Oral Anticoagulant Therapy During and After Coronary Angioplasty

The Intensity and Duration of Anticoagulation Are Essential to Reduce Thrombotic Complications

Jurriën M. ten Berg, MD; Barbara A. Hutten, Msc; Johannes C. Kelder, MD; Freek W.A. Verheugt, MD, PhD; H.W. Thijs Plokker, MD, PhD

Background—In the randomized Balloon Angioplasty and Anticoagulation Study (BAAS), the addition of oral anticoagulants to aspirin significantly reduced early and late events after coronary angioplasty. However, bleeding episodes were increased. The present report studied the intensity and the duration of anticoagulation as predictors of thrombotic and bleeding events.

Methods and Results—A total of 530 patients, 34% of whom received a stent, were treated with aspirin plus coumarins. Half of the patients were randomized to angiographic follow-up. The target international normalized ratio (INR) was 2.1 to 4.8 during angioplasty and 6-month follow-up. Thrombotic events were death, myocardial infarction, target lesion revascularization, and thrombotic stroke. Bleeding complications were hemorrhagic stroke, major extracranial bleeding, and false aneurysm. “Optimal” anticoagulation was defined as an INR in the target range for at least 70% of the follow-up time. There were 17 early thrombotic events (3.2%), 7 early bleeding episodes (1.3%), and 10 false aneurysms (1.9%). The incidence rate for both early thrombotic and bleeding events was lowest in patients in the target range. A total of 61 late thrombotic events occurred (11.6%). Optimal anticoagulation was an independent predictor of late thrombotic events (relative risk, 0.33; 95% CI, 0.19 to 0.57) and was associated with a 0.21 mm (95% CI, 0.17 to 0.42) larger vessel lumen at 6 months. Late bleeding episodes (1.4%) were lowest in patients in the target range.

Conclusions—Coumarins started before coronary angioplasty with a target INR of 2.1 to 4.8 led to the lowest procedural event rate, without an increase in bleeding episodes. During follow-up, optimal anticoagulation was associated with a decrease in the incidence of late events by 67% and a significant improvement in 6-month angiographic outcome. (Circulation. 2001;103:2042-2047.)

Key Words: angioplasty ■ coumarins ■ thrombosis ■ complications ■ restenosis

The results of percutaneous transluminal coronary angioplasty (PTCA) are hampered by the occurrence of acute vessel closure1 and restenosis.2 Mural thrombosis plays a causal role in the development of acute occlusions and possibly in restenosis.3–5 Mural thrombosis is only partly prevented by the routinely used combination of heparin and aspirin.6 Therefore, more powerful anticoagulants were tested. Two multicenter trials showed a significant reduction of early events after PTCA by direct antithrombins (hirudin and hirulog), but no effect on angiographic restenosis.6,7 The platelet glycoprotein IIb/IIIa receptor blockers also reduced early complications after PTCA, but again they had no effect on angiographic restenosis, although in the Evaluation of C7E3 (abciximab) in the Prevention of Ischemic Complications (EPIC) trial, clinical restenosis was reduced.8,9

In the prospective Balloon Angioplasty and Anticoagulation Study (BAAS), we were the first to study the effect of coumarins started before PTCA in addition to routine aspirin on early and late events.10 Coumarin therapy was started before PTCA to obtain an adequate level of anticoagulation during the procedure, and coumarins were continued for the 6 months after the procedure, in which restenosis takes place. This anticoagulation regimen reduced early and late (thrombotic) complications at the expense of a small increase in bleeding complications. In the present report, we studied the intensity and duration of anticoagulation as predictors of thrombotic and bleeding events. Furthermore, the relation between optimal anticoagulation and angiographic restenosis was evaluated.

Methods

Patients
The study population consisted of the patients who were prospectively randomized to the use of coumarins as part of the BAAS, which has been described previously.11
Medication
Aspirin (loading dose, 300 mg; then 100 mg/d) and coumarins (acenocoumarol or Syntron at 6 mg on the first day, 4 mg on the second, 2 mg on the third and thereafter until intervention) were started 1 week before intervention. The international normalized ratio (INR) was measured on the morning before PTCA and daily thereafter until discharge. The target INR was prespecified at 2.1 to 4.8 during the procedure and during follow-up. However, it was not a prerequisite to perform PTCA. Heparin was administered as a single bolus of 10 000 U immediately before the procedure. After discharge, coumarins were continued for at least 6 months or until an event occurred, and dosing was done by one of the regional Thrombosis Services. During the trial period, ticlopidine became available in the Netherlands. Once it became available, it was left to the discretion of the operator to start ticlopidine after stenting (loading dose, 500 mg; then 250 mg twice daily for 4 weeks) or to continue coumarins. There was a 1:1 randomization to angiographic follow-up. Patients were followed for 12 months.

