Coagulation Activity and Clinical Outcome in Unstable Coronary Artery Disease

J. Oldgren, R. Linder, L. Grip, A. Siegbahn, L. Wallentin

Abstract—In the current study, we investigated molecular markers of coagulation activity, ie, prothrombin fragment 1+2 (F1+2), thrombin-antithrombin (TAT) complex, soluble fibrin (SF), and D-dimer, and their relation to death, myocardial infarction, and refractory angina during and after anticoagulant treatment in unstable coronary artery disease. Patients with unstable coronary artery disease (N=320) were randomized to a 72-hour infusion with either inogatran, a low-molecular-mass direct thrombin inhibitor, or unfractionated heparin. During the 30-day follow-up, a 40% lower event rate was seen in patients with high compared with low baseline levels of TAT or SF. High baseline levels of coagulation activity were correlated with a larger decrease during treatment. Patients with decreased compared with raised F1+2 or TAT levels after 6 hours of treatment had a 50% lower event rate at 30 days (F1+2, P=0.04; TAT, P=0.02). At the cessation of antithrombin treatment, there was a clustering of cardiac events that tended to be related to a rise in the levels of TAT and the other markers. During long-term follow-up (median, 29 months), there was a relation between higher baseline levels of D-dimer (P=0.003) and increased mortality. High baseline levels of molecular markers of coagulation activity might identify patients with a thrombotic condition (as the major cause of instability) who are good responders to anticoagulant therapy, with a larger decrease in coagulation activity during treatment and a decreased risk of ischemic events. However, this early benefit is lost during long-term follow-up when high baseline levels of coagulation activity are associated with a raised risk of early reactivation and increased mortality. (Arterioscler Thromb Vasc Biol. 2001;21:1059-1064.)

Key Words: unstable angina ■ myocardial infarction ■ coagulation ■ thrombin inhibition

Unstable coronary artery disease, ie, unstable angina or non–Q-wave myocardial infarction (MI), is commonly caused by rupture or fissure of an atherosclerotic plaque.1 The exposure of a thrombogenic surface in the ruptured plaque triggers platelet activation and thrombus formation. Activation of the coagulation system in the acute phase of unstable angina or acute MI has been demonstrated by elevated levels of molecular markers of thrombin generation, ie, prothrombin fragment 1+2 (F1+2) and thrombin-antithrombin (TAT) complex, and of thrombin activity, such as fibrinopeptide A (FPA) and soluble fibrin (SF).2–6 Elevated levels of D-dimer, a marker of fibrin turnover, have also been found in patients with unstable angina.4,5 However, there are rather limited data concerning the prognostic importance of elevated coagulation markers in patients with unstable coronary artery disease. Furthermore, possible relations between the effect of changes in coagulation markers induced by anticoagulant treatment and clinical outcome in unstable coronary artery disease remain to be elucidated.

The Thrombin Inhibition in Myocardial Ischemia (TRIM) study7 enrolled 1209 unstable coronary artery disease patients in 61 Scandinavian centers during 1994 and 1995. The patients were randomized to 3 different doses of inogatran, a low-molecular-mass direct thrombin inhibitor,8,9 or standard unfractionated heparin. We previously reported changes in the markers of coagulation activity during and after treatment with either unfractionated heparin or inogatran in a substudy comprising 320 patients.10 The prespecified aim of the present study was to assess the influence of antithrombin therapy on coagulation activity and its relation to manifestations of myocardial ischemia during and after such treatment.

Methods

Patients and Design

The substudy population consisted of 320 consecutive patients in 19 of the 61 participating centers of the TRIM study. Details of the TRIM study protocol and the main results have previously been reported.7 Eligible for inclusion were men and postmenopausal women between 25 and 80 years of age with unstable angina, defined as the new onset of ischemic chest pain or rapid deterioration in previously stable angina during the last 4 weeks, or suspicion of a non–Q-wave MI. This clinical diagnosis had to be supported by either changes in the resting electrocardiogram, eg, ST-segment depression or T-wave inversion, or previously known coronary artery disease.

