Combined Warfarin and Antiplatelet Therapy After St. Jude Medical Valve Replacement for Mitral Valve Disease

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Objectives. The clinical effect of combined warfarin and antiplatelet therapy on the incidence of stroke and postoperative complications after mitral (plus aortic) valve replacement was studied and compared with that observed with warfarin therapy alone.

Background. It has been reported that combined warfarin and antiplatelet therapy may be effective but may be associated with an increased hemorrhagic risk. Therefore, definite benefits of the treatment in patients with an implanted prosthetic valve have not been clearly documented.

Methods. Between January 1980 and December 1992, 195 patients with a St. Jude Medical valve at the mitral (plus aortic) position were assigned to receive treatment with either warfarin alone (125 patients) or warfarin plus antiplatelet agents (70 patients), such as dipyridamole (150 or 300 mg daily, 14 patients) or ticlopidine (200 or 400 mg daily, 56 patients). A minimal dose of aspirin (10 to 40 mg) was added (29 patients) if the maximal platelet aggregation rate by collagen was not reduced. The target thrombotic level was 10% to 20%.

Results. The two treatment groups were similar with regard to gender and age distribution. The number of patients with atrial fibrillation, left atrial thrombus, history of previous stroke, simultaneous aortic valve operation and previously performed valve procedures were comparable in the two groups. Actuarial survival rate at 10 years was 98.3 ± 1.7% (mean ± SD) in the warfarin plus antiplatelet group and 90.3 ± 3.2% in the warfarin group ($p < 0.05$ at 1 and 9 to 12 years). The actuarial stroke-free rate at 10 years was 95.3 ± 3.4% and 84.3 ± 3.8%, respectively ($p < 0.05$ by the generalized Wilcoxon test). The actuarial complication-free rate at 10 years was 89.4 ± 4.3% and 67.9 ± 4.8%, respectively ($p < 0.05$ by the generalized Wilcoxon test). No hemorrhagic complications were seen in the warfarin plus antiplatelet group.

Conclusions. The results strongly indicate the effectiveness and safety of combined warfarin plus antiplatelet treatment after St. Jude Medical valve replacement for mitral (plus aortic) valve disease.

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Trials of the combined warfarin plus antiplatelet therapy have reported effective results in patients with prosthetic valves (10,11). Chesebro et al. (10) reported a lower incidence of thromboembolism and bleeding using the warfarin plus dipyridamole therapy in patients who received Starr-Edwards or Björk-Shiley valves (10), but another report (12) concerning prosthetic valves described other morbidity that might be affected by blood coagulability. The present study was designed to clarify whether warfarin plus antiplatelet therapy could reduce fatal or nonfatal morbidity compared with that observed with warfarin therapy alone.

Methods

Patients. Between January 1980 and December 1992, 195 patients receiving a St. Jude Medical heart valve at the mitral position (including a simultaneous aortic valve replacement using the St. Jude Medical valve) were allocated to receive treatment with either warfarin alone (125 patients) or warfarin plus antiplatelet agents (70 patients) in nonrandomized manner. Selection of treatment was left to the attending physicians, who were informed that either treatment was allowed. Patients who received another prosthetic valve in...
combination with the St. Jude Medical valve and 11 patients (5.3%) who died during the hospital period of various causes were excluded from the present study.

Forty-six of the 195 study patients (76 male, 119 female; mean age ± SD 49 ± 12 years [range 6 to 73]) had undergone 54 previous valve procedures, including 17 prosthetic valve replacements and 4 emergency operations for intractable active endocarditis, thrombosed disc valve or severe left ventricular dysfunction.

Preoperative coronary angiographic evaluation was performed in all but 13 patients, who required emergency operation or were <15 years of age. Coronary artery disease was defined as ≥50% lumen narrowing in at least one coronary artery. Cineventriculography was performed in all patients except those who had active infective endocarditis or were undergoing emergency operation. Left ventricular ejection fraction was calculated from end-diastolic and end-systolic volumes measured according to the Dodge area-length method (13).

