivariate Cox model analysis, the risk of thromboembolism increased with mitral valve location, lack of anticoagulation, age and history of thromboembolism (Table 4). Aspirin and dipyridamole were also evaluated in this model, and neither was associated with a reduced risk of thromboembolism. Valve type did not significantly change the risk of thromboembolism. Factors not significant in these patients but associated with thromboembolism in other studies include atrial fibrillation, year of operation, atrial size, presence of coronary artery disease and functional class.

Figure 3 shows the Kaplan-Meier curves for the incidence of thromboembolism for each valve location. The probability of freedom from a thromboembolic event at 5 years was 89% for patients with aortic, 85% for mitral and 95% for double valve replacement.

Bleeding events. One hundred eleven patients (2.3%/year) had a bleeding event. Risk factors associated with a bleeding event were anticoagulation and increased age (Table 4). The linearized rates of bleeding (%/year) for patients with (without) anticoagulation were 6.2 (1.6), 2.7 (1.1) and 4.5 (1.9) per patient-year for aortic, mitral and double valve replacement, respectively. Bleeding sites, complications and treatment at the time of the event are presented in Table 5. Fifty-one percent of these bleeding events were gastrointestinal. Blood transfusions were required in 54% of patients. Of 32 patients with a first bleeding event, 13 died as a result of cerebral bleeding, and fatal or nonfatal cerebral bleeding occurred in 19. Four patients died as a result of a second bleeding event. Kaplan-Meier curves for bleeding by valve location were similar (data not shown). At 5 years, the probabilities of freedom from a bleeding complication were 89%, 89% and 86% for patients with aortic, mitral and double valve replacement, respectively.

Anticoagulation. Table 1 shows the proportion of patients treated with anticoagulant agents at each of the three intervals before any thromboembolic event (at least 1 day). During the first 10 days after operation, 52% to 70% of prothrombin times were <1.5 × control. Patients who had aortic and mitral valve replacement and who were treated with anticoagulant agents had a similar prevalence of atrial fibrillation, previous thromboembolism and left atrial dimensions to those without anticoagulation. However, mitral valve recipients with anticoagulation for up to 90 days had a higher prevalence of atrial

Figure 2. Linearized rates of thromboembolic events by anticoagulation (AC) status and days after operation.

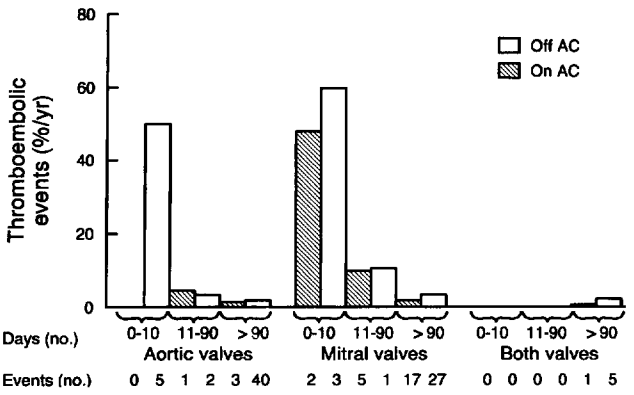

Table 4. Multivariate Cox Analysis

Variable	Thromboembolic Events			Bleeding Events		
	Coeff	SE	p Value	Coeff	SE	p Value
Valve replacement						
Aortic	−0.06	0.44	< 0.001*	−0.11	0.34	NS
Mitral	0.58	0.22	< 0.001*	−0.92	0.24	NS
Double	−0.06	0.44	< 0.001*	0.11	0.34	NS
Age†	0.02	0.007	0.014	0.04	0.01	
AC	−0.66	0.24	0.007	1.11	0.22	
Hx of TE	0.77	0.24	0.002			

*Testing valve location with two degrees of freedom. †Age is centered at the mean value. AC = anticoagulation; Coeff. = coefficient; Hx of TE = history of thromboembolism.

fibrillation both before ($p < 0.1$) and after ($p < 0.05$) operation.

