Journal of the American College of Cardiology
© 2000 by the American College of Cardiology
Published by Elsevier Science Inc.

Vol. 35, No. 3, 2000
ISSN 0735-1097/00/$20.00
PII S0735-1097(99)00598-7

Early and Long-Term (One-Year) Effects of the Association of Aspirin and Oral Anticoagulant on Thrombi and Morbidity After Replacement of the Mitral Valve With the St. Jude Medical Prosthesis

A Clinical and Transesophageal Echocardiographic Study

Patrick Laffort, MD, Raymond Roudaut, MD, Xavier Roques, MD, Stéphane Lafitte, MD, Claude Deville, MD, Jacques Bonnet, MD, Eugene Baudet, MD

Pessac, France

OBJECTIVES The aim of the study was to test the value of low dose aspirin associated with standard oral anticoagulants (OAC) after mechanical mitral valve replacement (MMRV) to reduce strands, thrombi and thromboembolic events.

BACKGROUND Strands and thrombi are thought to increase the risk of embolic events after MMVR, particularly in the immediate postoperative period.

METHODS Two hundred twenty-nine patients were prospectively recruited: 109 patients (group A+) were randomly assigned to aspirin (200 mg per day) with OAC and 120 patients (group A−) to OAC alone (international normalized ratio 2.5 to 3.5). All patients were subjected to multiplane transesophageal echocardiography at nine days and five months and were followed up for one year.

RESULTS At nine days and five months, there was a high and comparable incidence of strands in the two groups (group A+: 44%, 58%; group A−: 49%, 63%). However, the incidence of nonobstructive periprosthetic valve thrombi was significantly lower in group A+ at 9 days: 5% versus 13%, $p = 0.03$.

Total thromboembolic events were reduced in group A+ (9% vs. 25%, $p = 0.004$) although there was an increased incidence of gastrointestinal hemorrhage (7% vs. 0%). Overall mortality was 9% in group A+ and 4% in group A−. Valve-related events were similar in both groups. Early thrombi, but not strands, were associated with higher morbidity, especially thromboembolic events (30% vs. 13%, $p = 0.003$).

CONCLUSIONS One year after MMVR, the association of aspirin with OAC reduced thrombi and thromboembolic events, but not morbidity, due to an increase in hemorrhagic complications. (J Am Coll Cardiol 2000;35:739–46) © 2000 by the American College of Cardiology

Despite progress in valve design with new generation prostheses such as the St. Jude medical valve, patients with prosthetic mechanical mitral prostheses have an increased incidence of cardiac embolic events (1–3), particularly in the immediate postoperative period (4–8).

Transesophageal echocardiographic examinations (TEE) early in the postoperative period have shown a high incidence of strands or thrombi (9–12) attached to mechanical mitral prostheses. These accretions are now thought to influence morbidity (9,11,13,14) after mechanical valve replacement.

The benefit of early therapy with a combination of aspirin and an oral anticoagulant (OAC) after mechanical mitral valve replacement (MMVR) has yet to be established. In a prospective study (15), Turpie et al. demonstrated that adding aspirin decreased thromboembolic events and mortality although the meta-analyses are not in total agreement (4,16). The association of 160 mg/day aspirin was regarded as optional (17,18).

In order to determine the value of the association of low dose aspirin after MMVR, we undertook a prospective

From the Service d'Echocardiographie PR Roudaut, Cardiologic Hospital Haut-Leveque, 33600 Bordeaux-Pessac, France.

Manuscript received March 6, 1999; revised manuscript received October 5, 1999, accepted November 17, 1999.

Abbreviations and Acronyms

CAD	=	coronary artery disease
GIB	=	gastrointestinal bleeding
INR	=	international normalized ratio
MMVR	=	mechanical mitral valve replacement
MVR	=	mitral valve replacement
OAC	=	oral anticoagulant
RR	=	relative risk
TEE	=	transesophageal echocardiography
TTE	=	transthoracic echocardiography

randomized comparison of OAC alone with OAC plus aspirin in patients receiving a St. Jude medical prosthesis at the mitral position.

METHODS

Patients. The inclusion criterion for the study was the implantation of a St. Jude medical mechanical mitral valve. Patients were not included if they were unwilling to give informed consent or if they had contraindications to aspirin, anticoagulant therapy or transesophageal examination.

Study design and treatment protocol. In a randomized, controlled design, patients were allocated to one of two groups at random: the reference group was treated with OACs alone to maintain the international normalized ratio (INR) between 2.5 to 3.5, while the test group received a supplement of 200 mg aspirin from the first postoperative day along with the same anticoagulant treatment. The INR was 2.5–3.5 as recommended for the new generation of mechanical mitral prostheses (17,18).