We used a Bentley or Maxima oxygenator during cardiopulmonary bypass and maintained moderate hypothermia during aortic cross-clamping. In 1984, we introduced the use of a cold St. Thomas Hospital solution instead of cold glucose-insulin-potassium solution to protect the myocardium during cardiac arrest, and since February 1987 we have used the former exclusively. The posterior mitral leaflet preservation technique was used in only a small number of patients before December 1985 but has since been regularly applied except in patients with prosthetic valve failure or a small mitral annulus. Since 1982, we have oriented the mitral valve perpendicular to the natural leaflet. Before 1982 we used parallel orientation.

Anticoagulant therapy and follow-up. Anticoagulant and antiplatelet therapy were started on postoperative day 1 or 3. The daily dose of warfarin was based on the thrombostest level, which reflects the anticoagulation activity of Factors II, VII and X and protein induced by vitamin K antagonists (14) and was measured every 3 days during the hospital period and every 2 to 4 weeks after hospital discharge. The target thrombostest level was 10% to 20%. To inhibit platelet aggregation, since 1984 we have used ticlopidine (100 or 200 mg twice a day) instead of dipyridamole (150 or 300 mg/day in two or three divided portions). A minimal dose of aspirin (range 10 to 40 mg/day) was added if a maximal aggregation rate of platelet by collagen was not suppressed. The daily dose of antiplatelet agents was based on the maximal aggregation rate (15), which was measured every 6 months. If a patient manifested nausea, leukopenia, liver injury and other complications due to antiplatelet therapy, this therapy was discontinued.

Follow-up was completed in February 1993, and the following details were checked: cerebrovascular stroke, thromboembolic event in peripheral arteries, hemorrhage that necessitated blood transfusion, prosthetic valve endocarditis, structural or nonstructural deterioration of the prosthetic valve, myocardial infarction, malignant disease, reoperation and death. Definitions of mortality and morbidity followed the guidelines of Edmunds et al. (16). Cerebral infarction due to thromboembolism was defined as a neurologic deficit of sudden onset with evidence of a low density area by brain computed tomography or arterial occlusion documented by angiography.

If a neurologic deficit disappeared within 24 h, the patient was considered to have had a transient ischemic attack unless a high density area was noted on computed tomography. Follow-up ranged from 2 months to 13 years (average 6.5 ± 3.9). No patient was lost to follow-up.

Statistical analysis. Comparison of variables between the two groups was by the unpaired t test. Incidence was compared by chi-square analysis. Survival and stroke- and complication-free curves were constructed by Kaplan-Meier actuarial methods. Actuarial rates are presented as mean value ± 1 SEM, and the difference between the two groups was tested for significance by the generalized Wilcoxon test.

Results

Patient characteristics. Table 1 lists the baseline characteristics of the two groups at the time of operation. The two groups were similar with regard to gender and age distribution. Factors that may affect postoperative outcome, such as cardiac rhythm, left atrial thrombus, history of previous stroke, simultaneous aortic valve operation and previous valve procedures, were comparable between the two groups. The cumulative follow-up period was 845 patient-years in the warfarin group and 404 patient-years in the warfarin plus antiplatelet group. Of 70 patients in the warfarin plus antiplatelet group, 14 received dipyridamole and 56 ticlopidine. Aspirin was added in 29 patients on the basis of the maximal aggregation rate of platelet by collagen.

