

Comparing Warfarin With Aspirin After Biological Aortic Valve Replacement A Prospective Study

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Background—Patients with prosthetic heart valves have a higher risk of developing valve thrombosis and arterial thromboembolism. Antithrombotic therapy in the early postoperative period after biological aortic valve replacement (BAVR) is controversial. The American College of Cardiology/American Heart Association and European Society of Cardiology guidelines recommend the use of warfarin for the first 3 months after BAVR, although the American College Chest Physician guidelines suggest that the recommendations are very weak and that the risk/benefit is unclear. This prospective study investigated the efficacy of postoperative warfarin compared with aspirin in patients after aortic valve replacement.

Methods and Results—Patients undergoing BAVR between 2001 and 2002 received 2 antithrombotic therapies: 141 patients received warfarin for the first 3 months, and 108 patients received only aspirin. The major end points evaluated were the rate of cerebral ischemic events, bleeding, and survival. There were 3 and 5 postoperative cerebral ischemic events between 24 hours and 3 months for patients treated with aspirin and warfarin, respectively. After 3 months, the incidence of cerebral ischemic events did not differ between the 2 groups. The rate of major bleeding events, the stroke-free survival, and the overall survival rates were not statistically significant between the warfarin and aspirin groups.

Conclusions—There seem to be no advantages in performing early anticoagulation therapy compared with a low-antiplatelet regimen with regard to early cerebral ischemic events, bleeding, and survival. Currently there is no evidence to support the fact that warfarin is more effective than aspirin. (*Circulation*. 2004;110:496-500.)

Key Words: anticoagulants ■ aspirin ■ surgery ■ valves ■ prosthesis

Patients with prosthetic heart valves have a higher risk of developing valve thrombosis and arterial thromboembolism. However, antithrombotic therapy in the early postoperative period after biological aortic valve replacement (BAVR) is still controversial.

The American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines based on observational studies for the management of patients with valvular heart disease recommend the use of warfarin for the first 3 months after BAVR,^{1,2} whereas the American College Chest Physician (ACCP)³ guidelines provide a very weak recommendation about its use as well as an unclear risk/benefit statement.

Therefore, although some researchers consider the use of anticoagulation therapy appropriate in the prevention of thromboembolic cerebral events⁴⁻⁷ during the first 3 months, others express concern over its use because of the possibility of an increased risk of bleeding complications.⁸⁻¹¹

Anticoagulant-related bleeding in fact remains one of the significant causes of postoperative death, with an incidence rate that varies from 1.5% to 2.4% per patient-year.^{8,12}

Warfarin inhibits the vitamin K-dependent clotting factors. Its use represents an expensive treatment for which continuous laboratory tests and dose adjustments are necessary. Instead, the use of aspirin (acetylsalicylic acid [ASA]) represents an alternative antithrombotic treatment to warfarin. ASA inhibits platelet aggregation, thereby conferring some degree of protection against thrombosis-mediated vascular events. The advantages of using ASA are a minor risk of bleeding, lower cost, and a better quality of life.

Thus, the aim of this study was to compare the validity of 2 different regimens of therapy in the early postoperative period after BAVR and to evaluate the benefits, particularly in terms of survival and cerebral protection from thromboembolism.

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Methods

We performed an observational study using patients who were consecutively admitted to our institution. All patients undergoing regimens based on warfarin or ASA after BAVR between January 2001 and December 2002 were selected. The patients were checked for inclusion criteria such as diagnosis of sinus rhythm before and after the operation. Patients with the following characteristics were excluded: cerebral ischemia, coagulopathy, carotid atherosclerotic disease, peripheral vascular disease, concomitant mitral valve disease, double valve replacement, previous chronic anticoagulation therapy, allergies to ASA or warfarin, and atrial fibrillation (AF) at any time during the study. Patients experiencing an immediate cerebral event or an immediate major bleeding event (within the first 24 postoperative hours) were also excluded because the events happened before administration of ASA or warfarin therapy.

At our institution some surgeons strictly follow the ACC/AHA and ESC guidelines, whereas others do not. Those surgeons who do not follow the guidelines justify their decision by saying that the recommendations to use warfarin are weak, preferring then to use ASA.

All the operations were performed by 9 senior surgeons from our department. Patients received a specific regimen of therapy according to the surgeon's preference. Five surgeons gave ASA and 4 gave warfarin after operations. Therefore, the assignment of patient to treatment depended on which surgeon was on duty the day the patient underwent surgery.

