LOW-INTENSITY ORAL ANTICOAGULATION PLUS LOW-DOSE ASPIRIN VERSUS HIGH-INTENSITY ORAL ANTICOAGULATION ALONE: A RANDOMIZED TRIAL IN PATIENTS WITH MECHANICAL PROSTHETIC HEART VALVES

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Background: Mechanical heart valve replacement requires lifelong anticoagulant treatment. Aspirin has proved useful in further reducing thromboembolic events when added to oral anticoagulants. However, increased (gastrointestinal) bleeding was observed at the doses previously tested for this combination in heart valve prostheses. **Methods:** We performed a prospective randomized trial to compare the combination of low-intensity oral anticoagulants (international normalized ratio 2.5 to 3.5) plus aspirin (100 mg/day) (arm A) versus high-intensity oral anticoagulants alone (arm B) (international normalized ratio 3.5 to 4.5). Arm A included 258 patients and arm B 245 patients. The two groups were comparable for all baseline characteristics. **Results:** The outcomes of the study were embolism, valve thrombosis, and major hemorrhage. The median follow-up was 23 months. The two treatments offered similar antithrombotic protection. The incidence of embolic episodes was 1.32 per 100 patient-years (95% confidence interval 0.53 to 2.7) for arm A and 1.48 per 100 patient-years (95% confidence interval 0.59 to 3.03) for arm B. Major hemorrhage occurred in 1.13 per 100 patient-years (95% confidence interval 0.41 to 2.45) for arm A and 2.33 per 100 patient-years (95% confidence interval 1.17 to 4.14) for arm B. Gastrointestinal bleeding was not increased by this combined reduced dose of aspirin and coumarin. (*J Thorac Cardiovasc Surg* 1997; 113:910-6)

The past 20 years have witnessed dramatic improvements in the morbidity of prosthetic heart valves. Lifelong oral anticoagulation is recommended to reduce the incidence of systemic embolism. However, thromboembolism still arises in up to 2% of patients per year.¹ Several trials tested the combination of an oral anticoagulant plus an anti-

platelet agent in patients with prosthetic valves: the combined therapy tended to decrease the incidence and severity of embolic episodes with some increase in bleeding, mainly in the digestive tract.²⁻⁵ This was particularly true when aspirin at doses greater than 500 mg/day was combined with high-intensity coumarin. The optimal therapeutic range for any antithrombotic scheme should be consistent with adequate thromboembolic protection but as low as possible to avoid therapy-related bleeding. Major bleeding events range between 0.7% to 6.3% per patient-year^{1,6} and the incidence increases as the international normalized ratio (INR) increases.⁷ A recent metaanalysis⁸ has compared the efficacy and safety of combined antiplatelet plus anticoagulant therapy with anticoagulant monotherapy: the combined therapy significantly reduced embolism by 67% along with a significant but undesirable 60% increment in hemorrhagic events. Furthermore, an impressive twofold increment in major gastrointestinal and other bleeding raised the question about a safer dose of aspirin, if any, to be combined with oral anticoagulants.

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Evidence indicates that gastrointestinal symptoms and bleeding associated with aspirin are dose dependent.^{9,10} Low doses of aspirin have demonstrated clear cardiovascular benefits,¹¹ and the antithrombotic effects of aspirin were evident at doses greater than 100 mg/day. A recent trial in patients with heart valve disease aimed at a lower aspirin dose (100 mg/day) while maintaining an INR between 3 and 4.5.¹² However, the rates of bleeding showed that gastrointestinal and other major bleeding were still a problem for the aspirin group.

The efficacy and safety of the combination of low-dose aspirin plus a less intense oral anticoagulation has not been tested against standard-intensity oral anticoagulation. We performed a prospective randomized trial comparing oral anticoagulation (INR 2.5 to 3.5) in combination with 100 mg/day of plain aspirin versus oral anticoagulation alone (INR 3.5 to 4.5).

Methods

This study was opened for patient accrual in July 1988 and remained open through July 1992. The patients were followed up for a median of 23 months and for a maximum of 47 months. The study was open, because the investigators who saw the patients during the follow-up needed to adjust the acenocoumarol dosage to attain the targeted INR.

Patients with a mechanical prosthetic heart valve were randomized with a computer-generated program to arm A, oral anticoagulation (INR 2.5 to 3.5) plus aspirin (100 mg/day), or arm B, oral anticoagulation alone (INR 3.5 to 4.5).

