Effect of Coumarins Started Before Coronary Angioplasty on Acute Complications and Long-Term Follow-Up
A Randomized Trial

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Background—Coronary angioplasty frequently creates a thrombogenic surface, with subsequent mural thrombosis that may lead to acute complications and possibly stimulates the development of restenosis. Whether coumarins can prevent these complications is unclear. The objective of this open, randomized trial was to assess the clinical effect of coumarins started before coronary angioplasty and continued for 6 months.

Methods and Results—Before coronary angioplasty, 530 patients were randomly assigned to aspirin plus coumarins and 528 patients to aspirin alone. At the start of the angioplasty, the mean international normalized ratio was 2.7 ± 1.1; during follow-up, it was 3.0 ± 1.1. At 30 days, the composite end point of death, myocardial infarction, target-lesion revascularization, and stroke was observed in 18 patients (3.4%) treated with aspirin plus coumarin compared with 34 patients (6.4%) treated with aspirin alone (relative risk, 0.53; 95% CI, 0.30 to 0.92). At 1 year, these figures were 14.3% and 20.3%, respectively (relative risk, 0.71; 95% CI, 0.54 to 0.93). The incidence of major bleeding and false aneurysm during hospitalization was 3.2% and 1.0%, respectively (relative risk, 3.39; 95% CI, 1.26 to 9.11). The benefit of coumarins was observed in both stented and nonstented patients.

Conclusions—Coumarins in addition to aspirin started before PTCA and continued for 6 months was more effective than aspirin alone in the prevention of acute and late complications after coronary angioplasty. This benefit was accompanied by a small but significant increase in bleeding complications. (Circulation. 2000;102:386-391.)

Key Words: angioplasty • warfarin sodium • anticoagulants

Percutaneous transluminal coronary angioplasty (PTCA) has 2 major drawbacks: acute vessel closure and restenosis. PTCA damages the vessel wall, creating a thrombogenic surface. The subsequent formation of a mural thrombus plays a pivotal role in acute occlusion and possibly also in late restenosis after PTCA. The routinely used combination of heparin and aspirin reduces the formation of mural thrombi during angioplasty but is unable to abolish it completely. Thus, additional suppression of the thrombotic process could improve prognosis.

Oral anticoagulant therapy reduces the risk for recurrent ischemic events after myocardial infarction and after unstable angina. This suggests that coumarins can inhibit the formation of an occlusive thrombus at a thrombogenic surface. To reduce thrombotic complications during PTCA and possibly restenosis, it is probably mandatory that the level of anticoagulation already be adequate at the start of the procedure. Therefore, the oral anticoagulant treatment should be started well before PTCA.

To test this hypothesis, we conducted a randomized trial to assess the effect of coumarins started before PTCA and continued for 6 months on the early and 1-year outcome: the Balloon Angioplasty and Anticoagulation Study (BAAS).

Methods

Patients

Patients with symptomatic coronary artery disease planning to undergo PTCA were eligible. Exclusion criteria were acute myocardial infarction within 24 hours before PTCA, current use of oral anticoagulants, contraindications to coumarins or aspirin, target lesion in a bypass graft, and unwillingness or inability to provide written informed consent to participate in the trial. The study was conducted according to the principles of the Declaration of Helsinki and was approved by our institutional ethics committee.
Randomization
Patients were randomized by an independent telephone service to aspirin alone (ASA group) or to aspirin plus open coumarin treatment (coumarin group). The aim was to randomize patients with stable angina at least 1 week before PTCA and patients with unstable angina ≥1 day before PTCA.

Medication
Coumarins were started before PTCA and continued for 6 months. The target prothrombin time was 2.1 to 4.8 international normalized ratio (INR) at the start of the procedure and during follow-up. This target range was based on the results obtained in other trials. All patients were given aspirin (loading dose, 300 mg, then 100 mg/d) ≥24 hours before PTCA. Heparin was used only during PTCA: 10 000 U immediately before and 5000 U every hour during the procedure. Ticlopidine became available in the Netherlands during the trial period. Since then, when a stent was placed, it was left to the discretion of the operator to start ticlopidine (loading dose, 500 mg, followed by 250 mg twice a day for 4 weeks). When ticlopidine was given to patients randomized to coumarins, the oral anticoagulants were discontinued.