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Molecular Markers of Coagulation Activity

Three 5-mL tubes of citrated blood were obtained for analyses of molecular coagulation markers at baseline before the start of treatment; during infusion at the 6-, 24-, and 72-hour time points; and 4 and 24 hours after cessation of treatment. Samples were preferably obtained by direct venipuncture. The first 2 mL of blood was disposed, and within 30 minutes the sample was centrifuged at 2000 g for 20 minutes. Aliquots (500 µL) of plasma collected in 12 Eppendorf tubes were frozen and stored at −70°C until analysis. ELISAs from Enzygnost (Behringwerke AG) were used for the determination of F1+2, TAT, and SF, with reference intervals for healthy individuals of 0.4 to 1.5 nmol/L and of 1.2 to 5.0 µg/L, respectively; intra-assay and interassay coefficients of variation were between 5% and 9%. An ELISA (TintElize D-dimer, Biopool) was also used for analysis of D-dimer, with a reference range of 10 to 130 µg/L and a coefficient of variation of 7%.14

TABLE 1. Clinical Outcome in Relation to Pretreatment Levels of Coagulation Markers

<table>
<thead>
<tr>
<th>Prothrombin Fragment 1+2, nmol/L</th>
<th>TAT Complex, µg/L</th>
<th>SF, nmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events at 72 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events at 7 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events at 30 days</td>
<td></td>
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</tr>
</tbody>
</table>

Within 24 hours after the qualifying episode of chest pain, patients were randomized to blinded treatment with unfractionated heparin or 1 of 3 different fixed doses of inogatran. Low-, medium-, and high-dose inogatran patients received intravenous bolus injections of 1.10, 2.75, and 5.50 mg, respectively, followed by a continuous infusion of 2.0, 5.0, and 10.0 mg/h, respectively. Heparin was administered as a 5000-U intravenous bolus injection followed by infusion at 1200 U/h. All infusions were to be continued for 72 hours. Aspirin was given to 96% of the patients within the first day. β-Blockers were strongly recommended in the protocol, but ticlopidine and oral anticoagulants were not allowed.

End Points

Clinical end points were a composite of death, myocardial (re-)infarction, or refractory angina at 72 hours (the end of infusion), 7 days, and 30 days. MI was diagnosed by using standard clinical, electrocardiographic, and cardiac marker criteria.7 Refractory angina was defined as chest pain lasting ≥5 minutes with transient electrocardiographic changes despite maximal ongoing medication, leading to an additional coronary intervention. An independent end point committee evaluated all end points.15

A follow-up of long-term clinical outcome was performed at least 1 year after the patients entered the study. Information was obtained from hospital records and local or national registries. When data from these sources were missing, the patient’s status was checked by telephone interview.

Statistics

The levels of molecular coagulation markers are presented in tertiles. Correlations of baseline levels and changes during treatment of the respective coagulation markers were performed with Spearman rank tests. The significance of differences in changes of the coagulation markers during infusion between patients with and those without ischemic events during the 30-day follow-up was assessed with Mann-Whitney U tests. The maximum change in the level of each molecular coagulation marker from the cessation of treatment at 72 hours to those in samples taken 4 and 24 hours thereafter was individually calculated for each patient to detect reactivation in coagulation activity after discontinuation of the study drug. Continuous preentry characteristics are presented as means, with the significance of differences judged by Student’s t test. Discrete variables are described in terms of frequencies and percentages. Fisher’s exact test was used to judge the significance of differences in proportions. Probability of death during long-term follow-up was evaluated with the log-rank test. Multiple logistic regression analyses were performed to evaluate the influence of markers of coagulation activity, together with all relevant baseline characteristics, on the end points of the study and to assess the interaction between inogatran or heparin treatment and coagulation activity and their effect on the risk of ischemic events.

Results

The composite end point of death, MI, and refractory angina was less common in the heparin group compared with the 3 combined inogatran groups during the study drug infusion (2.6% versus 5.4%; P = 0.046) in the main TRIM study.7 However, there were no significant differences between heparin and the combination of the 3 inogatran groups or between any of the 3 inogatran groups concerning the composite end point after 7 or 30 days.7 The effects of different doses of inogatran and heparin on molecular markers of coagulation activity in this substudy population have previously been presented.16

Baseline Characteristics

There was no difference in baseline levels of F1+2, TAT, SF, or D-dimer between inogatran- and heparin-treated patients. Median age in the substudy group was 66 years, and patients above the median age had significantly higher levels of all markers (F1+2, 1.59 vs 1.14 nmol/L; TAT, 3.5 vs 2.9 µg/L; SF, 12 vs 10 nmol/L; and D-dimer, 148 vs 82 µg/L; P <0.001). Women had significantly higher baseline levels of F1+2 (median, 1.61 vs 1.38 nmol/L; P <0.001) and D-dimer (131 vs 102 µg/L; P =0.02) but lower SF levels (median, 9 vs 11 nmol/L; P =0.02) than did men. Patients with baseline values in the upper tertile of these coagulation markers had a higher proportion of concomitant diseases, for instance, diabetes mellitus and congestive heart failure; thus, ongoing treatment with cardiovascular drugs at admission was also more common. There were no significant differences concerning smoking habits, hypertension, inclusion diagnosis (unstable angina or non–Q-wave MI), previous MI, angio-plasty, or bypass surgery between patients with high and low baseline levels of coagulation activity (please see http://atvb.ahajournals.org).
TABLE 2. Clinical Outcome in Relation to Changes in Coagulation Markers From Baseline to 6 Hours