Patients received antiulcer treatment systematically. The follow-up was essentially clinical, but all patients benefited from transthoracic and transesophageal multiplane echocardiographic examinations. All patients were subjected to a preoperative coronary angiographic evaluation. Coronary artery disease (CAD) was defined as more than 50% narrowing of the lumen in at least one coronary artery.

Mitral valve replacements (MVR) were all performed by the same surgical unit and postoperative anticoagulation was standardized: intravenous infusion of heparin was started from the sixth postoperative hour (19); the dose was adjusted based on a tabular normogram and supplemented with three subcutaneous calcium heparin injections per day during the 24 postoperative hours to maintain an aPPT of twice the control valve. Oral anticoagulation was instituted 48 h after operation and subcutaneous injection of calcium heparin was continued until the INR had returned to 2. INR was then monitored to keep it in the target range 2.5 to 3.5. The patient's cardiologist was allowed to adjust the target range in the presence of embolic risk factors (20).

Echocardiographic study. The echocardiographic study was standardized and the operators were unaware of the

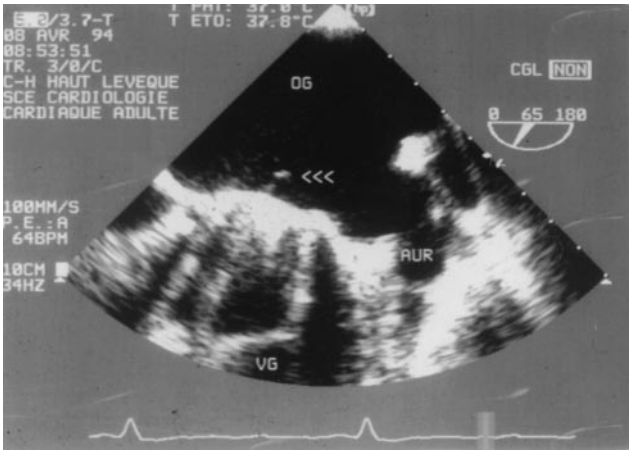

Figure 1. TEE view of a St. Jude medical mitral valve showing a strand on the atrial side of the prosthesis. TEE = transesophageal echocardiography.

treatment received by the patients. Transthoracic echocardiography (TTE) and TEE examinations were carried out in all patients eight days and five months after MVR using a Hewlett Packard Sonos 2500 (Imaging System, Andover) and a multiplane probe. The examinations were performed by five experienced operators and were recorded on videotapes. The technique was standardized and focused on the prosthesis with transgastric views for the ventricular side of the prosthesis and transesophageal views for each portion of the valves using the multiplane probe. Particular attention was focused on leaflet mobility, strands and thrombi (incidence, size and localization). Strands were defined as mobile linear echodense structures attached to the prostheses. They were generally less than 1 mm in width and several mm in length (Fig. 1). Thrombi were defined as well defined and circumscribed echodense masses attached to the prostheses and clearly seen throughout the cardiac cycle (Fig. 2). They were usually situated at the level of the atrial side of the sewing ring and were localized or ring-shaped. We also searched for the presence of thrombi in the left atrium or left appendage. Spontaneous echo contrast was considered grade 1 for low intensity echoes and grade 2 in the event of well defined spirals. The transesophageal echocardiograms were all reviewed independently by two experienced echocardiographers. In cases of discordance, a consensus was reached with the opinion of a third experienced echocardiographer.

Surgical technique. Prosthetic leaflets were implanted in the antianatomic orientation, and the prostheses were anchored to the valve annulus by a continuous suture.

Follow-up procedure. All the patients were subjected to clinical, laboratory and echocardiographic examinations at different times during the first operative year. All data were collected prospectively with the first day in-hospital as day 1. Patients were monitored prospectively by regular exami-

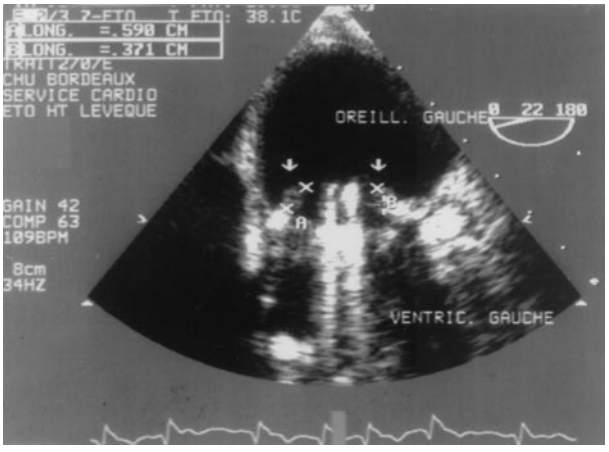

Figure 2. TEE view of a St. Jude medical mitral valve showing nonobstructive thrombus on the atrial side of the prosthesis. TEE = transesophageal echocardiography.

nations during the first postoperative year using a case report form filled out by the cardiologist and patients' general physicians. Data were collected and verified (including hospital visits for each patient) at one month, six months and one year.