Procedure
Patients with unstable angina were “cooled off” with aspirin and heparin, whenever possible, before PTCA. The aim was to obtain an INR in the target range before the procedure, but this was not a prerequisite to performance of PTCA. All patients had a femoral approach. A policy of provisional stenting was used. Arterial sheath removal was identical for the 2 groups: on the same day if the PTCA was performed in the morning and the next morning if the PTCA was performed in the afternoon. Routine assessment of the intensity of anticoagulation before sheath removal was not performed. Graft compression was done with a mechanical device for at least 1 hour and with a pressure bandage during bed rest for 12 hours.

Definitions and End Points
A residual stenosis <30% was considered an angiographic success. The primary end point was the composite of death, myocardial infarction, target-lesion revascularization, and stroke at 1 year. Acute myocardial infarction was defined as prolonged chest pain with new Q waves of ≥0.04 second in ≥2 contiguous leads or a new left bundle-branch block, or a rise in creatine phosphokinase (CPK) to ≥3 times the normal upper limit after the procedure or to ≥2 times during follow-up. The ECG and CPK were evaluated before and immediately after PTCA as well as the next day. Stent occlusion was defined as an angiographic success. Reintervention was based on both angiographic restenosis and recurrent chest pain with ECG or scintigraphic evidence of ischemia. Strokes were based on imaging as well as neurological evaluation and classified as ischemic or hemorrhagic. In the absence of imaging, stroke was classified as hemorrhagic.

The primary safety end point comprised major bleeding (defined as leading to hospitalization and/or death), blood transfusion or surgical intervention, and vascular groin complications. Minor bleeding was defined as leading to discontinuation of the study medication without hospitalization. Duplex ultrasonography of the groin was performed when a hematoma developed or when a false aneurysm or fistula was suspected.

Events were reviewed at regular intervals by a safety committee, which was blinded to the patients’ study medication.

Follow-Up
All patients were seen in outpatient clinics and contacted by telephone. Patients with coumarin treatment were referred to a regional thrombosis service for INR monitoring.

Time Spent in INR Categories
For each patient, the time spent in 4 predefined INR categories (≤2.1, 2.1 to 4.8, >4.8, and “missing”) was estimated until discontinuation of coumarins or until an event occurred. The numbers of days spent in these INR categories were estimated by the linear interpolation method.

Power Calculation
Assuming a rate of clinical end points in the control group of 30%, a reduction to 25% by the use of coumarins, and values of α=0.05 and β=0.8, almost 500 patients per group were required. Because we anticipated 5% of participants to have an unsuccessful PTCA or incomplete follow-up, a required total of 530 patients per group was calculated.

Statistical Analysis
The analysis was by intention to treat. The 2 groups were compared by Student’s t test for continuous variables and the χ² test, or when appropriate, Fisher’s exact test for discrete variables. Discrete variables were compared in terms of relative risks with 95% CIs. Event-free survival was calculated by the Kaplan-Meier method. Differences in survival times were assessed by the log-rank test. A value of P<0.05 was considered significant.

Results

Patient Population
From March 1996 to November 1997, a total of 1354 eligible patients were referred for PTCA. Of these, 253 patients with “Benestent-I–like indications” were included in other trials. Twenty-two patients refused to participate. Twenty-one randomized patients (9 ASA and 12 coumarins) were excluded from analysis for the following reasons: regression of the target lesion to <50% of the luminal diameter (9 patients),
TABLE 2. Angiographic Characteristics of the Treated Lesions