Only 29 of 112 patients were taking anticoagulant agents at the time of their first thromboembolic episode (Table 3). Sixty-two of 111 patients were taking anticoagulant agents at the time of their first bleeding event. Prothrombin time ratios were available in 27 of 62 patients and were <1.5 in 9, between 1.5 and 2.0 in 9 and >2.0 in 9.

Discussion

Thromboembolism. The present study shows a high incidence of thromboembolic episodes during the first 10 postoperative days for patients with aortic and mitral bioprosthetic valve replacement when anticoagulation is either not administered or is subtherapeutic, in part because warfarin therapy is started at 48 h and has a delayed onset. The risk of thromboembolism remained high after mitral valve replacement for at least 90 days (10%/year) after operation. Anticoagulation significantly decreased the incidence of thromboembolism. On the basis of pathogenesis and risk (1), the present data suggest that early anticoagulation to stable therapeutic levels and maintenance of the prothrombin time ratio at 1.5 to 2.0 (international normalized ratio 3.0 to 4.5) may be needed for a minimum of 3 months.

Patients with mitral valve replacement had the highest rate of thromboembolism, even with anticoagulation during the first 10 and 11 to 90 days after operation (48%/year and 9.9%/year, respectively). Reasons for this may relate to the high incidence of left atrial enlargement and atrial fibrillation (Table 1) and to three aspects of antithrombotic therapy independent of valve replacement location.

First, delay in achieving therapeutic levels of anticoagulation may result in early, rapid growth of valvular or atrial thrombus. Prothrombin times were <1.5 × control in 70% of measurements during the first 10 days after operation. The delay may be inherent in the longer half-life of certain vitamin K-dependent coagulation factors (especially Factors II, X and IX) and the 48-h delay in the start of warfarin administration. Substrates for high acute thrombogenicity include the valve excision site, prosthetic Dacron sewing rings common to all prosthetic valves, suture material and xenotropic valvular tissue, among other factors usually greater in patients with mitral valve replacement (dilated cardiac chambers and decreased cardiac output).

Second, variable and subtherapeutic prothrombin times increase the risk of thromboembolism in patients with prosthetic heart valves. Variability is probably as important as intensity (4,8). For example, Sauor et al. (8) reported high and similar rates of thromboembolism (4.0 and 3.7%/year) in moderate and high intensity anticoagulation groups, respectively, even though the target prothrombin time ratio was 1.5 ± 0.2 (international normalized ratio 2.65) and 2.5 ± 0.2 (international normalized ratio 9.0), respectively. In that study, 19 of 33 thromboembolic events occurred when the prothrombin time ratio (at the time of the event) was <1.5 × control (approximately half in each group) (8), which suggests high variability in both groups.

Third, starting warfarin therapy without simultaneous therapeutic heparin in situations of high thrombotic risk may enhance thrombosis (9). Maximal prevention may include early anticoagulation with heparin, initiation of oral anticoagulation on the day of operation and maintenance of international normalized ratio at 3.0 to 4.0 for 3 months, passivation of thrombosis on prosthetic or injured cardiac surfaces, platelet inhibitor therapy or a combination of these. Low dose aspirin (100 mg/day) combined with warfarin (international normalized ratio 3.0 to 4.5) has been successful (10).

Figure 3. Kaplan-Meier survival curves for first thromboembolic event after valve replacement.