End points and definitions. The primary outcome of the study was the composite triple end point of death, major thromboembolic events or major hemorrhage at one-year of follow-up. Death was defined as any death, regardless of cause. Thromboembolic events were classified as major or minor: major thromboembolic events were based on clinical criteria and included: stroke defined as a focal neurologic deficit of sudden onset that persisted for more than 24 h if a computerized tomographic scan of the brain excluded bleeding as a possible cause; coronary artery embolism, which was defined as the occurrence of acute ischemia in patients with previously normal coronary arteries; peripheral embolism was defined as the occurrence of acute ischemia caused by an embolism documented by angiography or surgery; valve thrombosis, which was defined as the deposition on the valve of a large obstructive thrombus necessitating surgery or fibrinolysis. Minor thromboembolic events included: nonobstructive prosthetic thrombi detected by systematic TEE and transient ischemic attacks defined as a focal neurologic deficit of sudden onset that persisted for less than 24 h.

Bleeding events were also classified as major or minor: major hemorrhage was defined as that associated with a sudden fall of 20 g per liter or more in hemoglobin level and necessitating a transfusion of at least two units of blood or any hemorrhage necessitating surgery and any intracranial bleeding. Other hemorrhages were considered to be minor but were all recorded. Hospital and late deaths as well as valve-related events were strictly defined according to the guidelines of the American Association for Thoracic Surgery (21).

Statistical analysis. The primary analysis included all randomized patients (intention to treat). The Fisher exact test was used to compare the two treatment groups with respect to the primary end point. A logistic regression model was used to study predictive factors of events at 1 year. The p value indicating statistical significance was set at 0.05.

RESULTS

Patients. From July 1994 to July 1996, 263 consecutive patients underwent an MVR with a St. Jude medical prosthesis in our department. Thirty-four patients were excluded on the grounds described in the Methods section, and 109 patients were assigned at random to receive OACs with 200 mg of aspirin per day and 120 to receive OACs alone.

Both groups were similar with respect to the important baseline characteristics that may influence outcome (Table 1). Patients were relatively old (mean age 63 years); fractional shortening was 31% in both groups; concomitant procedures were 48% similar in both groups (coronary artery bypass grafting was performed in 13% of patients and aortic replacement in 40% of patients). The patients were all followed up during the first postoperative year and none were lost to follow-up.

Anticoagulation in the two groups. During the first postoperative year, the mean international normalized ratio was 3.04 ± 0.25: 3.04 in the aspirin group and 3.03 in the reference group. The mean INR was in the target range in 79% of patients, below it in 7% and above it in 13% of patients without any significant difference between the two groups. aPPT and INR were also similar in the two groups during the early postoperative period.

Echocardiographic results. ***Early postoperative echocardiography (day 9).*** Transesophageal echocardiography was performed in 218 patients on day 9 (three patients died before TEE, three refused it and in five the examination could not be performed due to tamponade or hemodynamic instability). There was no difference in incidence of strands between the two groups although there was a reduced incidence of thrombi in the aspirin group (13.1% to 4.8%, $p = 0.03$). In both groups thrombi were generally small, localized on the atrial side of the sewing ring (mean width 4.2 mm) and nonobstructive and none required reoperation (Table 2).

Fifth month echocardiographic results. A second TEE was performed on 186 patients (12 patients died before the echocardiography study; 21 refused it; 2 patients lived too far away and in 8 patients the TEE was not carried out for medical reasons). There was a comparably high incidence of strands (61%) in the two groups at five months. Thrombi were less frequent than in the early postoperative period (6% vs. 9%), and in the aspirin group there was a lower incidence of thrombi (4% vs. 8%) with a smaller size (6 vs. 4 mm), but the difference was not statistically significant (Table 3).