The administration of low-molecular-weight heparin (LMWH) was started on the first postoperative day, whereas warfarin and ASA were started on day 2. In patients receiving warfarin, the use of LMWH was continued until warfarin reached therapeutic levels, as shown by a prothrombin time (PT) according to the international normalized ratio (INR) (range, 2.0 to 3.0). An institutional review committee approved the study. All patients were informed and asked to participate. Nobody refused to take part in the study. Anticoagulation with warfarin was maintained for 3 postoperative months, then discontinued and substituted with ASA. Those with concomitant coronary artery bypass grafting did not receive any double therapy of warfarin plus ASA. Patients were followed for operative and long-term survival, postoperative cerebral ischemia, postoperative bleeding events, length of intensive care unit stay, need for a repeated operation, and NYHA class at time of follow-up. Patients were clinically evaluated at fixed points in time (1, 3, and 6 months after the operation and at the end of the study). The clinical evaluation was always performed by the same physician (A.C.) and was based on an ECG and a predefined questionnaire. The questionnaire assessed the functional status, current medication, drug discontinuation since the operation, occurrence of strokes or other thromboembolic events, bleeding complications, and hospital admission for cardiac and noncardiac problems. The ECG enabled us to exclude patients with AF. All the PT trends were evaluated at the time of follow-up for those patients taking anticoagulant agents. All events such as thromboembolism, hemorrhage, and other valve-related complications were defined according to the framework devised by Edmunds et al.¹³ Postoperative cerebral events were divided into 2 time frames: early (between 24 hours and 3 months) and at follow-up.

Preoperative patient characteristics were evaluated following current guidelines. In particular, we considered hypertension according to Joint National Committee VI,¹⁴ diabetes mellitus according to the American Diabetes Association,¹⁵ and dyslipidemia according to National Cholesterol Education Program-Adult Treatment Panel II¹⁶ criteria. We also considered the European System for Cardiac Operative Risk Evaluation (EuroSCORE)¹⁷ to quantify the preoperative surgical risk.

Statistical Analysis

All data were compiled and stored on a computerized database. Data are expressed as mean±SD for continuous data and as percentages for categorical data. Univariate analysis (χ^2 and *t* test) was used to compare the characteristics of the groups of patients. Survival curves

TABLE 1. Characteristics of Patients at Baseline

	ASA (n=141)	Warfarin (n=108)	<i>P</i>
Sex			0.696
Male	54 (38.3)	44 (40.8)	
Female	87 (61.7)	64 (59.2)	
Age, mean, y	70.0±8.8	72.9±7.1	0.007
Hypertension*	69 (48.9)	55 (51.4)	0.701
Diabetes†	22 (15.8)	13 (12)	0.413
Dyslipidemia‡	37 (26.2)	30 (28)	0.752
Aortic pathology			0.131
Aortic stenosis	95 (67.4)	60 (55.6)	
Aortic insufficiency	19 (13.4)	23 (21.3)	
Mixed pathology	27 (19.1)	25 (23.1)	
LVEF, mean, %	57.1±13.6	55.6±13.6	0.405
NYHA (III–IV)	105 (74.5)	86 (79.6)	0.340
EuroSCORE	6.1±2.6	6.9±2.2	0.015

Values are number (%) unless indicated otherwise. LVEF indicates left ventricular ejection fraction.

*In the warfarin group, 1 patient had a missing hypertension value; therefore, the percentage has been calculated for 107 patients.

†There were 2 missing values in the ASA group and 1 in the warfarin group; therefore, the percentages have been calculated for 139 patients and 107 patients, respectively.

‡In the warfarin group, there was 1 missing value; therefore, the percentage has been calculated for 107 patients.

with the use of the Kaplan-Meier method were estimated to evaluate overall survival and freedom from stroke. For the overall survival analysis, the time to the event consisted of the interval between the beginning of the treatment after the surgery and the event (death). Patients who were alive at the last follow-up were considered censored. For freedom-from-stroke analysis, the time to event was considered as the frame interval between the beginning of the treatment and the occurrence of the stroke. Patients who did not experience a stroke and those who died were considered censored. To test the hypothesis of equality between survival curves, the log-rank test was used.

Hazard ratio (HR) was estimated to measure the association between the treatment and the event, and the 95% CI was also reported. The Cox model was used to adjust the association for possible confounders. The Fisher exact test was used to compare categorical data when the expected frequency of cells in a contingency table was <0.5. A set level of significance ($\alpha=0.05$) was chosen for decision making. The analysis was performed with the use of the statistical package STATA 7.