Patients were randomized either promptly after the operation (when anticoagulation was considered to be adequate) or at different variable intervals between the operation and the start of this study, switching from a different therapy to one of the two arms of this protocol. Patients with previous gastrointestinal bleeding and patients with a previous history of embolic episodes or suspected hemorrhagic tendency were excluded from the study.

Follow-up endpoints included thromboembolism and major hemorrhage. Cerebral embolism was defined as a sudden neurologic event (focal motor weakness, visual deficit, or speech disturbance) with a computed tomographic brain scan negative for intracranial bleeding and for which there was no other clinical explanation. Embolic events were graded as to the presence or absence of any residual sequel, but transient ischemic events were also considered. Peripheral embolism was diagnosed by angiography or surgery. Valve thrombosis was confirmed by surgery. Major hemorrhage was considered present when the patient died or required transfusion or hospitalization. All other bleeding episodes were defined as minor.

Anticoagulation was monitored by prothrombin time^{13,14} measured with the use of human brain thromboplastin with an international sensitivity index from 1.05

to 1.15 and a manual coagulation test. This was standardized using Argentine reference thromboplastin,¹⁵ controlled versus international reference thromboplastin.¹⁶ The prothrombin time ratio was converted into international normalized ratio (INR).

All the patients enrolled in the study gave informed consent. Patients were repeatedly instructed to report any symptoms suggestive of embolism or hemorrhage. The percentage of anticoagulation controls within the aimed therapeutic range was calculated for each year of follow-up in each patient.

Statistical methods. To test whether the proportion of embolism was the same in the two groups at follow-up, we tested for equal proportions from two independent samples.¹⁷ The same was done for major hemorrhage and for the combined endpoint of embolism or major hemorrhage.

Time free of events was calculated from the entry date until the first occurrence of an embolism, a major hemorrhage, or embolism and/or major hemorrhage. For each of the endpoints, we used the product-limit method of Kaplan-Meier¹⁸ to plot the curve in each group on time free of the endpoint. The log-rank test¹⁹ was used to test whether these curves were equal.

The proportional hazards model developed by Cox,²⁰ using the maximum partial likelihood ratio statistic, was used to assess the joint effect of treatment and patient characteristics (age, sex, valve design, valve position, postoperative cardiac rhythm, postoperative atrial size, interval between the operation and admission to the protocol, and concomitant coronary bypass procedure) on each of the three outcomes: embolism, major hemorrhage, and embolism and/or major hemorrhage.

All *p* values are two-sided; a level of 0.05 was considered significant. Egret (SERO, Seattle, Wash.) and Stata (Stata Corporation, College Station, Tex.) were used to perform all the statistical analyses.

Results

Patient characteristics. A total of 503 patients were randomized into the study. The baseline characteristics are shown in Table I. The two groups were comparable except for the higher prevalence of atrial fibrillation in arm A. Fifty-three (10.5%) of the 503 patients had concomitant surgical procedures, the most common being coronary artery bypass grafting in 21 (8%) patients in arm A and 13 (5%) patients in arm B.

The total follow-up was 529 years for arm A and 471 years for arm B. The median follow-up was 23 months. Thirty patients (nine from arm A, 21 from arm B) died. One patient (arm B) died after a cerebral hemorrhage. Twenty-nine deaths were unrelated to the antithrombotic therapy. Two patients were withdrawn from the protocol because chronic renal failure developed and it was difficult to maintain their anticoagulation level; 20 patients from

Table I. Baseline patient characteristics

	Arm A (n = 258)		Arm B (n = 245)	
	No.	%	No.	%
Median age (yr)	54		53	
Male patients	154	60	138	56
Female patients	104	40	107	44
Valve position				
Aortic	164	64	169	69
Mitral	79	31	69	28
Tricuspid	2	0.8	0	
Aortic and mitral	13	5	7	3
Valve type				
Starr-Edwards	63	24	67	27
Disc*	169	66	158	64
St. Jude Medical	14	5	9	4
Unknown	12	5	11	5
Cardiac rhythm				
Atrial fibrillation	53	20†	36	15
Synus rhythm	150	58	152	62
Pacemaker	2	1	5	2
Unknown	53	21	52	21
Associated surgical procedures				
CABG	21	75	13	52
Mitral commissurotomy	3	11	8	32
Others	4	14	4	16
Interval between surgery and admission to protocol				
<6 mo	128	50	121	49
≥6 mo	130	50	124	51

*Includes Björk-Shiley (Shiley, Inc., Irvine, Calif.), Medtronic Hall (Medtronic, Inc., Minneapolis, Minn.), Sorin (Sorin Biomedica Spa, Saluggia, Italy), and Omniscience (Medical Inc., Inver Grove Heights, Minn.).

