Aspirin, Warfarin, or the Combination for Secondary Prevention of Coronary Events in Patients With Acute Coronary Syndromes and Prior Coronary Artery Bypass Surgery

Thao Huynh, MD; Pierre Théroux, MD; Peter Bogaty, MD; James Nasmith, MD; Susan Solymoss, MD

Background—Patients with a non–ST-elevation acute coronary syndrome and prior CABG are at high risk of a recurrent ischemic event despite aspirin therapy. This trial investigated the potential benefit of secondary prevention with warfarin.

Methods and Results—In a double-blind randomized trial, 135 patients with unstable angina or non–ST-segment elevation myocardial infarction, with prior CABG, and who were poor candidates for a revascularization procedure received therapy with aspirin and placebo+warfarin, warfarin and placebo+aspirin, or aspirin and warfarin for 12 months. Warfarin was titrated to an international normalized ratio of 2.0 to 2.5. The primary end point (death or myocardial infarction or unstable angina requiring hospitalization 1 year after randomization) occurred in 14.6% of the patients in the warfarin-alone group, in 11.5% of patients in the aspirin-alone group, and in 11.3% of patients randomized to the combination therapy (P = 0.76). Subgroup analyses by risk features provided no indications that warfarin alone or in combination with aspirin could be of benefit over aspirin alone. Bleeding was more frequent in the 2 groups of patients administered warfarin.

Conclusions—Moderate-intensity oral anticoagulation alone or combined with low-dose aspirin does not appear to be superior to low-dose aspirin in the prevention of recurrent ischemic events in patients with non–ST-elevation acute coronary syndromes and previous CABG. (Circulation. 2001;103:3069-3074.)

Key Words: warfarin sodium ■ anticoagulants ■ aspirin ■ coronary disease

Cardiac events are frequent in patients with previous CABG and are associated with an impaired prognosis. Aspirin prevents graft closure during the first year after surgery, but its long-term benefit in this specific setting has not been documented. Warfarin had been evaluated in unstable angina, but no studies have addressed the specific population of patients with unstable coronary syndromes without ST elevation developing late after CABG. Because of the high frequency of flow stasis, thrombi, and fibrin-rich thrombi associated with venous graft disease, long-term anticoagulation with warfarin may be particularly beneficial in this situation. We tested the hypothesis that moderate-intensity warfarin (international normalized ratio [INR] 2 to 2.5) either alone or in combination with low-dose aspirin will be more effective than aspirin alone for the secondary prevention of coronary events in patients with previous CABG.

Methods

Selection of Patients
The present study was conducted at 4 referral cardiology centers in Quebec, Canada. All patients who presented with a diagnosis of unstable angina or non–ST-elevation myocardial infarction and prior CABG were considered for the study. The diagnosis of unstable angina was based on an accelerating pattern of chest pain occurring at rest or with minimal exertion or of a prolonged chest pain and normal serum levels of creatine kinase (CK). A non–ST-segment elevation myocardial infarction was diagnosed when serum CK-MB increased above the upper normal limit of the site in the absence of new Q waves on the ECG. Patients who had coronary angioplasty or repeat CABG during the index hospitalization were excluded; therefore, the study population was limited to patients who were poor candidates for a revascularization procedure. Other exclusion criteria were as follows: contraindication to the use of aspirin or warfarin, a treatable cause for angina pectoris, any major concomitant illness, congestive heart failure class 3 or 4 (New York Heart Association), uncontrolled systemic hypertension (blood pressure > 180/95 mm Hg), recent major trauma, alcohol or drug abuse, females with child-bearing potential, coronary angioplasty within the last 6 months, conditions mandating treatment with aspirin (such as previous stroke) or with warfarin (such as metallic valve prostheses), atrial fibrillation, or intracardiac thrombi. All patients gave informed consent to participate, and the institutional review board at each participating hospital approved the protocol.