<table>
<thead>
<tr>
<th>Prothrombin Fragment 1+2</th>
<th>TAT Complex</th>
<th>SF</th>
<th>D-Dimer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreasing</td>
<td>Increasing</td>
<td>P</td>
<td>Decreasing</td>
</tr>
<tr>
<td>No. of patients</td>
<td>257</td>
<td>51</td>
<td>189</td>
</tr>
<tr>
<td>Events at 72 hours</td>
<td>9 (3.5)</td>
<td>3 (5.9)</td>
<td>4 (2.1)</td>
</tr>
<tr>
<td>Events at 7 days</td>
<td>17 (6.6)</td>
<td>8 (16)</td>
<td>10 (5.3)</td>
</tr>
<tr>
<td>Events at 30 days</td>
<td>25 (9.7)</td>
<td>10 (20)</td>
<td>15 (7.9)</td>
</tr>
</tbody>
</table>

*Events* denotes a composite of death, myocardial (re)infarction, or refractory angina. Values shown are numbers of patients, with percentages of the group in parentheses.

P values were calculated by χ² or *Fisher’s exact test (2-sided).

Coagulation Activity at Baseline
High baseline levels of TAT, ie, in the top tertile, tended to be associated with a better clinical outcome during anticoagulant treatment. Similarly, no ischemic event was recorded during anticoagulant treatment in patients with high baseline levels of SF (Table 1). These results were more pronounced in the group of inogatran-treated patients, for whom those within the top tertile of TAT had a better outcome both at the end of infusion (P=0.02) and at the 30-day follow-up (P=0.03). Accordingly, SF levels in the top tertile were related to a better outcome at the end of infusion (P=0.02) and also with a trend toward a lower event rate at the 30-day follow-up (P=0.06). During treatment, there was a trend toward a lower event rate in patients with high baseline levels of D-dimer, but this difference decreased during follow-up (Table 1). Baseline levels of F1+2 were not related to short-term clinical outcome.

Changes in Coagulation Activity During Anticoagulant Treatment
High baseline levels were significantly (P<0.001) correlated with decreased levels of all 4 molecular coagulation markers after 6 and 24 hours of anticoagulant treatment. Two hundred fifty-seven patients (81%) in this substudy showed a reduction of F1+2 levels after 6 hours of treatment compared with baseline. The 51 patients with unchanged or increased levels had an approximately doubled event rate during the 30-day follow-up (Table 2). Heparin was more effective than inogatran in suppressing F1+2 levels after 6 hours of treatment compared with baseline. The 51 patients with unchanged or increased levels of SF at 6 hours compared with 75%, 69%, 55%, and 83% of the patients, respectively. The reactivation of coagulation activity was related to baseline levels of coagulation markers, with a significantly greater increase in F1+2 or D-dimer levels within 24 hours after cessation of treatment in patients with baseline levels in the top tertile of the respective coagulation marker. This pattern was seen in the total substudy population as well as in the subgroups of inogatran- and heparin-treated patients.

A reduction in TAT levels was seen in 61% of the patients at 6 hours. The event rate during follow-up was >2-fold elevated in the group of patients with unchanged or increased levels compared with the group with decreased TAT levels (Table 2). The group of patients without subsequent cardiac events during the 30-day follow-up had a median decrease in TAT of 0.6 μg/L from baseline to 6 hours compared with patients with subsequent cardiac events who had a small increase of only 0.1 μg/L (P=0.009). Decreased levels of SF at 6 hours were seen in 47% of the patients. The 7-day event rate was doubled for patients with unchanged or increased levels of SF at 6 hours compared with the group with decreased levels (Table 2). Of the 142 patients with decreased SF levels at 24 hours, 10 (7.0%) had an ischemic event during the 30-day follow-up compared with 22 (13%) of the 165 patients with increased or unchanged SF levels at 24 hours (P=0.07). Compared with patients with ischemic events, there was a significantly larger decrease in SF from baseline to 24 hours in patients without events during the 30-day follow-up (P=0.04). Compared with baseline, at 6 hours 54% of the patients had decreased D-dimer levels (Table 2). After 24 hours of treatment, 217 (71%) of the patients had decreased D-dimer levels and 5 (2.3%) of them had an adverse ischemic event during the infusion compared with 4 (4.4%) of the 90 patients with increased or unchanged D-dimer levels (P=0.5).