†p = 0.0438.

Table II. Adequacy of anticoagulation

	Arm A			Arm B		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Mean INR	3.05	3.18	3.1	3.78	4	4.06
Adequate (%)	46	49	47	32	36	37
Insufficient (%)	30	24	30	45	36	38
Excessive (%)	24	27	23	23	28	25

arm A (8%) and 20 patients from arm B (8%) were lost to follow-up.

Adequacy of anticoagulation. The median INR calculated for each year of evaluation was adequate in both arms of the protocol (Table II). Mean INRs for the first 3 years of follow-up were 3.11 in arm A and 3.98 in arm B ($p = 0.0000$ for the comparison of each of the years).

Thromboembolic episodes. The incidence of embolism was 2.7% (95% confidence interval [CI] 1.09 to 5.5) for arm A and 2.8% (95% CI 1.11 to 5.7) for arm B. The estimated survival free of embolism at 46 months was 94% (95% CI 0.87 to 0.97) for arm A

and 93% (95% CI 0.84 to 0.96) for arm B ($p = 0.7008$).

In arm A there were seven thromboembolic episodes (Table III). Total embolism rate was 2.7% or 1.32 episodes per 100 patient-years (95% CI 0.53 to 2.7); for cerebral episodes only, the rate was 1.9% or 0.94 episodes per 100 patient-years (95% CI 0.30 to 2.19). In arm B there were seven thromboembolic events (2.8%). One of the cerebral emboli underwent a hemorrhagic transformation. The annualized rate of embolism was of 1.48 episodes per 100 patient-years (95% CI 0.59 to 3.03). Prothrombin times at the time of the embolism were available in

Table III. *Thromboembolic episodes*

	Arm A (n = 258)		Arm B (n = 245)	
	No.	%	No.	%
Cerebral with sequelae	1	14	3	43
Cerebral without sequelae (TIA)	4	57	4	57
Valve thrombosis	1	14		
Peripheric	1	14		
Rate	7	2.7	7	2.8
Episodes per 100 patient-years	1.32		1.48	
	(95% CI 0.53 to 2.7)		(95% CI 0.59 to 3.03)	

TIA, Transient ischemic attack.

six of the seven patients in arm A: in five of the six patients (83%) the prothrombin times were within the therapeutic range, and in one (17%) anticoagulation was inadequate. In arm B, three of seven patients had prothrombin times (43%) within the therapeutic range, three (43%) had inadequate anticoagulation, and one (14%) had excessive anticoagulation. Two of the emboli in each group arose in patients who had atrial fibrillation.

Position of the valve. Of the seven patients having embolic events in arm A, four (57%) had mitral prostheses and three had aortic valves (43%). In arm B, two (29%) of the seven patients having embolic episodes had mitral prostheses and five (71%) had aortic valves. The rate of embolism for mitral and aortic valves in arm A was 5.06 or 2.5 (95% CI 0.68 to 6.28) episodes per 100 patient-years and 1.83 or 0.87 (95% CI 0.18 to 2.54) episodes per 100 patient-years, respectively. In arm B the rate of embolism for mitral and aortic valves was 2.82 or 1.44 (95% CI 0.17 to 5.10) episodes per 100 patient-years and 2.99 or 1.59 (95% CI 0.52 to 3.69) episodes per 100 patient-years, respectively. The estimated survival free of embolism at 46 months was 94% (95% CI 0.86 to 0.97) for mitral valves, 93% (95% CI 0.86 to 0.93) for aortic valves, and 100% for double prostheses ($p = 0.1321$).

Type of valve. The rates of embolism were 6.34 (95% CI 1.75 to 15.4) and 1.56 (95% CI 0.32 to 4.49) ($p = 0.0842$) for caged-ball versus non-caged-ball valves for arm A and 7.67 (95% CI 2.46 to 16.66) and 1.13 (95% CI 0.13 to 4.04) ($p = 0.0183$) for arm B, respectively.

Bleeding complications. The incidence of major bleeding was 2.32% (95% CI 0.85 to 4.99) for arm A and 4.49% (95% CI 2.26 to 7.89) for arm B. The estimated survival free of hemorrhage at 46 months was 97% (95% CI 0.92 to 0.99) for arm A and 91% (95% CI 0.84 to 0.95) for arm B ($p = 0.1064$).