### Table 1. Baseline Characteristics*

<table>
<thead>
<tr>
<th></th>
<th>Warfarin Group (n = 125)</th>
<th>Warfarin + AP Group (n = 70)</th>
<th>p Value (chi-square test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F</td>
<td>51/74</td>
<td>25/45</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>7 to 73</td>
<td>6 to 67</td>
<td>NS</td>
</tr>
<tr>
<td>Mean ± SD AF</td>
<td>49.2 ± 11.8</td>
<td>49.8 ± 11.3</td>
<td>NS</td>
</tr>
<tr>
<td>LA thrombus</td>
<td>16 (13)</td>
<td>14 (20)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>29 (23)</td>
<td>17 (24)</td>
<td>NS</td>
</tr>
<tr>
<td>AVR + MVR</td>
<td>20 (16)</td>
<td>14 (20)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous valve surgery</td>
<td>25 (20)</td>
<td>21 (30)</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up duration</td>
<td>845</td>
<td>404</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Factors that affect postoperative outcome were comparable between the two groups. Unpaired t test. Unless otherwise indicated, values presented are number (%) of patients. AF = atrial fibrillation; AP = antiplatelet agents; AVR = aortic valve replacement; LA thrombus = left atrial thrombus; MVR = mitral valve replacement.
Table 2 lists preoperative cardiac status and the number of patients who received each cardioplegic solution and mitral leaflet preservation technique. The type of mitral lesion, incidence of abnormal coronary anatomy and left ventricular ejection fraction were comparable between the two groups. The St. Thomas Hospital solution was used more frequently in the warfarin plus antiplatelet group compared with the warfarin group (p < 0.01). However, there were no significant differences between the group that received the St. Thomas Hospital solution (95 patients) and those that received the glucose-insulin-potassium solution (100 patients) with regard to actuarial survival rate (at 5 and 10 years was 98.3 ± 1.7% at both dates in the warfarin plus antiplatelet group and 93.4 ± 2.4% and 90.3 ± 3.2%, respectively, in the warfarin group (Fig. 1). There was a significant difference between the two groups at 1 year and at 10 to 12 years (p < 0.05). No significant difference was observed between the two survival curves by the generalized Wilcoxon test.

Cerebrovascular strokes and stroke-free rate. Cerebral infarction and transient ischemic attack occurred in six patients, respectively, in the warfarin group. However, only two patients experienced cerebral infarction in the warfarin Figure 1. Actuarial survival rate in the patients receiving warfarin (W) plus antiplatelet (AP) therapy and in those receiving warfarin therapy alone after St. Jude Medical mitral valve replacement (Ope). A significant difference was observed between the two groups at 1, 9, 10 (p < 0.05) and 11 years postoperatively (p < 0.01). However, the generalized Wilcoxon test revealed no significant difference between the two survival curves.
plus antiplatelet group (Table 4). These two patients had basilar artery occlusion and received direct thrombolytic revascularization using urokinase or tissue plasminogen activator through a microcatheter placed in the basilar artery. Details have been reported elsewhere (17). One patient had a subcortical hemorrhage during prosthetic valve endocarditis, and one patient with long-term hemodialysis had a subdural hematoma. No patient had intracranial hemorrhage in the warfarin plus antiplatelet group. The actuarial stroke-free rate at 5 and 10 years was 98.4 ± 1.6% and 95.3 ± 3.4%, respectively, in the warfarin plus antiplatelet group and 89.3 ± 3.1% and 84.3 ± 3.8% in the warfarin group (Fig. 2). Significant intergroup difference was confirmed by the generalized Wilcoxon test (p < 0.05).

Late postoperative complications and complication-free rate. Table 5 summarizes the late postoperative complications, including strokes and death from various causes. The proportion of cardiac or valve-related deaths and myocardial infarction was higher in the warfarin group than in the warfarin plus antiplatelet group. The cause of reoperation was hemolytic anemia in three patients, paravalvular leakage in one patient and idiopathic intestinal hemorrhage in one.

The first four of these patients had received a Björk-Shiley prosthetic valve and the latter a Carpentier-Edwards porcine valve at the time of reoperation. Of the five patients with a myocardial infarction, coronary angiographic findings in two patients showed a progression of stenotic lesions compared with the preoperative lesion, whereas in three other patients preoperative coronary angiography showed normal findings. The actuarial complication-free rate, including all complications listed in Table 5, at 5 and 10 years was 92.4 ± 3.3% and 89.4 ± 4.3%, respectively, in the warfarin plus antiplatelet group, and 77.5 ± 4.0% and 67.9 ± 4.8%, respectively, in the warfarin group (Fig. 3). Significant intergroup difference was confirmed by the generalized Wilcoxon test (p < 0.05).