Reactivation After Cessation of Anticoagulant Treatment
There were signs of reactivation of coagulation activity within 24 hours after cessation of anticoagulant treatment, with an increase in F1+2, TAT, SF, and D-dimer levels in 85%, 89%, 55%, and 83% of the patients, respectively. The reactivation of coagulation activity was related to baseline levels of coagulation markers, with a significantly greater increase in F1+2 or D-dimer levels within 24 hours after cessation of treatment in patients with baseline levels in the top tertile of the respective coagulation marker. This pattern was seen in the total substudy population as well as in the subgroups of inogatran- and heparin-treated patients.

An adverse clinical event early after cessation of treatment, ie, at days 4 to 7, occurred in 9 (5.0%) of the 181 patients with signs of reactivation of thrombin generation marked by an increase in TAT levels after discontinuation of the study drug infusion. In contrast, none of the 83 patients with unchanged or decreased TAT levels after cessation of treatment died or experienced an MI or refractory angina at days 4 to 7 (P=0.06). The median increase in TAT levels within 24
hours after cessation of treatment was 4.6 μg/L in patients with an adverse clinical event at days 4 to 7 and 1.0 μg/L in patients without such an event after cessation of treatment (P=0.03). Increases in F1+2, SF, and D-dimer levels after cessation of treatment were, though not significant, related to 38%, 64%, and 57% higher adverse event rates, respectively, at days 4 to 7.

**Long-Term Follow-Up**
Long-term follow-up data were obtained for 286 of the 320 patients at a median of 29 months (minimum, 12 months; maximum, 50 months) after entering the study. Baseline levels of D-dimer were a strong predictor of long-term mortality, and furthermore, there was a trend toward a relation between high baseline levels of F1+2 and TAT and an increased long-term risk of mortality (the Figure).

**Logistic Regression Models**
A multivariate logistic regression analysis that included relevant baseline characteristics—age, sex, congestive heart failure, diabetes mellitus, hypertension, previous MI, and previous angioplasty or bypass surgery—and high baseline levels of any of the 4 coagulation markers demonstrated that only age and congestive heart failure were independent predictors of death, myocardial (re-)infarction, or refractory angina up to 30 days. However, a model that included either increasing levels of either F1+2 or TAT during the first 6 hours or increasing levels of SF during the first 24 hours together with baseline characteristics revealed that increasing levels of any of these 3 coagulation markers, together with age and congestive heart failure, were independent predictors of death, myocardial (re-)infarction, or refractory angina up to 30 days. Logistic regression models with interaction terms did not indicate a difference between inogatran or heparin treatment with respect to a prediction of clinical outcome by baseline levels or increasing coagulation activity during treatment.

**Discussion**
Several epidemiological studies have identified elevated levels of molecular markers of thrombin generation and activity as well as fibrin turnover, such as F1+2, FPA, and D-dimer, as risk indicators for future cardiovascular events in apparently healthy men.16–18 There are also data suggesting a relation between adverse in-hospital outcome (death or MI) and high levels of FPA in samples drawn after the first 24 hours from patients with unstable angina without concomitant anticoagulant treatment.19 However, there are few studies on the influence of anticoagulant treatment with respect to the relation between these molecular markers and clinical outcomes in patients with unstable coronary artery disease. A relation between lower levels of FPA after 24 hours of treatment and improved Thrombolysis In Myocardial Infarction flow and greater cross-sectional area on repeated angiography have been reported in 163 patients with unstable angina after treatment with unfractionated heparin or hirudin, an-
other direct thrombin inhibitor.20 Another trial of 64 unstable angina or acute MI patients who developed in-hospital recurrent ischemia despite ≥72 hours of unfractionated heparin infusion found higher levels of F1 + 2 and FPA before the event.21

Coagulation Activity at Admission and During Anticoagulant Treatment
In the present study of patients with unstable coronary artery disease, we found a relation between higher baseline levels of molecular markers for thrombin generation and activity, TAT, and SF and a lower rate of cardiac events, ie, death, MI, or refractory angina, during anticoagulant treatment. This result was more pronounced during and after treatment with inogacran, a low-molecular-mass direct thrombin inhibitor, than with heparin treatment. High baseline levels were correlated with a decrease in the respective coagulation marker during treatment. An early decrease in the levels of molecular markers of thrombin generation and activity during anticoagulant treatment was also related to improved clinical outcome during the 30-day follow-up.