Table IV shows the sites of major and minor bleeding episodes. There were six (2.32%) major bleeding episodes in arm A (1.13 per 100 patient-years; 95% CI 0.41 to 2.45), and 11 (4.49%) in arm B (2.33 per 100 patient-years; 95% CI 1.17 to 4.14). This represents a reduction in the relative risk of major bleeding for the less intense anticoagulation arm of 52% (95% CI 0.19 to 1.38) ($p = 0.2731$). Three cerebral hemorrhages occurred in arm B and one was fatal. The incidence of major gastrointestinal bleeding was higher in arm B (2.45% or 1.27 per 100 patient-years; 95% CI 0.46 to 2.75) than in arm A (0.77% or 0.37 per 100 patient-years; 95% CI 0.04 to 1.35).

In arm A, a duodenal ulcer was identified as a predisposing factor in one of three patients with gastrointestinal bleeding; in one patient with gynecologic bleeding, a previous bleeding tendency was identified. In arm B, five of the 11 patients with major bleeding had possible predisposing factors: recent cranial trauma, lung carcinoma, vascular malformation in three patients with cerebral bleeding, chronic renal failure, and bacterial endocarditis in two patients with gastrointestinal bleeding. Even after the exclusion of patients with a predisposing cause, the rate of gastrointestinal bleeding was more than double in the arm with more intense anticoagulation without aspirin (Table IV).

Four (66%) of the six patients with hemorrhagic complications in arm A had slightly excessive anticoagulation, one (17%) had adequate anticoagulation, and the remaining patient (17%) had insufficient anticoagulation. In arm B, three (27%) of the 11 with hemorrhagic complications had excessive anticoagulation (one with a fatal cerebral hemorrhage) and five (45%) had insufficient anticoagulation.

Failure-free survival. Thromboembolism or major hemorrhage occurred in 13 patients in arm A

Table IV. Bleeding episodes

	Arm A (n = 258)		Arm B (n = 245)	
	No.	%	No.	%
<i>Major bleeding</i>				
Intracranial			3*	27
Gastrointestinal†	3	50	6	54
Menorrhagia	3	50	1	9
Soft tissue hematoma			1	9
Rate	6	2.3%	11	4.5
Episodes per 100 patient-years	1.13		2.33	
	(95% CI 0.41 to 2.45)		(95% CI 1.17 to 4.14)	
<i>Minor bleeding</i>				
Hematuria	12	34	6	15
Epistaxis	10	28	8	19
Gastrointestinal†	2	6	6	15
Menorrhagia	4	11	3	7
Ecchymoses	1	2.8	8	19
Hemoptysis			2	5
Gingival bleeding			2	5
Proctorrhagia	1	2.8	5	12
Others	5	14	1	2.4
Rate	35	14	41	17

*One lethal.

†The total number of gastrointestinal hemorrhages after the exclusion of patients with a potential predisposing cause was 4 or 0.76 per 100 patient-years (95% CI 0.20 to 1.92) and 10 or 2.12 per 100 patient-years (95% CI 1.02 to 3.86) for arms A and B, respectively ($p = 0.1425$).

(5.03% or 2.45 per 100 patient-years; 95% CI 1.31 to 4.16) and 18 patients in arm B (7.34% or 3.82 per 100 patient-years; 95% CI 2.28 to 5.97). The actuarial risk of embolism and major bleeding at 40 months (Fig. 1) was 10% for arm A and 15% for arm B ($p = 0.1576$). This represents a relative risk reduction of 69% (95% CI 0.34 to 1.37) ($p = 0.3732$).

Cox multivariate analysis. Several Cox models were performed, using treatment and the set of patient characteristics at diagnosis, that will lead to an adjusted effect of treatment on outcomes.

One set of models was developed for embolism, in which the presence of postoperative atrial size (>50 mm) was a statistically significant predictor of embolism.

Finally, a Cox model was developed for the joint effect of embolism and major hemorrhage, in which postoperative atrial size was the only significant predictor of events.

Discussion

In this randomized trial, we demonstrated that the addition of 100 mg daily aspirin to a less intense oral anticoagulation program offered the same antithrombotic protection and did not increase the risk of bleeding than a more intense anticoagulant-alone regimen. Moreover, a better quality of life (event-

free survival) and a tendency toward fewer and milder episodes of cerebral embolism were offered by the combined treatment. Although embolism was more prevalent in caged-ball valves in both groups, the difference reached statistical significance only in the anticoagulant-alone group.