Discussion

Warfarin is known to interfere with the coagulation cascade in the activation of Factors II, VII, IX and X;
therefore, it is considered to be the most effective drug for reducing intravascular thrombogenesis. However, the primary thrombogenic mechanism starts from the adhesion and aggregation of platelets with endothelium mediated by the von Willebrand factor and fibrinogen (18). For these reasons, combined anticoagulant therapy using warfarin plus antiplatelet agents may be more effective than either therapy alone. Platelets are activated by both adenosine diphosphate–mediated and cyclooxygenase-mediated activation mechanisms. In general, dipyridamole exerts a mild blocking action on both activation mechanisms, whereas ticlopidine blocks only the former, and a low dose of aspirin (10 to 80 mg) interferes exclusively with cyclooxygenase. The characteristics of each drug help to modulate platelet aggregation activity. If a target control level of maximal aggregation rate (40% to 60% by adenosine diphosphate [10 μmol] 30% to 50% by collagen [2 μg/ml]) cannot be achieved, then the daily dose of antiplatelet agents is varied depending on the maximal aggregation rate of platelet by each agonist.

Survival rate. Although some multicenter trials using antiplatelet agents demonstrated a significant reduction in cardiac mortality in patients with unstable angina (19,20), few reports have confirmed an improvement in postoperative survival rate after prosthetic valve replacement. Compared with previous reports in the United States (2,4,5), the actuarial survival rate in both groups was higher, probably owning to the younger patients and lower incidence of complicated coronary artery disease in the present series. One important finding in the present study is the higher survival rate obtained in the warfarin plus antiplatelet group. The warfarin group includes four patients who died suddenly of unknown causes. In a randomized trial, Turpie et al. (12) reported that in patients with valve replacement, vascular death, including sudden death from unknown causes and myocardial infarction, occurred less frequently in the warfarin plus antiplatelet treatment group than in the warfarin plus placebo treatment group (12). Davies et al. (21) related the effect of platelet aggregation in intramyocardial artery to sudden cardiac death in patients with unstable angina. However, no reports have described what role platelet aggregation activity plays in hypertrophied cardiac muscle. Further investigation is needed to clarify the relation between coagulability and ventricular arrhythmias.

Hemorrhage and stroke. At the beginning of the study, we thought that hemorrhagic risk might increase in the warfarin plus antiplatelet group, which is probably why relatively fewer patients received the combined treatment. Fortunately, no intracranial or other major hemorrhage occurred, although a slightly increased rate of subcutaneous hemorrhage was observed.

The principal finding of the present study is that the incidence of cerebrovascular stroke, including hemorrhage, was significantly reduced in the warfarin plus antiplatelet group (0.5%/patient-year) compared with 1.7%/patient-year in the warfarin group, which was similar to previous reports with warfarin (1–3). This success is considered to be attributed to a strict anticoagulant regimen and safely controlled platelet aggregation activity. Chesebro et al. (10) emphasized the danger of aspirin compared with dipyridamole in combination with warfarin (10). Compared with the moderate dose of aspirin (500 mg/day) used in their study, our patients received 10 to 40 mg/day of aspirin on the basis of measured platelet aggregation activity. In the study of Turpie et al. (12), the daily dose of aspirin was fixed at 100 mg because of the potential increased risk for hemorrhage with doses of >100 mg/day. Balsano et al. (9) reported the efficacy of ticlopidine treatment over aspirin therapy, although some adverse reactions were seen. In the present study, two patients had neutropenia and skin eruption, respectively, and required discontinuation of ticlopidine treatment because of massive hemorrhage. We believe that the lower incidence of hemorrhage in the present series is due to the lower, more appropriate dose of antiplatelet agent and a less intensive warfarin treatment regimen (a thrombotest level 10% to 20% is equivalent to prothrombin time [international normalized ratio] of 1.8 to 2.8).

Other nonfatal morbidity. The remarkable reduction in the incidence of postoperative complications in the warfarin plus antiplatelet group (Table 5) in the present study occurred mainly because stroke, cardiac or valve-related death and myocardial infarction were less common. Many investigators have reported successful prevention of graft occlusion (8) and a protective effect against myocardial infarction (12,19,20) by antiplatelet agents. These achievements support the results in the present study. Another reason for our high success rate might be an inclusion of fewer patients with complicated coronary artery disease than those included in previous studies (1–3).

Conclusions. A higher survival rate, lower incidence of cerebrovascular strokes and better quality of life with fewer postoperative complications were obtained with the combined warfarin plus antiplatelet therapy after St. Jude Medical valve replacement for mitral (plus aortic) valve disease. The present study confirms that it is time to reconsider the advantages of combined warfarin plus antiplatelet treatment after mechanical valve replacement.

References