<table>
<thead>
<tr>
<th></th>
<th>ASA Group (n=751)</th>
<th>Coumarin Group (n=778)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target vessel, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>45.3</td>
<td>47.8</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>23.0</td>
<td>22.0</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>31.6</td>
<td>29.9</td>
</tr>
<tr>
<td>Left main coronary artery</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Restenotic lesion, %</strong></td>
<td>4.5</td>
<td>7.3</td>
</tr>
<tr>
<td><strong>Ostial location of lesion, %</strong></td>
<td>14.8</td>
<td>14.8</td>
</tr>
<tr>
<td><strong>Bifurcated lesion, %</strong></td>
<td>8.8</td>
<td>8.0</td>
</tr>
<tr>
<td><strong>Moderate or severe calcification, %</strong></td>
<td>22.9</td>
<td>24.2</td>
</tr>
<tr>
<td><strong>Angulation &gt;45°, %</strong></td>
<td>21.3</td>
<td>21.1</td>
</tr>
<tr>
<td><strong>Eccentric lesion, %</strong></td>
<td>66.9</td>
<td>68.5</td>
</tr>
<tr>
<td><strong>Occluded lesion, %</strong></td>
<td>5.3</td>
<td>7.2</td>
</tr>
<tr>
<td><strong>Lesion length, mm</strong></td>
<td>11.7±6.3</td>
<td>12±6.2</td>
</tr>
<tr>
<td>&gt;10 mm, %</td>
<td>64.0</td>
<td>58.1</td>
</tr>
<tr>
<td><strong>Stenosis, % of luminal diameter</strong></td>
<td>80.5±12.4</td>
<td>79.6±12.5</td>
</tr>
<tr>
<td><strong>Balloon size, mm</strong></td>
<td>3.06±0.45</td>
<td>3.05±0.45</td>
</tr>
<tr>
<td><strong>Maximal inflation pressure, atm</strong></td>
<td>12±3.3</td>
<td>12±3.4</td>
</tr>
<tr>
<td><strong>No. of lesions treated per patient</strong></td>
<td>1.4</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Continuous variables are mean±SD. P=NS for all comparisons.

TABLE 3. Clinical and Angiographic Characteristics of the Stented Patients

<table>
<thead>
<tr>
<th></th>
<th>ASA Group (n=188)</th>
<th>Coumarin Group (n=181)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>59.4±10.2</td>
<td>59.9±10.2</td>
</tr>
<tr>
<td><strong>Risk factors, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>9.5</td>
<td>8.8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21.8</td>
<td>23.8</td>
</tr>
<tr>
<td>Total cholesterol &gt;5 mmol/L</td>
<td>69.7</td>
<td>79.9</td>
</tr>
<tr>
<td>Smoking in preceding half year</td>
<td>34.6</td>
<td>33.7</td>
</tr>
<tr>
<td><strong>Previous myocardial infarction, %</strong></td>
<td>39.9</td>
<td>40.3</td>
</tr>
<tr>
<td><strong>Angina class III or IV (CCS), %</strong></td>
<td>68.1</td>
<td>71.9</td>
</tr>
<tr>
<td><strong>Ejection fraction &lt;50%, %</strong></td>
<td>19.7</td>
<td>16.6</td>
</tr>
<tr>
<td><strong>Total No. of stented lesions</strong></td>
<td>222</td>
<td>224</td>
</tr>
<tr>
<td>Left anterior descending, %</td>
<td>46.8</td>
<td>46.4</td>
</tr>
<tr>
<td><strong>Calcification, %</strong></td>
<td>19.8</td>
<td>26.3</td>
</tr>
<tr>
<td><strong>Angulation &gt;45°, %</strong></td>
<td>22.5</td>
<td>20.5</td>
</tr>
<tr>
<td><strong>Length, mm</strong></td>
<td>12.8±6.1</td>
<td>11.8±5.8</td>
</tr>
<tr>
<td><strong>Stenosis, % of luminal diameter</strong></td>
<td>80.5±12.9</td>
<td>79.5±11.5</td>
</tr>
<tr>
<td><strong>Balloon size, mm</strong></td>
<td>3.06±0.45</td>
<td>3.05±0.45</td>
</tr>
<tr>
<td><strong>Maximal inflation pressure, atm</strong></td>
<td>16±3.8</td>
<td>16±3.6</td>
</tr>
<tr>
<td><strong>Stents for dissection, %</strong></td>
<td>42.3</td>
<td>53.1</td>
</tr>
<tr>
<td><strong>Bail-out stenting, %</strong></td>
<td>26.1</td>
<td>22.8</td>
</tr>
<tr>
<td><strong>No. of stents per lesion</strong></td>
<td>1.12</td>
<td>1.08</td>
</tr>
<tr>
<td><strong>Total stent length, mm</strong></td>
<td>20.8±9.8</td>
<td>19.8±7.8</td>
</tr>
</tbody>
</table>

CCS indicates Canadian Cardiovascular Society classification. Continuous variables are mean±SD. P=NS for all comparisons.

preferred medical treatment (3), progression necessitating CABG (7), and aspirin allergy not known at the time of randomization (2). The clinical (Table 1) and angiographic (Table 2) baseline characteristics of the 2 groups were comparable. Approximately 25% of the patients were hospitalized before PTCA, and 12% had been admitted for unstable angina with ST-segment changes and were “cooled off” with aspirin and heparin before PTCA (Table 1).