Definitions of Events and Angiographic Outcome
Death comprised all deaths, regardless of the cause. Myocardial infarction was defined previously.13 ECG and creatine kinase were evaluated before and immediately after PTCA and on the day after PTCA. Reintervention was based on both restenosis and evidence of ischemia. A stroke was based on imaging and on neurological evaluation, and it was classified as ischemic or hemorrhagic. In the absence of imaging, stroke was classified as hemorrhagic. Major bleeding was defined as acute bleeding leading to hospitalization and/or death, blood transfusion, or surgical intervention. A false aneurysm was diagnosed by duplex sonography. The primary angiographic end point was the minimal luminal diameter (MLD) of each dilated segment at follow-up. Total occlusion was imputed as MLD = 0 mm.

Events were classified as early (day 0 to 14 after PTCA) or late (day 14 to 365). A safety committee reviewed adverse events at regular intervals.

Optimal Anticoagulation
“Optimal” anticoagulation was defined as an INR in the target range for >70% of the follow-up time.

Estimation of Time Spent in Different 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 1 year after PTCA. The number of days spent in these INR categories was estimated using the linear interpolation method.14 This method assumes that the INR value between 2 consecutive measurements varies linearly. If the time between 2 consecutive measurements exceeds 28 days, the INR is considered not predictable for the middle part of this interval.

Calculation of Early Event Rate
The thrombotic and bleeding events were allocated to a particular INR category by the value of the last INR on the day of the event. The incidence rates of both thrombotic and bleeding events were calculated as the total number of events in a particular INR range divided by the number of patient-years spent in that INR range.14

Statistical Procedures and Calculation of Risk Factors for Late Thrombotic Events and Angiographic Outcome
A univariate analysis was performed for the association of optimal anticoagulation and the occurrence of thrombotic events. Subsequently, a multivariate logistic regression analysis was used to control this association for preselected covariates, including age, sex, hypertension, diabetes mellitus, smoking, unstable angina before PTCA, ejection fraction <50%, left anterior descending lesion, total occlusion, length of the lesion, and randomization to follow-up angiography. The significance of a linear trend for the time spent in the INR target range and the occurrence of late thrombotic events was also determined.

The association of optimal anticoagulation and the MLD at follow-up was studied by univariate analysis using Student’s t test and by multivariate analysis using linear regression. Patients who were not randomized to follow-up angiography were excluded from this analysis.

Results
Patients
From March 1996 through November 1997, a total of 530 patients were randomized to the use of coumarins (Table 1). Coumarins were started a median of 6 days (range, 4 to 9) before PTCA. A total of 242 stents were placed in 181 patients (34.1%). In 21 of these stented patients (12%), the oral anticoagulants were substituted by ticlopidine. Follow-up angiography was performed in 239 patients, and the quantitative angiographic analysis was based on 297 lesions.

<table>
<thead>
<tr>
<th>Risk factors, n (%)</th>
<th>530</th>
<th>400 (75.5)</th>
<th>400 (75.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>51</td>
<td>9.6</td>
<td>9.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>106</td>
<td>20.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>405</td>
<td>76.4</td>
<td>76.4</td>
</tr>
<tr>
<td>Cholesterol-lowering therapy</td>
<td>156</td>
<td>29.5</td>
<td>29.5</td>
</tr>
<tr>
<td>Smoking in preceding 6 mo</td>
<td>163</td>
<td>30.8</td>
<td>30.8</td>
</tr>
</tbody>
</table>

### TABLE 1. Characteristics of the Patients and the Lesions

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>530</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60.3±9.8</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>400 (75.5)</td>
</tr>
<tr>
<td>Risk factors</td>
<td>51</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9.6</td>
</tr>
<tr>
<td>Hypertension</td>
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</tr>
<tr>
<td>Smoking in preceding 6 mo</td>
<td>30.8</td>
</tr>
</tbody>
</table>