Table 1. Baseline Characteristics

	Total	Group A+*	Group A−†
Number of patients	229	109	120
Age (yrs)	63	63	63
Male gender	115	61	54
P diameter‡ (mm)	29	29.5	29.2
Valve pathology			
Regurgitation	149 (65.0%)	70 (64.2%)	79 (65.8%)
Stenosis	25 (10.9%)	12 (10.9%)	13 (10.8%)
Combined	35 (15.2%)	16 (14.6%)	19 (15.8%)
Endocarditis	18 (7.8%)	10 (9.1%)	8 (6.6%)
Pannus	2 (0.8%)	1 (0.8%)	1 (0.8%)
Rhythm nonsinus	112 (48.9%)	54 (49.5%)	58 (48.3%)
Shortening fraction	31%	31%	32%
LAD§ (mm)	48	49	47
Thromboembolic history	34 (14.8%)	19 (17.4%)	15 (12.5%)
CAD	35 (15.2%)	21 (19.2%)	14 (11.6%)
Concomitant procedures (% of patients)	112 (48.4%)	54 (49.5%)	58 (48.3%)
CABG	31 (31.5%)	19 (16.4%)	12 (10%)
Aortic (SJM) replacement	92 (40.1%)	42 (38.5%)	50 (41.6%)
Tricuspid valve repair	8 (3.4%)	4 (3.6%)	4 (3.3%)

*Group with aspirin; †group without aspirin; ‡prosthetic diameter; §left atrial diameter.
CABG = coronary artery bypass grafting; CAD = coronary artery disease; LAD = left atrial diameter; SJM = St. Jude medical valve.

RESULTS

Principal outcome events (Table 4). Mortality at one year was higher, but not significantly so, in the aspirin group (9% vs. 4%). Total thromboembolic events were observed in 9% of group A+ versus 25% of group A− ($p = 0.004$). However, in the group with aspirin, there was a higher incidence of gastrointestinal bleeding (GIB) (7% vs. 0%). The incidence of the primary outcome of the study (mortality, major thromboembolic events and major hemorrhage) did not differ significantly (29% group A+ vs. 16% group A−). Valve-related events were 36% in both groups.

Mortality. The early mortality (30 days—including hospital mortality) was 3.5%; six patients in the aspirin group (three myocardial failure, two septic shock, one GIB) and two patients (myocardial failure) in the group without aspirin.

The late mortality was 4%: four patients (two sudden death, one cardiac failure, one malignancy) in the aspirin group and three patients (one sudden death, one malignancy, one traumatic) in the group without aspirin. The total valve-related mortality was 4.8%: 7.3% in the aspirin group and 2.5% in the group without aspirin (not significant).

Thromboembolic events. Major embolic events occurred in five (4.1%) of the 120 patients in the group without aspirin (one prosthetic thrombosis necessitating surgery and four stroke) and in one (0.9%) of the 109 patients in the aspirin group (one peripheral embolism).

Minor embolic events occurred in 25 (20.8%) patients in the group without aspirin (18 prosthetic nonobstructive thrombi and seven transient ischemic attacks) and in nine (7.5%) patients in the group with aspirin (five prosthetic

Table 2. Incidence of Strands and Thrombi at Nine Days

	Number (%) of Patients			
	Total	A+	A−	p Value
Number of patients	218	104	114	
TEE (postoperative days)	9.1	9.2	9.1	
Strands	102 (46.7%)	46 (44.2%)	56 (49.1%)	ns
Thrombi	20 (9.1%)	5 (4.8%)	15 (13.1%)	0.03
Thrombi width (mm)	4.2	4.6	4.1	ns
Strands length (mm)	7.1	7.1	7.1	ns

TEE = transesophageal echocardiography

Table 3. Incidence of Strands and Thrombi at Five Months

	Total	A+	A−	p Value
Number of patients	186	87	99	
Strands	114 (61.2%)	51 (58.6%)	63 (63.6%)	ns
Thrombus	12 (6.4%)	4 (4.5%)	8 (8%)	ns
Thrombi width (mm)	5.7	4	6.6	ns

nonobstructive thrombi and four transient ischemic attacks).

Total thromboembolic events (also including 23 nonobstructive thrombi) occurred in 10 (9.1%) of the aspirin-treated patients and in 30 (25%) of the group without aspirin ($p = 0.004$). The incidence of thromboembolic events (excluding prosthetic nonobstructive thrombi, which depended on the day the TEE was performed) fell over time (Fig. 3). Five (29.4%) occurred during the first postoperative month and none occurred after the eighth month.

Hemorrhagic complications. Major hemorrhage occurred in 31 patients (13.5%). This was significantly more frequent in the aspirin group (21 patients, 19.2%) than in the group without aspirin (10 patients, 8.3%, $p = 0.02$). These major hemorrhages were often tamponade (15 patients, 6.5%), but eight patients (3.4%), all in the aspirin group, developed gastrointestinal bleeding. Other forms of hemorrhage included hematoma (three patients), hemothorax (two patients) and genitourinary bleeding (three patients).