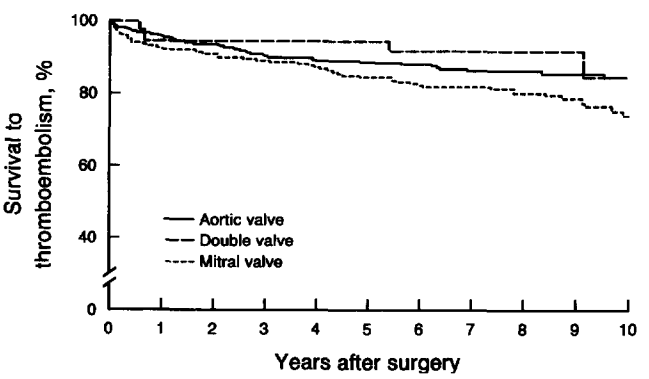

Table 5. Site of and Therapy for First and Second Bleeding Events

	Valve Replacement							
	Aortic		Mitral		Aortic and Mitral		Total	
	First	Second	First	Second	First	Second	First	Second
No. of events (%/yr)	59 (2.3)	13 (11.1)	41 (2.1)	6 (4.0)	11 (3.0)	2 (7.4)	111 (2.3)	21 (7.2)
Site (% of total [%/yr])								
Cerebral*	12%	0	22%	33%	27%	0	17%†	10%
Gastrointestinal‡	56%	85%	49%	67%	36%	50%	51%	76%
Urinary	15%	15%	5%	0	9%	50%	11%	14%
Epistaxis	0	0	2%	0	0	0	1%	0
Other	17%	0	22%	0	27%	0	20%	0
Transfusion (% of total events [%/yr])	32%	69%	44%	67%	64%	50%	54% (1.2)	67%
Therapy at event								
Anticoagulation	39%	23%	78%	83%	64%	50%	56%	43%
Aspirin	29%	46%	5%	0	9%	0	18%	29%
Neither	32%	31%	17%	17%	27%	50%	26%	29%
Death (% of total [%/yr])	8%	15%	20%	33%	0	0	12% (0.3)	19%

*Four of seven of aortic, nine of nine mitral and two of three double valve recipients had anticoagulation at time of event. †13 fatal and 6 nonfatal = 19/111 (17%). ‡18% of aortic, 70% of mitral and two of four double valve recipients had anticoagulation at time of event.

Short-term anticoagulation in all patients for 2 to 3 months after operation has resulted in very low rates of thromboembolism (11). This group (A. F. Carpentier, personal communication, January 1994) also starts a heparin infusion ~6 h after operation to mildly prolong the activated partial thromboplastin time to slightly above the upper limit of normal; after chest tubes have been removed, heparin is increased to an activated partial thromboplastin time of 1.5 to 2.0 times control. Oral anticoagulation is started when patients resume oral intake, and heparin infusion is continued until the prothrombin time has been in the therapeutic range for 2 days.

Our thromboembolism rates for patients with aortic, mitral and combined valve replacement are higher than those reported by Hartz et al. (12), Zussa et al. (13) and Reul et al. (14). Inclusion of stroke, transient cerebral ischemia and coronary and peripheral artery thromboembolism; questioning of both patients and physicians by letter and telephone for thromboembolic events; and review of local hospital records for patients readmitted to the hospital may account for our higher rates. The low rates of thromboembolism (although higher with atrial fibrillation) reported by Oyer et al. (15) may be explained by anticoagulation in all patients for 6 weeks. Spencer et al. (16) documented a similar survival free of thromboembolism for patients with aortic and mitral valve replacement.

Approximately 90% of the emboli clinically affected the brain or retina, the most sensitive organs for symptomatic detection. It is likely that some peripheral thromboembolic episodes went undetected; therefore, the true embolic rate is probably higher. Emboli caused permanent disability or death in 42% of patients; this rate is very similar to those in previously reported series of younger patients with older mechanical valves (17,18).

Although patients with double valve replacement had the lowest rates of thromboembolism, the overall incidence in this small (also nonrandomized) group was not statistically different from that in patients with mitral or aortic valve replacement. Lower rates of thromboembolism for multivalve than mitral valve replacement have also been reported by Gallo et al. (19) and Zussa et al. (13), although their patients had anticoagulation for at least 3 months.