### References

1. Canadian Cardiovascular Society classification was used.
2. Values are mean±SD or n (%).
3. *Values are mean±SD, median (interquartile range).
4. Values are mean±SD or n (%).
5. *Canadian Cardiovascular Society classification was used.
6. †Values are mean±SD, median (interquartile range).
7. †Values are mean±SD, median (interquartile range).
8. †Values are mean±SD, median (interquartile range).
9. †Values are mean±SD, median (interquartile range).
10. †Values are mean±SD, median (interquartile range).
11. †Values are mean±SD, median (interquartile range).
12. †Values are mean±SD, median (interquartile range).
13. †Values are mean±SD, median (interquartile range).
14. †Values are mean±SD, median (interquartile range).
Early INR Values
The time spent in the 4 predefined INR categories during the first 14 days after PTCA or until an event occurred are depicted in Table 2. The patients spent 62.2% of the time in the target range.

Early Thrombotic Events and INR-Specific Incidence Rates
No adverse events occurred before PTCA, and coumarins were not discontinued before intervention in any patient. No significant differences at baseline were found between the groups of patients in different INR categories. A total of 17 patients (3.2%) suffered from an early thrombotic event. Most events were early reinterventions and procedure-related myocardial infarctions, of which one was fatal (Table 3). In one patient, an event occurred but the INR value was erroneously not measured before the procedure. Thus, the INR-specific incidence rates were calculated using 94% of the events. The incidence rate was lowest in patients in the target range, with 57 complications per 100 patient-years (Figure 1). The patients spent 82.1% of their follow-up time in the target range.

Early Bleeding Complications
In 6 patients, excess site bleeding occurred, and in one patient, gastrointestinal bleeding occurred (1.3%). Ten patients (1.9%) developed a false aneurysm (Table 3). All bleeding episodes occurred within 36 hours from intervention, and none was fatal. The early complication rate was lowest in patients in the target range, with 57 complications per 100 patient-years (Figure 1).

Late INR Values
During follow-up, the mean number of INR measurements per patient was 13.4 ± 4.7. In 42 patients, no INR values were available during follow-up (Table 4). The percentage of time spent in the INR categories during follow-up for the remaining 488 patients is depicted in Table 2. The patients spent 82.1% of their follow-up time in the target range.

Predictors of Late Thrombotic Events
There were no significant differences at baseline between the patients with optimal anticoagulation and those with “suboptimal” anticoagulation during follow-up. After day 14, a total of 61 thrombotic events (11.6%) occurred, mostly target lesion revascularizations. Three patients died suddenly (Table 3). In the 44 patients in whom no INR values were available, 3 events occurred. Thus, the analysis was based on 95% of the events.

By univariate analysis, optimal anticoagulation was associated with a reduced event rate (relative risk [RR], 0.39; 95% CI, 0.25 to 0.61), and unstable angina before PTCA was associated with an increased event rate (RR, 1.96; 95% CI, 1.13 to 3.40).

By multivariate analysis, optimal anticoagulation was associated with a lower event rate (RR, 0.33; 95% CI, 0.19 to 0.57), and this effect was present for both stented (RR, 0.20; 95% CI, 0.10 to 0.40) and nonstented patients (RR, 0.37; 95% CI, 0.20 to 0.69). Furthermore, there was a significant linear trend for optimal anticoagulation and events: for every 10% of the time spent in the target range, the risk was reduced by 21% (P = 0.0001). Unstable angina was associated with an increased event rate (RR, 2.20; 95% CI, 1.09 to 4.44).

Predictors of Angiographic Outcome
The patients with optimal anticoagulation had a more favorable angiographic outcome than those with suboptimal anticoagulation. The MLD at follow-up was significantly larger in these patients (1.81 ± 0.66 versus 1.57 ± 0.72 mm; P = 0.01; Figure 2), the late loss was smaller (0.53 ± 0.65 versus 0.73 ± 0.65 mm; P = 0.049), the net gain was larger (0.79 ± 0.69 versus 0.64 ± 0.70 mm; P = 0.15), and the diameter stenosis at follow-up was smaller (38 ± 18% versus 45 ± 22%; P = 0.02) when compared with patients with suboptimal anticoagulation.

By univariate analysis, several factors were associated with the MLD at follow-up (Table 5). Optimal anticoagulation led to a 0.24 mm (95% CI, 0.04 to 0.44) larger MLD at 6 months.