The difference between the two groups was due solely to the increase in gastrointestinal bleedings (eight vs. 0, $p = 0.003$). Major hemorrhage decreased markedly with time (Fig. 3); 16 (51.6%) occurred in the first postoperative month and only two (6.4%) in the last six months. Minor hemorrhage (essentially epistaxis, hematoma and genitourinary) occurred in 45 patients (19.6%): 25 (22.9%) in the group with aspirin and 20 (16.6%) in the group without aspirin.

Reoperations. Reoperations were comparable in both groups: five (one endocarditis, three perivalvular leaks and one hemolysis) in the aspirin group and four (three perivalvular leaks and one hemolysis) in the control group.

Quality of anticoagulation and late morbidity. Seventy-two percent of patients with late thromboembolic events had INR <2.5 and, for the late major hemorrhages, 76% occurred in patients with an INR >3.5.

Early thrombi and morbidity. It can be seen from the results in Table 5 that the early incidence of thrombi was associated with more valve-related events (50% vs. 27%) due primarily to a higher incidence of thromboembolism (30% vs. 13%, $p = 0.0003$, relative risk ([RR]) = 6.3).

Risk factors of morbidity. After multivariate analysis (Table 6), only thromboembolic history emerged as an independent risk factor of morbidity ($p = 0.04$).

DISCUSSION

This study represents the largest randomized trial comparing OAC to OAC plus aspirin after MMVR with the same bileaflet valves. It is the first study comparing OAC and the association of an antiaggregant with an OAC using the lower INR range of 2.5–3.5 currently recommended for the new generation prostheses. The patients were evaluated both clinically and by TEE examinations over a one year period after operation.

Table 4. Principal Outcome Events at One Year

	Number (%) of Patients			
	Total	A+	A−	p Value
Number of patients	229	109	120	
Mortality	15 (6.5%)	10 (9.1%)	5 (4.1%)	ns
Major hemorrhages	31 (13.5%)	21 (19.2%)	10 (8.3%)	0.02
Major thromboembolic events	6 (2.6%)	1 (0.9%)	5 (4.1%)	ns
End point events	52 (22.7%)	32 (29.3%)	20 (16.6%)	ns
Minor thromboembolic events	34 (14.8%)	9 (8.2%)	25 (20.8%)	0.007
Reoperation	9 (3.9%)	5 (4.5%)	4 (3.3%)	ns
Total thromboembolic events	40 (17.4%)	10 (9.1%)	30 (25%)	0.001
Number of patients with events	88 (38.4%)	42 (38.5%)	46 (38.3%)	ns
Number of patients with valve related events	84 (36.6%)	40 (36.6%)	44 (36.6%)	ns

JACC Vol. 35, No. 3, 2000
March 1, 2000:739–46

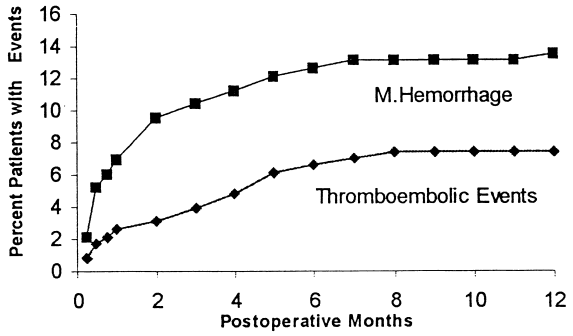

Figure 3. Cumulative risk of thromboembolic events (excluding nonobstructive thrombi) and of major hemorrhages.

Study limitations. We did not administer placebo in the test group with OAC alone, but it was a randomized prospective design and blind concerning the echocardiographic study. The aspirin dosage, 200 mg, is debatable and a lower dosage (80 mg) could be as efficient and less gastrotoxic, but we did not wish to depart from the doses recommended in vascular pathology. It was close to the 160 mg dose of the American College of Chest Physicians' recommendations and the guidelines of the European Society of Cardiology.

Morbidity. The early mortality of 3.4% and late mortality of 3% at one year were comparable with the data in the literature. Similar results have been reported by Baudet (3.8% and 2.4% patient year) (5) and Jegaden (3.5% and 2.6% patient year) (22) on late survival after MVR with the St. Jude medical prosthesis.