Study Protocol
In a double-blind parallel-group study design, patients were randomized to 1 of 3 parallel study groups: (1) aspirin plus placebo-warfarin,
TABLE 1. Clinical Characteristics of Study Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Warfarin + Placebo (n=46)</th>
<th>Aspirin + Placebo (n=46)</th>
<th>Aspirin + Warfarin (n=44)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD), y</td>
<td>67±12</td>
<td>68±11</td>
<td>66±12</td>
<td>0.90</td>
</tr>
<tr>
<td>Females, %</td>
<td>13.6</td>
<td>17.8</td>
<td>29.3</td>
<td>0.18</td>
</tr>
<tr>
<td>Mean LVEF, %</td>
<td>30.9</td>
<td>29.4</td>
<td>29.4</td>
<td>0.99</td>
</tr>
<tr>
<td>LVEF &lt;40%, %</td>
<td>53.3</td>
<td>41.3</td>
<td>56.8</td>
<td>0.29</td>
</tr>
<tr>
<td>Interval between randomization and CABG, y</td>
<td>8.5</td>
<td>7.2</td>
<td>6.9</td>
<td>0.20</td>
</tr>
<tr>
<td>Prior MI, %</td>
<td>62.2</td>
<td>56.5</td>
<td>72.7</td>
<td>0.38</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>31.1</td>
<td>17.8</td>
<td>20.5</td>
<td>0.29</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>37.8</td>
<td>34.8</td>
<td>38.6</td>
<td>0.73</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>62.2</td>
<td>43.5</td>
<td>68.2</td>
<td>0.11</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>15.6</td>
<td>17.4</td>
<td>25.0</td>
<td>0.50</td>
</tr>
<tr>
<td>CCS class &gt;3, %</td>
<td>13.3</td>
<td>13.0</td>
<td>20.5</td>
<td>0.30</td>
</tr>
<tr>
<td>Cardiac catheterization,* %</td>
<td>57.7</td>
<td>65.2</td>
<td>52.2</td>
<td>0.46</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction. Values are mean percentage unless specified differently.
*During index hospitalization.

(2) warfarin plus placebo-aspirin, or (3) aspirin plus warfarin. Aspirin was administered as a daily dose of 80 mg in nonenteric coated form. Warfarin was given as crystalline warfarin sodium tablets (Coumadin). Placebo tablets were supplied by Dupont Pharma Canada. In-hospital follow-up visits were scheduled at 1, 3, 6, and 12 months of treatment. The study drugs were terminated at the 12-month follow-up visit, and aspirin (325 mg daily) was prescribed to all patients. Patients were reevaluated 1 month after the discontinuation of the study drugs.

Study Monitoring

Measurements of INR were performed 3 days and 1 week after study drug initiation. Subsequent visits were scheduled depending on INR stability. Hemoglobin and hematocrit were monitored at the time of INR determination. Unblinded pharmacists or physicians, not otherwise involved in the study and patient care, adjusted warfarin to a target INR of 2.0 to 2.5 by using a predefined algorithm. To maintain the double-blind integrity, patients assigned to aspirin plus placebo-warfarin therapy also had regular blood tests and mock placebo-warfarin adjustments. Major bleeding was defined as a fall in hemoglobin of ≥2 g/L or requiring blood product transfusion. Minor bleeding was defined as all other bleeding events reported by the patients and/or health care professionals. In the event of clinically significant bleeding, the study drugs were discontinued, and patients were transfused as necessary. Compliance was defined as 100% of study medication taken (pills were counted by research coordinators). Study drugs could be temporarily interrupted for major illnesses, elective surgeries, and dental treatment. The study code was broken only when it was essential for optimal patient management.

Other Therapies

Concomitant medications could be prescribed at the discretion of the attending physicians, but drugs known to interact with warfarin or to increase the bleeding risk (barbiturates, NSAIDs, and salicylates) were prohibited during the whole study period. All patients received aspirin at the end of the 12-month study period, when study drugs were discontinued.

Study End Points

The primary study end point was a composite end point of any-cause death, myocardial infarction, or unstable angina requiring a new hospitalization. Other end points were performance of reperfusion procedure (either percutaneous or open chest). Myocardial infarction was defined as typical chest pain or discomfort lasting ≥30 minutes and associated with elevated serum CK-MB levels (above the upper normal limit of the site) or with new Q waves. Unstable angina was considered as a study end point only when it was severe enough to require hospitalization and there was a confirmed diagnosis at hospital discharge. Atypical chest pain requiring hospitalization was not counted as an end point. All events were classified before conditions of the blind study were revealed.