In 34.4% of the patients, coumarins were started ≥1 week, in 83.5% >3 days, and in 4.5% only 1 day before the procedure. At the start of the angioplasty, the mean INR was 2.7±1.1. In 7 patients, the INR data were missing.

Procedural Outcomes

Stents were placed in 35.5% of the ASA and 34.1% of the coumarin patients. The baseline characteristics of the stented patients did not differ significantly in the 2 groups (Table 3), except for the use of ticlopidine. In 54% of the stented ASA patients, ticlopidine was added to the medication, and in 12% of the stented coumarin patients, the oral anticoagulants were substituted by ticlopidine. None of the patients received a platelet glycoprotein (GP) IIb/IIIa receptor blocker.

30-Day Outcome

The mean time interval from randomization to PTCA was 11.8 days in the coumarin group and 12.4 days in the ASA group (P=0.9). There were no adverse events before the initial PTCA. The angiographic success rate was 99% in both groups. In the coumarin group, 2 patients (0.4%) died: 1 of procedure-related myocardial infarction and 1 of hemorrhagic stroke. In the ASA group, 3 patients (0.6%) died: 1 of multiorgan failure caused by cholesterol emboli, 1 of procedure-related myocardial infarction despite urgent CABG, and 1 of pneumonia. Overall, a primary end point was observed in 18 patients (3.4%) in the coumarin group and in 34 patients (6.4%) in the ASA group (relative risk, 0.53; 95% CI, 0.30 to 0.92) (Table 4).

Coumarins also decreased the incidence of primary end points in the patients who received a stent: 12 (6.6%) in the coumarin group and 24 (12.8%) in the ASA group (relative risk, 0.52; 95% CI, 0.27 to 1.01). In both groups, 6 subacute stent occlusions occurred (3.2%), all resulting in a myocardial infarction.

Overall, the incidence of major bleeding and vascular groin complication was low (Table 4). In the coumarin group, there were 7 major bleedings (1.3%) and 10 false aneurysms (1.9%); in the ASA group, there was 1 major bleeding (0.2%) and 4 false aneurysms (0.8%). None of these bleedings were fatal, and 6 were located in the groin. Eleven false aneurysms were closed by ultrasound-guided compression or insertion of collagen, and only 2 patients needed surgical correction.

The mean hospital stay was 2.4±2.6 days (range, 1 to 28 days) in the coumarin group versus 2.2±2.5 days (range, 1 to 34 days) in the ASA group (P=0.3).

30- to 365-Day Outcome

Follow-up was 100% complete. During follow-up, the mean INR was 3.0±1.1 in the coumarin group: 82% of the time, the INR values were within, 11% of the time below, and 4% of the time above the target range. INR data were missing 3% of the time.
In the coumarin group, there were 4 late deaths: 1 due to hemorrhagic stroke and 3 sudden deaths. In the ASA group, the 3 late deaths were due to hemorrhagic strokes. There were no late myocardial infarctions, and 1 coumarin patient had a nonfatal ischemic stroke. Target-lesion revascularization occurred less often in the coumarin group: 56 (10.6%) versus 75 (14.3%) in the ASA group (relative risk, 0.74; 95% CI, 0.54 to 1.03) (Table 4).

For stented patients, the late outcome was similar in the 2 groups: target-lesion revascularization occurred in 11.2% in the coumarin and in 12.4% in the ASA group and any event in 12.4% and 13.0%, respectively.

After discharge, 5 coumarin patients (0.9%) suffered a major gastrointestinal bleeding versus none of the ASA patients (P = 0.062).

### All Events at 1 Year
At 1-year follow-up, the primary end point occurred significantly less often in the coumarin group than in the ASA group (Table 4). The Kaplan-Meier curve showed a 1-year event-free survival of 86% in the coumarin group versus 80% in the ASA group (P = 0.01) (Figure).

### Unstable Angina
In the coumarin group, there were 62 patients with unstable angina (11.7%). Coumarins were started only 3.3 ± 2.8 days (median, 3 days; range, 1 to 15 days) before PTCA. The mean INR in this unstable group was lower than in the patients with stable angina: 2.4 ± 0.9 versus 2.7 ± 1.1 (P = 0.05), respectively. Coumarins did not improve outcome in the subgroup of patients with unstable angina: the 1-year event-free sur-
vival in the unstable coumarin patients was 73%, compared with 74% in the aspirin patients (P=0.9).