Our morbidity data were also comparable with those of other authors. Total thromboembolic events (17.4%) seem high, especially in the group without aspirin (25%) because nonobstructive prosthetic thrombi discovered by early TEE were included. After excluding these thrombi, our total thromboembolic events of: 7.4% at one year (10% in the group without aspirin) were comparable with literature data. Butchard (7) demonstrated that linearized rates of thromboembolic events were 21% patient year in the first month after MVR (21% also in our study) and 9% each month from the first to the fifth month (6% in our study) and 2.5% during the last month of the first postoperative year (1.8% in this study).

With respect to major bleeding, in the patients treated with anticoagulant alone, our rates were consistent with those reported in the review from Petitti (23) of anticoagulant therapy. As in other studies, the incidence of hemorrhage decreased during the first postoperative year; for Landefeld (8) it decreased from 3% per month during the first month to 0.8% per month during the first year and 0.3% thereafter.

In the patients treated with aspirin, our gastrointestinal bleeding rate of 7% was similar to the 6% patient-year of Chesebro (24) but higher than the 3% patient year reported by Turpie (15). This may be accounted for, in part, by the lower dose of enteric-delayed aspirin used and by the higher rates of hemorrhagic complications after the first postoperative months. In our study, there was no evidence of gastrointestinal bleeding after the fourth month.

OAC associated with antiaggregant after MVR. Studies differ in terms of type and localization of valve prosthesis used, but also in INR range and in aspirin doses. The studies of Altman (25) and Dale (26) were carried out on ball prostheses, while that of Chesebro (24) had a high INR range and that of Turpie (15) was carried out on various types of prosthesis including bioprostheses and different localizations. We focused here on the St. Jude medical mitral prosthesis.

Altman (25) found a benefit for the combined treatment, but Dale did not. In the study of Chesebro (24) the increase in major hemorrhage overrode the benefit of the decrease in incidence of thromboembolic complications, and the trial was stopped. In the Canadian study, the decrease in thromboembolic events and deaths offset the increase in major hemorrhage, and the combined treatment was thought beneficial. We noted in our study a decrease in

Table 5. Early Thrombi and Morbidity

	Number (%) of Patients		
	TH+	TH−	p Value
Number of patients	20	198	
Mortality	3 (15%)	9 (4.5%)	ns
Major hemorrhages	1 (5%)	27 (13.6%)	ns
Thromboembolism events*	6 (30%)	9 (13.6%)	p = 0.0003 RR = 6.3
Reoperation	0	9 (4.5%)	
Total events	10 (50%)	54 (27.2%)	p = 0.01 RR = 1.9
Valve related events	10 (50%)	51 (25.7%)	p = 0.008 RR = 2

*Thromboembolism events excluding prosthetic nonobstructive thrombi.
RR = relative risk; TH+ = patients with thrombus; TH− = patients without thrombus.

Table 6. Risk Factors of Morbidity

	Morbidity*	p Value
Number of patients†	88/229	
Thromboembolic history yes	20/34 (58.8%)	0.01
Thromboembolic history no	68/195 (34.8%)	RR = 1.6 (1.2–2.3)
Cardiomegaly yes	18/49 (36.7%)	0.006
Cardiomegaly no	31/180 (17.2%)	RR = 2.1 (1.3–3.4)
Fractional shortening <25%	9/34 (26.4%)	ns
Fractional shortening >25%	79/195 (40.5%)	
Nonsinus rhythm yes	42/112 (37.5%)	ns
Nonsinus rhythm no	46/117 (39.3%)	
Thrombi (i.e) yes	10/20 (50%)	0.01
Thrombi (i.e) no	54/198 (27.2%)	RR = 1.9 (1.2–3)
Strands (i.e) yes	42/102 (41.1%)	
Strands (i.e) no	37/116 (31.8%)	ns
Spontaneous echo contrast (i.e) yes	30/98 (30.6%)	ns
Spontaneous echo contrast (i.e) no	49/120 (40.8%)	

*Patients with end points events; †number of patients with events.
Multivariate analysis: thromboembolic history: p = 0.04.
(i.e) = initial examination; RR = relative risk.

thromboembolic events but with a corresponding increase in major hemorrhage and a corresponding increase, albeit slight, in mortality in the aspirin group. We could not, therefore, conclude that aspirin offered any overall benefit. In the two published meta-analyses comparing both treatments, Cappelleri (16) concluded in favor, while Cannegieter (4) advised against the combined treatment. We feel that the combination is only likely to benefit a subgroup of patients with high thromboembolic risk.