Statistical Analyses

The study was terminated prematurely after enrollment of half the planned number of patients because of difficulty in recruiting because of the high rate of conventional or investigatory procedures performed in otherwise qualifying patients. The baseline characteristics of the 3 study groups were compared by χ² and Student tests. End-point events were group-classified by the intention-to-treat principle. Intergroup differences for event rates were compared by the χ² statistics with the use of 2×3 tables. The event rates for the primary end point of death, myocardial infarction, and documented recurrent unstable angina were displayed by the Kaplan-Meier survival method and tested for statistical significance by the log-rank statistic. Events rates were also compared in subgroups with higher risk features identified by univariate and multivariate analyses of the baseline characteristics associated with an impaired prognosis. Statistical significance was defined by a value of P<0.05. The SPSS Base 10.0 (SPSS Advanced Models 10.0 statistical software) served for the statistical analyses.

Results

The baseline clinical characteristics of patients in the 3 study groups are shown in Table 1. Mean age, left ventricular systolic function (left ventricular ejection fraction [LVEF]), and time elapsed after CABG were similar among the patients. Although no statistically significant differences existed between the 3 groups, there were more patients that were female and had prior MI, diabetes, and functional impairment by angina in the group assigned to aspirin+warfarin and fewer patients with depressed LVEF (<40%) in the group assigned to aspirin+placebo than in the other 2 groups. More than 60% of the patients had prior myocardial infarction. Cardiac catheterization was performed in 60% of patients during the index hospitalization. The time...
elapsed between the last CABG and occurrence of the index acute coronary event averaged 7.5 years.

Table 2 shows the medical treatment received at the time of randomization. Patients in the warfarin+placebo group more often received ACE inhibitors and lipid-lowering drugs and less often received β-blockers; patients assigned to aspirin+placebo less often received diuretics and ACE inhibitors; and patients in the combination group more often received nitrates.

Table 3 presents the study end points for the 3 treatment arms, and the Figure presents the cumulative event rates. No statistically significant differences existed between groups in the incidence of the primary end point. End points regrouped as per the composite of any-cause mortality, MI, or UA requiring rehospitalization. Primary end point is any-cause mortality, MI, or UA requiring rehospitalization.

Baseline characteristics associated with an impaired prognosis were as follows: age ≥65 years (relative risk [RR] 1.65, \( P = 0.19 \)), male sex (RR 2.32, \( P = 0.11 \)), diabetes (RR 2.23, \( P = 0.07 \)), and Canadian Cardiovascular Society (CCS) angina class ≥3 (RR 1.83, \( P = 0.31 \)). Treatment effects in all subgroups showed no trends to a benefit with Coumadin alone or in combination with aspirin over aspirin alone. Thus, the event rates in the aspirin-alone, aspirin-placebo, and warfarin+aspirin groups were, respectively, as follows: in patients aged <65 years, 40%, 22.7%, and 19%; in patients aged ≥65 years, 41.7%, 34.8%, and 36.8%; among women, 9%, 0%, and 10%; among men, 15.7%, 15.3%, and 13.8%; among diabetics, 13%, 18%, and 30%; among patients with LVEF <40%, 11%, 8%, and 12%; and among patients in CCS class 3 or 4 at randomization, 6.3%, 0%, and 9.1%.

Patients using diuretics at the time of entry into the study had rates of 15.6%, 6.5%, and 13.6%, respectively, and those using ACE inhibitors had rates of 13.3%, 8.7%, and 9.1%, respectively.

Table 4 shows the distribution of complications among the 3 treatment arms. Minor bleeds were more frequent in patients receiving warfarin (\( P = 0.02 \)), either as single therapy (8.9%) or in combination (9.8%), than in those receiving only aspirin (1.5%). Major bleeding occurred only in patients receiving the anticoagulant. Two patients on warfarin+placebo and 2 patients on warfarin+aspirin required blood transfusions. In the present study, compared with warfarin alone, the addition of 80 mg of aspirin to warfarin treatment resulted in no excess bleeding. No significant excess in clinical events occurred in the month after cessation of the study drugs, with all patients administered open-label aspirin (Figure).