**Discussion**

This trial is the first to study the effect of coumarin pretreatment on clinical outcome after PTCA. Coumarins in addition to routine aspirin reduced the incidence of procedure-related complications as well as late target-lesion revascularization by almost 30%.

**Previous Studies**

Until now, only 2 small studies had been conducted in the early years of PTCA, which concluded that oral anticoagulants were not more effective than aspirin after PTCA. These trials, however, were hampered by serious shortcomings. Thornton and colleagues randomized 248 patients after successful PTCA to aspirin or coumarins. The coumarins was used regularly in only 74% of the patients, and an adequate prothrombin time was achieved in only 35% of the patients. Unfortunately, clinical events were not reported. Another study by Urban and colleagues included only 110 patients, also excluding patients with a complicated procedure, and no information on the level of anticoagulation obtained was given. In our opinion, these small numbers of patients with inadequate anticoagulation do not allow proper judgment of the role of coumarins in angioplasty. Moreover, these 2 studies lack the essential timing of anticoagulation in relation to PTCA, because a preventive effect can be anticipated only if coumarins are started before angioplasty, thus before vessel wall injury and mural thrombosis can lead to acute complication and restenosis.

**Provisional Stenting**

Our study showed that coumarins pretreatment was also beneficial for patients who received a stent. Our stent occlusion rate, which was similar in the 2 groups, was higher than reported in recent randomized trials. However, one has to realize that in our study, patients received a stent because of complications during the procedure and that patients with suboptimal stenting were included in the analysis. The lower stent occlusion rates reported in the literature come primarily from trials that compared different antithrombotic regimens after optimal stent placement, excluding patients with suboptimal results. Nevertheless, these randomized trials showed that the combination of aspirin and ticlopidine was superior to aspirin and oral anticoagulants in preventing stent occlusion. Again, in these trials, coumarins were started after stenting. Our results suggest that pretreatment with coumarins could be useful in preventing thrombotic complications during the first days after stenting, awaiting the delayed onset of action of ticlopidine. This observation is corroborated by the fact that the coumarin group did better despite significantly less frequent use of ticlopidine. However, our results do not suggest that coumarins reduce in-stent restenosis.

**Suboptimal Anticoagulation**

Our data indicate that coumarins are effective only when a stable level of anticoagulation is obtained before the procedure. Coumarins did not improve outcome in the small group of patients in whom it was started shortly before PTCA. In this situation, a platelet GP IIb/IIIa receptor blocker is probably a better option.

**Platelet GP IIb/IIIa Receptor Blockers**

An important question concerns the relevance of coumarin treatment in the present era, when many patients are treated with platelet GP IIb/IIIa receptor blockers. In our hospital, as in many other Western hospitals, the widespread use of these drugs is hampered by cost. Our study shows good results without the use of platelet GP IIb/IIIa receptor blockers. Furthermore, coumarin treatment is a relatively inexpensive means to reduce thrombotic complications. The cost of 6 months of coumarin treatment in the Netherlands, including INR monitoring, is close to $150 per patient.
Bleeding
The reduction of thrombotic complications by coumarins was offset by a small increase in bleeding during hospitalization. Our bleeding rate, however, was far lower than in previous trials that studied coumarins as antithrombotics after stenting.18-21 The higher bleeding rate in these trials may have been caused by heparin, which was continued for several days after stenting, awaiting stable anticoagulation with coumarins.18-21 In our study, coumarin pretreatment obviated the need for postangioplasty heparin. During follow-up, we noted a small increase in major extracranial bleeding and a substantial increase in minor bleeding in the coumarin group. Importantly, however, none of the bleedings were fatal, and most were procedure-related and could be treated by transfusion or nonsurgical interventions without a significant increase in the mean hospital stay.

Study Limitations
During the trial period, ticlopidine became available in the Netherlands, which led to differences in antithrombotic treatment after stenting. However, we do not think that this difference has essentially influenced the study results. The better results in the coumarin group cannot be due to the use of ticlopidine, because only 12% of the stented coumarin patients were treated with ticlopidine versus 54% of the stented ASA patients. Moreover, there were no statistically significant differences in the stented study groups (Table 3).

Conclusions
Coumarin pretreatment in addition to aspirin and continued for 6 months was more effective than aspirin alone in the prevention of acute and late complications after coronary angioplasty, at the expense of a small increase in bleeding complications.

Acknowledgments
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