In the study of Turpie (15), 30% of patients had CAD, and the benefit in the group with aspirin was largely due to the reduction in sudden death, deaths due to acute myocardial infarction and to acute heart failure (1 vs. 12). Moreover, in the group without aspirin, 21% of patients with CAD died or had thromboembolic events against only 2% of the patients with CAD in the aspirin group. The association of aspirin may, thus, be of more benefit in patients with CAD. Thromboembolic events, but also major hemorrhages, are more frequent in the early postoperative period, so it does not seem advisable to restrict aspirin just to the early postoperative period.

The association of aspirin is probably of value in patients with echographically demonstrated thrombi in view of their high risk of thromboembolic complications. We showed here that this association reduced both the size and number of these thrombi. A thromboembolic history also emerged as a risk factor of morbidity. Nevertheless, we did not identify any particular subgroup that significantly benefited from the aspirin/anticoagulant combination.

Anticoagulation and morbidity. Our results are in agreement with previously reported studies (27,28), with most of the major hemorrhages being observed in patients receiving too intense anticoagulation and most of the thromboembolic events occurring in patients with inadequate anticoagulation. Anticoagulant therapy, thus, needs to be titrated accurately after MVR in order to minimize complications. So the AREVA (29) study (aortic prosthesis) recommends a less intense anticoagulation to reduce the risk of hemorrhagic events. Nevertheless, in a Canadian study (30), patients treated with aspirin plus warfarin at a lower target INR of 2.0 to 2.5 had equivalent antithrombotic efficacy but without reduction of bleeding compared with patients with aspirin plus warfarin at an INR of 3.0 to 3.5. However, adjustment of target INR may be required in the presence of patient-related embolic risk factors (19), and, in our subgroup of patients with related embolic risk factors, the target INR could have been higher. In fact, these patients were often more intensely anticoagulated by their cardiologists. So, in our subgroup of patients with thromboembolic history, which we found had a higher risk of thromboembolic events, the INR (3.2) was higher.

Conclusion. After MVR, there is a high incidence of fibrin strands, which was not reduced by administration of aspirin. On the other hand, the presence of early thrombi after MVR leads to increased morbidity and risk of thromboembolic events, which are reduced by aspirin. Systematic early postoperative TEE, thus, would seem to be of value to detect these often asymptomatic thrombi with a potentially high thromboembolic risk.

The early association of aspirin with OAC after MVR reduced thromboembolic events but also increased gastrointestinal bleeding and did not reduce overall morbidity 1 year after MVR by the St. Jude medical prosthesis.

In summary, we do not recommend the systematic association of aspirin with OAC after MVR, but the intensity of OAC should be adapted according to the patient related risk factors. This association may prove more beneficial in the subgroups of patients with high thromboembolic risk such as those with a thromboembolic history,

those where thrombi were detected by TEE soon after operation and probably those with associated CAD.

Acknowledgments

We thank Chene G, MD from the Service d'Information Médicale, Department of Medical Information (Pr R. Salamon) of the University Hospital of Bordeaux for her valuable assistance with the statistical analysis.

Reprint requests and correspondence: Dr. Patrick Laffort, Service de Cardiologie Pr Roudaut, Hôpital Haut-Leveque, Avenue de Magellan, 33604 Pessac, France. E-mail: lfr.Cardio@bordeaux.inserm.fr.