Patients with higher baseline levels of molecular markers of thrombin generation and activity and of fibrin turnover were at higher risk, as indicated by greater age and a higher prevalence of concomitant diseases such as diabetes mellitus and congestive heart failure. Therefore, the association of high coagulation activity with improved short-term clinical outcome was intriguing. A plausible explanation for the relation between high coagulation activity and improved clinical outcome might be that high levels of these markers identify patients with a thrombotic condition (as the major cause of instability) who are good responders to anticoagulant therapy. Such an explanation would be in accordance with the larger decrease in coagulation activity during treatment and the decreased risk of ischemic events. In contrast, increasing levels of these markers during anticoagulant treatment might indicate therapeutic failure, with continuing thrombus formation and a raised risk of future events. These results seem in accordance with a trend to a higher rate of late re-MI in patients with acute MI and persistent high F1 + 2 levels despite ongoing unfractionated heparin treatment 12 hours after thrombolytic treatment.22

Reactivation and Long-Term Follow-Up
A reactivation increase in hemostatic markers after discontinuation of unfractionated heparin and direct thrombin inhibitor therapy has previously been described, although a definite association with adverse ischemic events has not yet been established.23–25 In the present study, despite concomitant treatment with aspirin, there were signs of clinical reactivation, with a clustering of ischemic events after cessation of the 72-hour anticoagulant infusion.7 There was also a trend for a relation between an increase in thrombin generation and activity and fibrin turnover, as indicated by early increases in F1 + 2, TAT, SF, and D-dimer levels, and a higher cardiac event rate during the first 4 days after cessation of anticoagulant therapy.

Long-Term Strategy
Much of the initial benefit of anticoagulant treatment was already lost a few days after cessation of treatment due to reactivation events.7 These findings support the concept of a protective effect of thrombin inhibitors in patients with thrombotic disease and elevated coagulation activity but no sustained effect, due to coagulation reactivation when the treatment is terminated.26 In contrast to the initial effects, there were higher baseline levels of thrombin generation (F1 + 2 and TAT) and fibrin turnover (D-dimer) associated with an increase in mortality during long-term follow-up, in accordance with findings in epidemiological studies.16–18 Both of these findings indicate the need for improved long-term strategy in patients with unstable coronary artery disease, ie, continued long-term treatment with a coagulation inhibitor27 or elimination of the culprit lesion by revascularization.28

Limitations
Although these molecular markers seem to be promising for identifying groups of patients at high short-term risk of adverse ischemic events, individual risk assessment is very difficult because of the considerable interindividual dispersion.10 Furthermore, none of these 4 markers of coagulation activity were independent predictors of long-term risk for adverse ischemic events in this study.

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References


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### Table I - on-line supplement to Oldgren J, Coagulation Activity and Clinical Outcome in UCAD

**Pre-entry characteristics**

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<tr>
<th></th>
<th>prothrombin fragment 1+2 (nmol/L)</th>
<th>thrombin-antithrombin (µg/L)</th>
<th>soluble fibrin (nmol/L)</th>
<th>D-dimer (µg/L)</th>
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<td>&lt;1.14</td>
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<td>65</td>
<td>70**</td>
<td>62</td>
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<tr>
<td>Weight (mean, kg)</td>
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<tr>
<td>Females (%)</td>
<td>14</td>
<td>26</td>
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<td>Non-Q-wave MI (%)</td>
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<td>Stable angina (&gt;4 wk, %)</td>
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<td>Congestive heart failure (%)</td>
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<td>Diabetes mellitus (%)</td>
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<td>Betablockers (%)</td>
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<td>Lipid lowering drugs (%)</td>
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<td>26</td>
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<tr>
<td>Nitrates, long-term (%)</td>
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<td>59</td>
<td>68</td>
<td>58</td>
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<td>ACE-inhibitors (%)</td>
<td>9</td>
<td>16</td>
<td>20</td>
<td>11</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01 Chi-square or t-test for differences between groups with molecular coagulation markers in the bottom+middle tertile versus the top tertile. Abbreviations: F1+2 = prothrombin fragment 1+2; TAT = thrombin-antithrombin; MI = myocardial infarction; ACE = angiotensin converting enzyme.