By multivariate analysis, 3 factors were independently associated with the MLD at follow-up (Table 5). Optimal anticoagulation led to a 0.21 mm (95% CI, 0.05 to 0.38) larger MLD. This effect was present both in stented (0.15 mm; 95% CI, −0.15 to 0.45) and nonstented lesions (0.22 mm; 95% CI, 0.02 to 0.42 mm).
Late Acute Bleeding Complications
Two patients suffered a fatal hemorrhagic stroke (0.4%). A 54-year-old man without concomitant disease who had INR values in the target range developed a cerebellar hematoma on day 109 (INR 2.9) and was operated on but died on day 250. A 75-year-old woman with hypertension and diabetes mellitus had INR values above the target range for 2 days after PTCA but was discharged with INR values in the target range. She was readmitted with the clinical signs of a stroke at the referring hospital on day 17 and died immediately, having an INR of 7.0. One patient had a nonfatal hemorrhagic stroke (0.2%) and recovered completely. This was a 71-year-old man without concomitant disease who had INR values in the target range and who developed an occipital hematoma on day 196, after having discontinued coumarins 41 days previously. Five patients (0.9%) suffered late major extracranial bleeding. For one patient with major bleeding, the INR category could not be calculated. The incidence rate for major bleeding episodes was lowest in patients in the target range, with 2.4 complications per 100 patient-years. Below the target range, 10 bleeding complications per 100 patient-years occurred, and above the range, 13 bleeding complications per 100 patient-years occurred.

**TABLE 4. Reasons for Absence of INR Values During Follow-up**

<table>
<thead>
<tr>
<th>Reason</th>
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</tr>
</thead>
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<td>PTCA failed</td>
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</tr>
<tr>
<td>Ticlopidine treatment after stenting</td>
<td>21</td>
</tr>
<tr>
<td>No coumarins prescribed at discharge</td>
<td>1</td>
</tr>
<tr>
<td>Primary end point before day 14</td>
<td>5</td>
</tr>
<tr>
<td>Primary safety end point before day 14</td>
<td>5</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>5</td>
</tr>
<tr>
<td>Emigration</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal surgery</td>
<td>1</td>
</tr>
</tbody>
</table>

Ticlopidine Use
Ticlopidine became available halfway through the study period. Coumarin pretreatment showed a similar reduction of events in the year before ticlopidine became available (1996) compared with the year when ticlopidine was used (1997).

**Discussion**
In BAAS, coumarins started before PTCA in addition to routine aspirin reduced the occurrence of cardiac events by 30% during the first year of follow-up. In the present study, we obtained evidence that the intensity, as well as the duration, of anticoagulation was essential to obtain this beneficial effect. An INR in the target range during PTCA led to the lowest incidence of procedural events without increasing bleeding episodes. There were more bleeding episodes in patients with an INR below the target range than in patients with an INR in the range, suggesting that procedural bleeding episodes are not primarily related to the level of anticoagulation but are due to suboptimal puncture and sheath removal techniques. With respect to late events, the patients with an INR in the target range for at least 70% of the follow-up time had a 67% risk reduction and their vessel lumens were significantly larger at 6 months.

Thrombosis plays an essential role in the development of abrupt vessel closure, and thrombin is a key factor in this process. This was unequivocally demonstrated in 2 clinical trials in which thrombin inactivation by r-hirudin and Hirulog led to a significant reduction of early complications. In the BAAS trial, coumarins were also shown to reduce thrombotic complications, especially when the INR was in the target range. This result confirms our hypothesis that coumarins should be started before intervention to avoid paradoxical early prothrombotic effects from suppression of proteins C and S before inhibiting factors II, VII, IX, and X.

Thrombosis may also play a role in the restenosis process. However, the use of antithrombotics such as r-hirudin or Hirulog has not been shown to reduce the
restenosis rate. This lack of effect on restenosis may be due to the fact that hirudin is not an inhibitor of thrombin production. Therefore, soon after cessation of r-hirudin or Hirulog, thrombin activity is anticipated. Another reason may be the duration of anticoagulation. There is evidence in animal studies and in humans that after plaque rupture, activation of the coagulation mechanism persists for a very long time. Furthermore, some experimental data showed that longer anticoagulation leads to less restenosis. In the BAAS trial, coumarins reduced the late event rate after PTCA; this was primarily due to a reduction of target lesion reinterventions. In this study, the coumarins were not only started before the procedure to obtain adequate anticoagulation during PTCA, but the level of anticoagulation was also well controlled during the 3 to 6 months after the procedure when restenosis takes place. The multivariate analysis performed in the present study showed that if an adequate level of anticoagulation can be obtained for at least 70% of the follow-up time, angiographic restenosis is reduced. These results suggest that thrombosis indeed plays a role in the restenosis process.