REFERENCES

1. Michel PL, Acar J. Prothèses valvulaires mécaniques et biologiques et traitements antithrombotiques. In: Samama MM, Acar J, editors. Traitement Antithrombotique, Masson Edit. 3rd edition. Paris, 1998: 143–75.
2. Acar J, Michel PL, Iung B. Les accidents thromboemboliques des prothèses valvulaires: incidence, prévention et traitement en 1997. Sang Thrombose Vaisseaux 1997;9:172–8.
3. Aupart M, Diemont F, Babuty S, et al. Résultats intermédiaires avec la prothèse valvulaire à ailettes CarboMedics. Arch Mal Coeur 1997;90:457–62.
4. Cannegieter SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation 1994;89:635–41.
5. Baudet EM, Puel V, McBride JT, et al. Long-term results of valve replacement with the St. Jude medical prosthesis. J Thorac Cardiovasc Surg 1995;109:858–70.
6. Butchard EG, Lewis PA, Grunkemeier GL, et al. Low risk of thrombosis and serious embolic events despite low intensity anticoagulation. Circulation 1988;78 Suppl I:166–77.
7. Butchard EG, Lewis PA, Bethel JA, et al. Adjusting anticoagulation to prosthesis thrombogenecity and patient risk factors: recommendations for the Medtronic Hall valve. Circulation 1991;84 Suppl III: 61–9.
8. Landefeld CS, Goldman L. Major bleeding in outpatients treated with warfarin: incidence and prediction by factors known at the start of outpatient therapy. Am J Med 1989;87:144–52.
9. Iung B, Cormier B, Dadez E, et al. Small abnormal echos after mitral valve replacement with bileaflet mechanical prostheses: predisposing factors and effect on thromboembolism. J Heart Valve Dis 1993;2: 259–66.
10. Bonnefoy E, Perinetti M, Girard C, et al. Echocardiographie transoesophagienne systématique dans les 24 premières heures postopératoires après remplacement valvulaire mitral. Arch Mal Coeur 1995;88:315–9.
11. Malergue MC, Temkine J, Slama M, et al. Intérêts de l'échocardiographie transoesophagienne systématique postopératoire précoce des remplacements valvulaires mitraux. Une étude prospective sur 50 patients. Arch Mal Coeur 1992;85:1299–304.
12. Guéret P, Vignon P, Fournier P, et al. Transesophageal echocardiography for the diagnosis and management of nonobstructive thrombosis of mechanical mitral valve prosthesis. Circulation 1995;91:103–10.
13. Orsinelli DA, Pearson AC. Detection of prosthetic valve strands by transesophageal echocardiography: clinical significance in patients with suspected cardiac source of embolism. J Am Coll Cardiol 1995;26: 1713–8.
14. Freedberg RS, Goodkin GM, Perez JL, et al. Valve strands are strongly associated with systemic embolization: a transesophageal echocardiographic study. J Am Coll Cardiol 1995;26:1709–12.
15. Turpie AGG, Gent M, Laupacis A, et al. A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement. N Engl J Med 1993;329:524–9.
16. Cappelleri JC, Fiore LD, Brophy MT, et al. Efficacy and safety of combined anticoagulant and antiplatelet therapy versus anticoagulant monotherapy after mechanical heart-valve replacement: a meta-analysis. Am Heart J 1995;130:547–52.
17. Stein PD, Alpert JS, Dalen JE, et al. Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves. Chest 1998;114:602s–10s.
18. Chesebro TH, Fuster RV. Optimal antithrombotic therapy for mechanical prosthetic heart valves. Circulation 1996;94:2055–6.
19. Baudet E. Anticoagulation chez les porteurs de prothèses valvulaires cardiaques. Mouv Card Vasc 1995;1:229–32.
20. Gohlke-Barwolf C, Acar J, Oakley C, et al. Guidelines for prevention of thromboembolic events in valvular heart disease. Eur Heart J 1995;16:1320–30.
21. Edmunds LH, Clark RE, Cohn LH, et al. Guidelines for reporting morbidity and mortality after cardiac valvular operations. J Thorac Cardiovasc Surg 1988;96:351–3.
22. Jegaden O, Eker A, Delahaye F. Thromboembolic risk and late survival after mitral valve replacement with the St. Jude medical valve. Ann Thorac Surg 1994;58:172–8.
23. Petitti DB, Strom BL, Melmon KL. Duration of warfarin anticoagulant therapy and the probabilities of recurrent thromboembolism and hemorrhage. Am J Med 1986;81:255–9.
24. Chesebro JH, Adams PC, Fuster V, et al. Antithrombotic therapy in patients with valvular heart disease and prosthetic heart valves. J Am Coll Cardiol 1986;8:41B–56B.
25. Altman R, Boullon F, Rouvier J, et al. Aspirin and prophylaxis of thromboembolic complications in patients with substitute heart valves. J Thor Cardiovasc Surg 1976;72:127–9.
26. Dale JD, Myhre E, Storstein O, et al. Prevention of arterial thromboembolism with acetylsalicylic acid. Am Hear J 1977;94:101–11.
27. Farah E, Enriquez-Sarano M, Vahanian JP, et al. Thromboembolic and hemorrhagic risk in mechanical and biological aortic prostheses. Eur Heart J 1984;5 Suppl D:43–7.
28. Fuster V, Pumphrey CW, Mc Goon MD, et al. Systemic thromboembolism in mitral and aortic Starr-Edwards prostheses: a 10–19 year follow-up. Circulation 1982;66 Suppl I:I157–61.
29. Acar J, Iung B, Boissel JP, et al. AREVA: multicenter randomized comparison of low doses versus standard dose anticoagulation in patients with mechanical prosthetic heart valves. Circulation 1996;94: 2107–12.
30. Turpie AGG, Gent M, Cruickshank MK, et al. Randomized comparison of moderate (INR 3.0–3.5) with low intensity (INR 2.0–3.5) anticoagulant therapy in patients with prosthetic heart valves treated by aspirin (100 mg/day). Circulation 1998;98 Suppl 1:768.