Results

A total of 275 consecutive patients undergoing BAVR were identified. Eighteen of them were excluded because of AF during follow-up, 7 died in the hospital before starting therapy, and 1 had an immediate stroke in the first 24 hours, leaving 249 patients available for study. One hundred forty-one patients received antiplatelet therapy with low-dose ASA (100 mg/d) starting on day 2 after surgery. A second group of 108 patients underwent anticoagulation therapy with warfarin and LMWH.

The preoperative patient characteristics of both groups are summarized in Table 1. There were 98 male and 151 female patients. Bioprostheses used were Carpentier-Edwards (53%), Toronto (8%), More (11%), Sheligh (9%), Mosaic

TABLE 2. Operative Parameters

	ASA (n=141)	Warfarin (n=108)	P
Emergency	1 (0.7)	4 (3.7)	0.168*
AVR	84 (59.6)	57 (52.8)	0.101
AVR+1 SVG	16 (11.4)	9 (8.4)	
AVR+2 SVG	2 (1.4)	5 (4.6)	
AVR+LIMA+1 SVG	9 (6.4)	13 (12.0)	
AVR+LIMA+2 SVG	8 (5.7)	4 (3.7)	
AVR+LIMA	13 (9.2)	7 (6.5)	
AVR+AAR	3 (2.1)	5 (4.6)	
Bentall procedure	3 (2.1)	8 (7.4)	
AVR+MV repair	3 (2.1)	0 (0.0)	
Aortic cross-clamp time, min	87.2±27.1	93.5±32.8	0.100
Cardiopulmonary bypass, min	111.6±33.4	118.4±45.3	0.180
Stented	109 (77.3)	90 (83.3)	0.452
Stentless	32 (22.7)	18 (16.7)	

Values are number (%) unless indicated otherwise. AVR indicates aortic valve replacement; SVG, saphenous vein graft; LIMA, left internal mammary artery (graft); AAR, ascending aorta replacement; and MV, mitral valve.

*Fisher exact test.

(6%), Mitroflow (6%), Epic (3%), and Freedom (4%). Forty-eight percent of patients treated with ASA were hypertensive compared with 51% in the warfarin group. Fifteen percent of patients among those treated with ASA were diabetics versus 12% who were treated with warfarin. The distributions of aortic pathologies, such as aortic stenosis, aortic insufficiency, and mixed pathology, were similar in both groups. The left ventricular ejection fraction was 57.1±13.6% in the ASA group and 55.6±13.6% in the warfarin group. None of these differences were statistically significant. The mean age between the 2 groups differed significantly: 70 years in the ASA group compared with 73 years in the warfarin group ($P=0.007$). The mean EuroSCORE also differed significantly: 6.1 in the ASA group and 6.9 in the warfarin group ($P=0.015$).

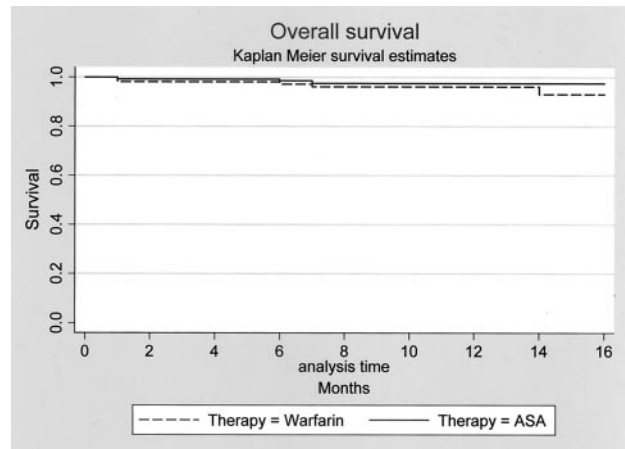
Operative variables are presented in Table 2. The great majority of patients underwent isolated BAVR (59% in the ASA group and 53% in the warfarin group; $P=NS$). None of

TABLE 3. Postoperative Data

	ASA (n=141)	Warfarin (n=108)	P
Perioperative (30-day) death	1 (0.7)	2 (1.9)	0.581*
Death at follow-up	3 (2.1)	5 (4.6)	0.299*
NYHA at follow-up (III–IV)	6 (4.3)	8 (7.4)	0.285
Postoperative cerebral ischemia (first episode)			
24 h to 3 mo	3 (2.1)	5 (4.6)	0.299*
>3 mo	1 (0.7)	3 (2.8)	0.319*
Major bleeding	3 (2.1)	4 (3.7)	0.473*
Need for AVR redo	2 (1.4)	1 (0.9)	1.000*

Values are number (%). AVR indicates aortic valve replacement.