Multivariate analysis. Of the variables analyzed in the multivariate Cox analysis, valve location, history of thromboembolism, increasing age and lack of treatment with anticoagulant agents were predictive of thromboembolism. Patients with aortic valve replacement had the lowest estimated risk, whereas those with mitral valve replacement had the highest. Patients with anticoagulation are estimated to have a lower risk than those with no treatment. In our retrospective study, the finding that aspirin did not show a beneficial effect does not confirm previous retrospective findings that aspirin alone may be sufficient to prevent thromboembolic episodes in patients with bioprostheses (20–23). Treatment with dipyridamole also did not reduce the incidence of thromboembolism.

None of the other known risk factors examined, such as atrial fibrillation or left atrial size, were significant predictors of increased risk; however, one of these risk factors was present in >90% of patients with mitral valve replacement. Sixty-one percent of mitral and combined bioprosthetic valve recipients had atrial fibrillation before or after operation, and <10% had normal-sized left atria. Left atrial size, age >60 years, possible left ventricular dysfunction and even hypertension under treatment all add risk for thromboembolism in patients with atrial fibrillation (24–26). This high overall incidence of risk may account in part for the high rates of thromboembolism in the present study.

Bleeding. The rates of bleeding in our series are slightly higher than those previously reported (16,27,28), perhaps because we recorded all bleeding episodes regardless of anticoagulation status. Other studies analyzed only bleeding secondary to warfarin and aspirin treatment, but as shown in the present multivariate analysis, age is a very important risk factor

for bleeding independent of anticoagulant or antiplatelet therapy. At the time of bleeding, 56% of patients were taking warfarin, 18% were treated with aspirin. Therefore, the risk of bleeding increased with age and treatment with anticoagulants. Bleeding events were independent of valve location. The higher rates of bleeding observed in the aortic valve recipients may reflect their older age.

Study limitations. This was a retrospective study. Anticoagulation or antiplatelet therapy, or both, was not randomized. However, follow-up and thromboembolic and bleeding event information were obtained for all but two patients. Although we know when patients were taking warfarin, complete quantitative data on prothrombin times >90 days after operation were insufficient to address completely the adequacy of long-term anticoagulation. Therefore, all analyses were based on the presence or absence of medical treatment. In addition, there were no data for left atrial size (Table 1) because echocardiographic studies were not performed in the early patients in this study.

Conclusions. Patients with bioprosthetic aortic or mitral valve replacement have a high risk of thromboembolism during the first 10 days, high (mitral) to medium (aortic) risk at 11 to 90 days after operation and medium (mitral) to low (aortic) risk thereafter. Strategies for prevention should be based on pathogenesis and risk of thromboembolism (1).

Because of the high incidence of thromboembolism, all patients with bioprostheses may benefit from early anticoagulation with heparin starting 6 h after operation to prolong activated partial thromboplastin time to slightly above the upper limit of normal, an increase to an activated partial thromboplastin time of 1.5 to 2.0 × control 6 h after chest tubes are removed, oral low dose aspirin (80 to 100 mg) 48 h after operation and oral anticoagulation starting the night before operation (29) for 3 months after operation (4) at an international normalized ratio of 3.0 to 3.5. Those with risk factors (atrial fibrillation, enlarged left atrium or notable left ventricular dysfunction) should receive long-term anticoagulation at an international normalized ratio of 2.0 to 3.0 regardless of valve location(s). Thus, aortic valve recipients and mitral valve recipients with reversible or no risk factors may be able to avoid long-term anticoagulation, but patients >60 years old have a risk of 4.6%/yr of myocardial infarction, stroke or vascular death and thus probably should receive daily aspirin. High risk patients with concomitant coronary artery bypass grafting or vascular disease should probably also receive low dose aspirin in addition to warfarin, in keeping with the prospective study of Turpie et al. (10). Older patients are at a higher risk for both thromboembolic and bleeding episodes; in this group, a careful selection of patients at high risk for thromboembolism and strict control of anticoagulation and blood pressure (<150/90 mm Hg, perhaps with beta-adrenergic blocking agent therapy to decrease pulse pressure) may diminish bleeding complications while preventing thromboembolism. These therapeutic strategies currently appear prudent but need testing in a prospective, randomized study.

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