The rate of completion of protocol was high among the 3 groups. The reasons for premature cessation of study medications were diverse; most of the reasons for cessation were medical conditions requiring nonstudy use of warfarin or aspirin. Three patients had to stop the study drugs because of bleeding. Nonstudy use of warfarin was required in 5 patients on warfarin+placebo, 2 patients on aspirin+placebo, and 2 patients on aspirin+warfarin. Three patients (1 in each treatment group) were lost to follow-up.

**Discussion**

No benefit of warfarin alone or of warfarin+aspirin compared with aspirin alone could be documented for the secondary prevention of ischemic events in the present study of patients with previous CABG and an acute coronary syndrome (ACS). The composite end point and the various

<table>
<thead>
<tr>
<th>Events</th>
<th>Warfarin+Placebo (n=45)</th>
<th>Aspirin+Placebo (n=46)</th>
<th>Warfarin+Aspirin (n=44)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point, %</td>
<td>14.1</td>
<td>11.5</td>
<td>11.4</td>
<td>0.76</td>
</tr>
<tr>
<td>Death, %</td>
<td>0.7</td>
<td>0.0</td>
<td>1.6</td>
<td>0.34</td>
</tr>
<tr>
<td>MI, %</td>
<td>3.0</td>
<td>0.8</td>
<td>2.9</td>
<td>0.43</td>
</tr>
<tr>
<td>UA, %</td>
<td>12.6</td>
<td>11.5</td>
<td>10.6</td>
<td>0.88</td>
</tr>
<tr>
<td>PCI, %</td>
<td>4.4</td>
<td>0.8</td>
<td>3.3</td>
<td>0.12</td>
</tr>
<tr>
<td>Repeat CABG, %</td>
<td>1.5</td>
<td>1.5</td>
<td>1.6</td>
<td>0.99</td>
</tr>
</tbody>
</table>

UA indicates unstable angina requiring rehospitalization; PCI, percutaneous coronary intervention; and MI, myocardial infarction. Primary end point is any-cause mortality, MI, or UA requiring hospitalization.
components of the end point were all less frequent in the aspirin-alone group. More frequent interventions were also performed during follow-up in patients receiving Coumadin, although they were poor candidates for surgery, suggesting a lack of a benefit of the anticoagulation in preventing severe angina as well as recurrent ischemic events.

ACS in patients with previous CABG is usually associated with fibrin-rich blood clot, more extensive coronary artery disease, and an impaired prognosis. Other specific features of high risk in the study population included mean age >65 years, a high incidence of previous myocardial infarction and of diabetes mellitus, a low LVEF (30±2%), and, most important, selection of patients evaluated as poor candidates for a new revascularization procedure by coronary angiography and, for noncatheterized patients, by a coronary anatomy known to be poorly suitable for revascularization.

Despite these high-risk features, the primary end point in the present study was relatively infrequent, less than expected, and composed primarily of recurrent unstable angina with a relatively low rate of death or myocardial infarction. These figures are in contrast to those of previous studies, including one from our center, in which rates as high as 30% were reported. The improved prognosis possibly reflects a more aggressive use of conventional and investigative intervention procedures in patients with severe angina as well as the progress made in medical therapy in recent years, with emphasis on drugs that achieve plaque passivation and better control of the disease process. Such drugs include lipid-lowering agents, ACE inhibitors, and antithrombotic therapy. Yet, medical management in the study remained suboptimal, with 20% of the hyperlipemic patients not being on lipid-lowering therapy at the time of randomization, 25% of patients with depressed LVEF not being on ACE inhibitors, and 25% of the patients remaining active smokers.