*Fisher exact test.

**Figure 1. Overall survival.**

the differences between the variables reported in Table 2 were statistically significant. The mean intensive care unit stay for patients treated with ASA and with warfarin differed (2.1 ± 1.4 and 2.8 ± 2.2 days, respectively; $P=0.003$).

All episodes of cerebral ischemia and bleeding events are reported in Table 3. Three ischemic events in the immediate postoperative period (24 hours to 3 months) were observed among patients treated with ASA (2.1%), whereas 5 events were observed in patients treated with warfarin (4.6%). The difference was not statistically significant. Late thromboembolic events occurred in 1 patient in the ASA group (0.7%) and in 3 patients in the warfarin group (2.8%). The number of late ischemic events was not significantly different ($P=0.319$). Of all the patients with ischemic events, none had an altered PT (INR between 2 and 3 for warfarin) on hospital admission. For 2 patients the late thromboembolic event was fatal; both were part of the anticoagulation group.

Bleeding events in the early postoperative period occurred in 3 patients in the ASA group (2.1%); all the cases were gastrointestinal bleeding and were resolved with conservative treatment. All the patients had a negative history for previous gastrointestinal pathology. In patients treated with warfarin, there were 4 episodes of major bleeding (3.7%); 1 case was saphenous vein harvest site bleeding, 2 cases had mediastinal bleeding, and 1 had intracranial bleeding. The patient affected by intracranial bleeding died on day 20 after surgery. Only 1 case of all bleeding events occurred after the first 3 months of observation (gastrointestinal bleeding of patient treated with ASA). All the patients with a bleeding event on warfarin had an INR >3 (mean, 3.95 ± 0.84) at the time of readmission to the hospital.

The incidence rate in the warfarin group was 0.004 (5 deaths per 1179 months at risk), whereas it was 0.002 in the ASA group (3 deaths per 1289 months at risk). One patient experienced perioperative death (<30 days) in the ASA group (0.7%), and 2 patients experienced perioperative death (1.9%) in the warfarin group. These incidences were not statistically different between the 2 groups ($P=0.581$). Three patients in the ASA group (2.1%) and 5 patients in the warfarin group (4.6%) ($P=0.299$) died during follow-up. Figure 1 shows the Kaplan-Meier curves for overall survival.

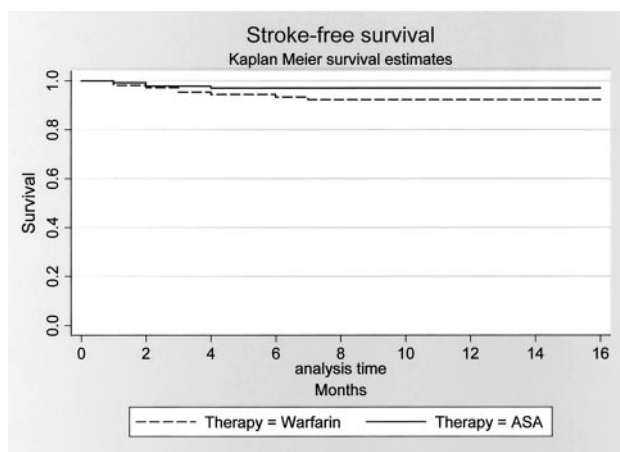


Figure 2. Stroke-free survival.

Survival curves are not significantly different between the 2 groups (HR=1.88; 95% CI, 0.44 to 7.97; $P=0.386$). A similar result was obtained when the HR was adjusted for age and EuroSCORE (HR=1.50; 95% CI, 0.35 to 6.52). Late deaths caused by a neurological event were observed in 1 patient in the ASA group and 2 patients in the warfarin group. Stroke-free survival rates were not significantly different among the 2 treatment groups (HR=2.62; 95% CI, 0.79 to 8.69; $P=0.102$) (Figure 2).