Until now, few trials have studied the effect of oral anticoagulant therapy on late restenosis after PTCA in humans. Clinical restenosis was studied in 2 small studies in the early years of PTCA. It was concluded that oral anticoagulants were not more effective than aspirin as adjunctive treatment after PTCA, but there are essential shortcomings in these studies: Coumadin was started after PTCA and an acceptable level of anticoagulation was obtained in only a minority of the patients during follow-up. The other report was an angiographic follow-up study. Kastrati and colleagues studied the effect of antiplatelet therapy versus oral anticoagulants on restenosis in a total of 432 patients who were all stented. There was no difference in restenosis between the antiplatelet group and the oral anticoagulation group. However, again, the oral anticoagulation was only started after stenting, with overlapping heparin until a stable level of anticoagulation was reached. Our results suggest that stable anticoagulation with coumarins is more effective than unfractionated, intravenous heparin.

Finally, is there any evidence in the literature for an optimal level of anticoagulation during and after PTCA? Our trial is the only study that used coumarin pretreatment with an adequate level of anticoagulation during and after the procedure. The target INR of 2.1 to 4.8 was reached in a high percentage of the patients and led to the lowest incidence of thrombotic events without increasing the risk of bleeding. Further evidence to support a higher level of anticoagulation (INR >2.0) comes from trials that studied the effect of oral anticoagulants that were started after myocardial infarction or

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**TABLE 5. Predictors of 6-Month Angiographic Outcome**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MLD, mm</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate analysis</td>
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<td></td>
</tr>
<tr>
<td>Reference diameter per mm</td>
<td>0.64</td>
<td>0.52 to 0.76</td>
<td>0.0001</td>
</tr>
<tr>
<td>MLD after dilatation per mm</td>
<td>0.56</td>
<td>0.43 to 0.68</td>
<td>0.0001</td>
</tr>
<tr>
<td>Stent</td>
<td>0.17</td>
<td>0.00 to 0.33</td>
<td>0.049</td>
</tr>
<tr>
<td>Optimal anticoagulation</td>
<td>0.24</td>
<td>0.04 to 0.44</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes</td>
<td>−0.41</td>
<td>−0.67 to −0.15</td>
<td>0.008</td>
</tr>
<tr>
<td>Multivariate analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference diameter per mm</td>
<td>0.47</td>
<td>0.35 to 0.59</td>
<td>0.0001</td>
</tr>
<tr>
<td>MLD after dilatation per mm</td>
<td>0.30</td>
<td>0.17 to 0.42</td>
<td>0.0001</td>
</tr>
<tr>
<td>Optimal anticoagulation</td>
<td>0.21</td>
<td>0.05 to 0.38</td>
<td>0.01</td>
</tr>
</tbody>
</table>

MLD indicates change in minimal luminal diameter at follow-up.
unstable angina. In these trials, an INR value >2.0 led to a reduction of events, whereas lower levels of anticoagulation (INR ≤2.0) did not show any effect.21–23 The largest randomized trial of this issue, which studied 3400 hospital survivors of myocardial infarction, calculated the optimal INR to be between 3.0 and 4.0.24

Recently, clopidogrel has become standard therapy for patients after stenting due to its rapid onset of action and strong antithrombotic effect.25 The combination of clopidogrel and pretreatment with oral anticoagulant therapy might reduce procedure-related complications even further, but we do not think clopidogrel would reduce restenosis, because Kastrati et al20 showed no effect with the use of ticlopidine. In BAAS, patients were not randomized to undergo stenting or balloon angioplasty only, but stents were placed for bailout situations and suboptimal results. This policy of provisional stenting makes a further subdivision of the effect of coumarins and/or ticlopidine on stented and nonstented patients difficult because stents and ticlopidine were given for procedural and thrombotic complications, which makes the balloon and stent group dissimilar from the start of the follow-up.

Conclusions
The present study showed that coumarins started before PTCA with a target INR of 2.1 to 4.8 led to the lowest procedural event rate, without increasing bleeding episodes. During follow-up, optimal anticoagulation not only decreased the incidence of late thrombotic events by 67%, but also significantly improved 6-month angiographic outcome.

Acknowledgments
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References
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