With the premature discontinuation of the study and an observed event rate less than expected, the sample size of the present study was suboptimal. It provided 60% power to detect a 15% risk difference, 70% power to detect a 20% risk difference, and 88% power to detect a 25% difference between groups at a value of P<0.05. However, Coumadin alone, compared with aspirin alone, was associated with an increased absolute risk of 2.6%, and the combination of Coumadin with aspirin was associated with a minimal decrease of 0.1% (RR reduction of 0.87%), providing a low probability of a significant gain with Coumadin. A sample size >50 000 of patients would be required to document an eventual benefit of the combination Coumadin+aspirin over aspirin for a high futility index, assuming that the observed event rates were not confounded by an imbalance in the baseline characteristics of patients. Differences were indeed observed between groups, although they were not statistically significant. Subanalysis of the results by variables influencing prognosis did not influence results, and no favorable trends emerged in any end point favoring Coumadin alone or in combination. However, it remains possible that the differences observed, a combination of various differences, or other undetected differences could have had an impact on the results. Indeed, the univariate and multivariate analyses of determinants of prognosis suffered a similar lack of power as the outcome end points. Therefore, the present results should be interpreted as highly suggestive but not conclusive.

Although no studies with aspirin and Coumadin have previously specifically addressed the specific population of patients with previous CABG developing an ACS, a large body of experience has been gained with aspirin, warfarin, and the combination in unstable angina and in CABG in general. The efficacy of aspirin in the prevention of death and myocardial infarction in patients with unstable angina has been well documented, as has the efficacy of aspirin in maintaining venous graft patency when initiated at the time of surgery. However, long-term benefits to maintain graft patency are less well documented. Warfarin used alone can prevent recurrence of unstable anginabut has not been shown to be more effective than aspirin in maintaining graft patency.
The combination of antiplatelet and antithrombotic therapy has been extensively studied. In a primary prevention trial in high-risk men, low-intensity oral anticoagulation (INR 1.5) and low-dose aspirin (75 mg daily) had additive benefit. However, a low-intensity regimen was ineffective in large secondary prevention trials addressing patients with previous CABG and patients with a recent myocardial infarction, although post-CABG patients appeared to have derived some benefit, years after the discontinuation of Coumadin. The combination therapy with moderate-intensity anticoagulation to INR 2 to 3 might be more interesting. In a small angiographic study, Williams and Stewart suggested less deaths, myocardial infarctions, strokes, and rehospitalizations in patients receiving the combination therapy compared with aspirin alone. Another small study by Cohen et al showed a trend to a reduction in coronary events with the combination therapy. Favorable trends were also found in the Organization to Assess Strategies for Ischemic Syndromes (OASIS) program, with fewer coronary events with the combination therapy. Favorable mechanisms of the disease are also very much rewarding. The prolongation of low-molecular-weight heparins atherosclerosis and the need for revascularization over a 4-year period were significantly reduced with aggressive lowering of LDL cholesterol levels. Therefore, the treatment currently recommended for the management of ACS in high-risk patients with previous CABG is aspirin, clopidogrel, ACE inhibitors, and an aggressive control of risk factors aided by lipid-lowering drugs.

**Clinical Implications**

Although pathophysiological considerations make a strong case for the prolonged use of combined antiplatelet and anticoagulant drugs, the various attempts made so far in that direction have not been rewarding. The present study, although not conclusive because it was underpowered by a low event rate, was composed of high-risk patients with venous graft disease most likely to benefit from anticoagulation. The prolonged administration of low-molecular-weight heparins recently tested in 4 trials yielded no benefit, although 1 of the trials showed a benefit in the first few months of treatment that was not maintained, however, at the 6-month follow-up. Specific inhibitors of coagulation factor Xa, oral heparins, and oral antithrombin drugs represent new therapeutic opportunities that need to be explored. However, more potent antiplatelet therapy may be a better approach to secondary prevention. Oral glycoprotein IIb/IIa receptor antagonists have failed in this regard, but the Clopidogrel in the Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial recently showed that combination of aspirin and clopidogrel added significant benefit to aspirin alone in the prevention of recurrent ischemic events in patients with non–ST-elevation ACS.

Therapeutic measures addressing other pathophysiological mechanisms of the disease are also very much rewarding. The low event rates observed in our population compared with historical controls support this hypothesis. In the Post Coronary Artery Bypass Graft trial of the National Heart, Lung, and Blood Institute, the number of grafts with progression of atherosclerosis and the need for revascularization over a 4-year period were significantly reduced with aggressive lowering of LDL cholesterol levels. Therefore, the treatment currently recommended for the management of ACS in high-risk patients with previous CABG is aspirin, clopidogrel, ACE inhibitors, and an aggressive control of risk factors aided by lipid-lowering drugs.

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