Discussion

The clinical use of biological valves has increased in previous years because of better quality and durability of these prostheses.^{18–20} However, the optimal postoperative management of biological valves remains under discussion. Many regimens have been described. These regimens have included no anticoagulation or antiplatelet therapy at any time,^{21,22} ASA or warfarin for 6 weeks,¹² warfarin for 4 to 12 weeks followed by no therapy,^{5,23,24} warfarin for 3 months followed by ASA for 1 to 2 years,²⁵ long-term use of ASA only,^{26,27} subcutaneous heparin for 1 to 4 weeks followed by or associated with warfarin for 1 to 3 months,²⁸ and ticlopidine for the first 3 months.²⁹ The guidelines published by the AHA/ACC, ESC, and ACCP^{1–3} clearly recommend the use of an anticoagulation regimen for the first 3 months after BAVR in patients with no thromboembolic risk factors. These guidelines were developed to try to minimize the risk of thromboembolism during the high-risk period for such events.^{5,6} To date, no randomized trials and few retrospective studies have compared the effectiveness of different regimens in preventing postoperative thromboembolism and hemorrhage after BAVR.

Babin-Ebell et al¹¹ and Joyce and Nelson³⁰ found no benefit in early warfarin therapy compared with ASA and concluded that standard anticoagulation did not seem to be beneficial. Authors of 4 retrospective studies^{9,31–33} suggested the use of ASA therapy alone without short-term anticoagulation.

In a recent investigation by Moinuddeen et al,¹⁰ 195 patients undergoing BAVR were analyzed retrospectively. They found no statistically significant difference in cerebral

ischemic events or bleeding complications between patients treated with warfarin for the first 3 postoperative months and patients treated with ASA. In contrast to all this evidence, Heras et al⁶ showed an extremely high early thromboembolic rate in patients without anticoagulation therapy. They concluded that early anticoagulation therapy at stable therapeutic levels, maintaining the PT ratio at 1.5 to 2.0 (INR, 3.0 to 4.5), may be needed for a minimum of 3 months. This high recommended level of anticoagulation therapy can explain the higher rate of bleeding in these patients compared with those previously reported.^{25,34,35} Turpie et al³⁶ introduced a low-dose anticoagulation regimen in which the therapeutic target range was 2.0 to 2.3 INR, showing that serious bleeding complications seemed to be avoidable. In 1995 Orszulak et al²¹ showed that early use of warfarin was beneficial only on a specific subset of patients who received BAVR. Nevertheless, in 1998 a review by Tiede et al³⁷ recommended the use of warfarin therapy for all patients.

The results of this first prospective study indicate no significant difference in the overall postoperative incidence of cerebral ischemia in both groups studied. In the high-risk period of the first 3 months, the number of events in the anticoagulation group is more than double that in the antiplatelet therapy group. However, that difference did not reach statistical significance. This might be due to the small number of patients assessed in our study. Besides that, the presence of a low ejection fraction, paced rhythm, and increased age did not seem to be related to a major risk of thromboembolism. In contrast with previous reports, we did not note any advantages in using warfarin in this selected group of patients. The rates of bleeding were similar in the 2 groups, probably because of the use of mild anticoagulation. The 2 groups were statistically different with respect to age and EuroSCORE, although the 2 differences did not seem to be clinically relevant. However, the statistical adjustment for these 2 variables did not change the results of the study.

This study did not show any statistical superiority of one therapeutic regimen over another in the early postoperative period after BAVR in a selected cohort.

We tried to minimize the risk of biased results in our study by performing a prospective study, using strict inclusion criteria and obtaining complete follow-up. Moreover, patients were treated according to the surgeon's preference, which depended on who was on duty the day of surgery, which gives the allocation a certain degree of unpredictability. This condition represented the original background of the study. However, we are aware of the limitations of this study, which are the small number of patients enrolled, the single-center participation, and the fact that it is not a randomized study. The questions that we raise are as follows.

First, is there evidence that warfarin is better than ASA in patients without risk factors undergoing BAVR in reducing thromboembolic events?

Second, should we administer warfarin in the absence of evidence about the superiority of warfarin to ASA, in light of the fact that warfarin needs frequent venipuncture for monitoring and complex dose adjustments in patients undergoing surgery or biopsy procedures; has higher health costs; has an negative impact on the patient's quality of life and on the

patient's compliance with the therapy³⁸; and has several drug interactions?

Third, are we sure that administering warfarin for the first 3 months after the operation (INR 2.5) allows time for endothelialization of the sewing ring,³⁴ suture knots, and valve leaflets?

The results of our study show that we are not able to give clear answers to these questions. A large randomized controlled study is probably the only way to handle these questions to update guidelines on antithrombotic management of biological prosthetic valves.

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