When this trial was designed, the currently suggested practice for patients with prosthetic heart valves was to prolong the INR from 3.0 to 4.5.²¹ The last consensus on oral anticoagulation²² suggested a lower INR of 2.5 to 3.5 for patients with non-caged-ball prostheses. This recommendation was substantiated in a literature review.²³ However, there are no randomized clinical trials comparing the old (3 to 4.5) versus the newer (2.5 to 3.5) recommended intensities. Moreover, a substantial number of patients with old, more thrombogenic prostheses still attend the anticoagulation clinics. Whether the same level of anticoagulation is required when coumarin is combined with a platelet inhibitor is unknown. The addition of aspirin to oral anticoagulation showed a significant reduction in the rate of thromboembolism.^{2,3} However, the incidence of gastrointestinal bleeding was increased when aspirin was given at dosages of 1 gm/day² or 250 mg twice daily.³ Despite the excessive bleeding, the thromboembolic protection was sometimes poor.⁴ In a recent study by Altman and associates,⁵ lower intensity

Fig. 1. Efficacy and safety. Cumulative risk of events (embolism and/or major hemorrhage) attributable to antithrombotic therapy.

anticoagulation was as effective as and safer than a higher intensity regimen, at least when combined with two platelet inhibitors. The lack of a control group treated with warfarin alone and the fact that most of the hemorrhages occurred within the targeted level of anticoagulation raises the question about the minimal (but still effective) dosage of aspirin.

If the deleterious effect of aspirin is a function of the dose,⁹ one can speculate whether a lower dose could retain efficacy while reducing the bleeding. Recently, low-dose aspirin has proven successful in lowering cardiac and cerebral vascular events. Turpie and coworkers¹² found that 100 mg aspirin added to warfarin (INR 3 to 4.5) reduced significantly the embolic rates, when compared with a warfarin-alone regimen of similar intensity. However, the mean INRs for both aspirin and placebo groups were similarly low (3.1 and 3), and 49% of the INR measurements fell below the targeted level. Thus it might be feasible that such low levels of anticoagulation were not optimum to prevent embolism in the warfarin-alone group, raising uncertainties about the performance of the combined therapy if tested against a more intense, better performing anticoagulant-alone regimen. The safety

of the association might be questioned, because more total, major, and gastrointestinal hemorrhages occurred among patients treated with warfarin plus aspirin.¹² A recent metaanalysis that confirmed the benefits of adding aspirin to coumarin in further reducing thromboembolism revealed an impressive increment in iatrogenic bleeding, which makes unacceptable the combination of doses of aspirin greater than 100 mg or intensities greater than INR 3.5.⁸ Recent trials aimed at a less intense anticoagulant schedule: INR below 3.5.^{24, 25} An adequate embolism protection and a reduced risk of hemorrhagic complications was found. Unfortunately, these trials did not include standard (intense) anticoagulation or combined anticoagulant-plus-aspirin groups. Moreover, in Turpie's trial the warfarin-alone arm (mean INR 3.1) showed a higher (4.6 per 100 patient-years) incidence of embolism. Hence evidence about the antithrombotic efficacy of low-intensity anticoagulation alone is conflicting, and it is not clear whether results from these less intense regimens can be improved by adding aspirin or other antiplatelet agents.

In our study we had a low incidence of systemic embolism in both arms (1.32 and 1.48 per 100 patient-

years). Most of our episodes were cerebral (five of seven in arm A and seven of seven in arm B) and left no neurologic deficit in four of five and four of seven patients. Despite the similarly low incidence of embolism, the aspirin arm showed a tendency to more benign (transient) cerebral episodes. Furthermore, patients having caged-ball valves benefited from the combined therapy. This benefit was not counterbalanced by an increase in bleeding: we found the rate of major bleeding episodes in the less intense arm (1.13 and 2.33 per 100 patient-years, respectively) dropped by more than half. Gastrointestinal bleeding was not increased by the addition of aspirin.

Our results indicate that the addition of low-dose aspirin to a low-intensity oral anticoagulant regimen in this selected population free from gastrointestinal hemorrhage or hemorrhagic history conferred antithrombotic protection as effectively as the high-intensity "standard" anticoagulation without increasing the likelihood of major hemorrhages. The effects were not limited to any particular subgroup of patients with mechanical valves. Further trials seem warranted, looking for special subgroups (elderly patients or those with coronary or cerebrovascular disease) that could be particularly benefited by the combination therapy.

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