Activated partial thromboplastin time and clinical outcome after thrombin inhibition in unstable coronary artery disease

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Aims Direct thrombin inhibitors have failed to prove superiority over unfractionated heparin in several clinical trials of unstable coronary artery disease. We have investigated the relationship between activated partial thromboplastin time levels and adverse clinical events, i.e. death, myocardial (re-)infarction or refractory angina.

Methods and Results One thousand two hundred and nine patients with unstable coronary artery disease were randomized to 72 h infusion with inogatran, a low molecular mass direct thrombin inhibitor, or unfractionated heparin. During 30 days follow-up there was no significant difference between inogatran and unfractionated heparin treatment as regards clinical outcome. 11.6% of the 464 inogatran treated patients with activated partial thromboplastin time above the median at 6 h (44 s) had a clinical event in 7 days, and 6.6% of the 423 patients with activated partial thromboplastin time below the median (P=0.01). After 30 days the event rate was still 41% higher in the inogatran patients with activated partial thromboplastin time above the median (P=0.06). Activated partial thromboplastin time in quartiles indicated a direct relationship between higher activated partial thromboplastin time and worse outcome. In contrast, during heparin infusion there was a trend for improved clinical outcome with activated partial thromboplastin time above the median, but this benefit was lost after cessation of treatment.

Conclusions Higher activated partial thromboplastin time levels during inogatran treatment are related to increased risk of death, myocardial infarction or refractory angina. This might, at least in part, be explained by differences in anticoagulant mechanisms between direct thrombin inhibitors and heparin, and further emphasizes the poorly defined optimal activated partial thromboplastin time range during treatment with direct thrombin inhibitors in unstable coronary artery disease.

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Key Words: Anticoagulants, myocardial infarction, prognosis, thrombosis, unstable angina.

Introduction

Unstable coronary artery disease, i.e. unstable angina or non-Q wave myocardial infarction, is commonly caused by coronary thrombosis superimposed on a ruptured atherosclerotic plaque[1]. Antiplatelet therapy with aspirin reduces short- and long-term risk of death and myocardial infarction after an episode of unstable coronary artery disease[2–4]. Anticoagulant treatment with heparin has also been demonstrated to be effective in the acute phase of unstable coronary artery disease[5–7]. Furthermore, the combination of aspirin and heparin is more effective than aspirin alone. However, this beneficial effect might be lost after cessation of heparin treatment[8,9]. Several attempts have been made to improve anticoagulant treatment, either with prolonged heparin administration[9] or newer anticoagulant drugs, such as direct thrombin inhibitors[10,11].

The Thrombin Inhibition in Myocardial Ischemia (TRIM) study, a dose-finding and safety study, enrolled 1209 unstable coronary artery disease patients in 61 Scandinavian centres during 1994 and 1995. Patients were randomized to three different doses of inogatran (Astra-Hässle AB, Mölndal, Sweden), a novel low molecular mass thrombin inhibitor[12,13], or standard unfractionated heparin. Although all three inogatran groups reached predicted inogatran plasma concentration levels, there was no dose–response relationship...
between the inogatran groups concerning clinical outcome, and no benefit compared to heparin\(^{[14]}\). The 72 h infusion therapy was monitored with activated partial thromboplastin time. In this study we also investigated the relationship between activated partial thromboplastin time levels in individual patients and death, myocardial (re-)infarction, refractory angina and bleeding.

**Methods**

**Patients and design**

Details of the TRIM study protocol have previously been reported\(^{[14]}\). Those eligible for inclusion were men and post-menopausal women between 25 and 80 years of age with unstable angina, defined as new onset of ischaemic chest pain or rapid deterioration of previously stable angina during the last 4 weeks, or suspicion of a non-Q-wave myocardial infarction. This clinical diagnosis had to be supported by either changes in a resting ECG, e.g. ST depression or T-wave inversion, or indication of a previous coronary artery disease. The major exclusion criterion was any condition indicating increased bleeding risk. Informed consents were obtained from the patients prior to inclusion and the study protocol was approved by the local ethic committees of all participating centres and by the national medical product agencies of the participating countries.

Treatment was initiated within 24 h of the qualifying episode of chest pain. Patients were randomized to blinded treatment with unfractionated heparin or to one of three 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\(^{-1}\) respectively. Heparin was administered as a 5000 IU intravenous bolus injection followed by infusion with 1200 IU . h\(^{-1}\). All infusions were to be continued for 72 h. Aspirin and beta-blockers were strongly recommended and ticlopidine and oral anticoagulants were not allowed.

**Activated partial thromboplastin time monitoring**

Blood samples for activated partial thromboplastin time analyses were obtained at baseline and during infusion at 6, 24 and 48 h. They were immediately analysed using the routine method of the clinical chemistry laboratory in each of the participating centres. The study drug infusion rate was reduced by 10% if activated partial thromboplastin time was 3-4 times the lower reference level at each centre, and by 20% if activated partial thromboplastin time exceeded the reference level four times. If activated partial thromboplastin time exceeded the reference value six times, the infusion was temporarily stopped for 1-2 h and then re-started with a 20% reduction. Activated partial thromboplastin time was re-measured 4 h after all adjustments, and if needed further reductions were made. Upward adjustments of infusion rates were not allowed. Results for activated partial thromboplastin time are presented both in seconds and as an activated partial thromboplastin time ratio, i.e. activated partial thromboplastin time during infusion divided by baseline activated partial thromboplastin time.

**Plasma concentrations and thrombin time**

Blood samples were obtained after 6 h of inogatran infusion from 80 low, 82 medium and 71 high dose patients and after 48 h from 207 low, 199 medium and 208 high dose patients, respectively. The plasma concentration of inogatran was determined using a liquid phase chromatography-mass spectrometry method after solid-phase extraction of the compound from plasma\(^{[13]}\).

In 67 patients thrombin time was measured after 6 h infusion to correlate the anticoagulant effect of inogatran to plasma concentrations.

**End-points**

Clinical end-points were a composite of death, non-fatal myocardial infarction or refractory angina at 72 h (the end of infusion), and 7 and 30 days. Myocardial infarction was diagnosed using standard clinical and enzymatic criteria. Refractory angina was defined as chest pain lasting \(\geq 5\) min with transient ECG changes, despite maximal ongoing medication, leading to an additional coronary intervention. An independent end-point committee evaluated all end-points. Bleeding was classified as minor or major; the later defined as either: intracranial haemorrhage, bleeding leading to death, requiring blood transfusion, leading to prolonged hospitalization or persistent disability, or a drop in haemoglobin of more than 30% from baseline.

**Statistics**

All treatment comparisons were performed according to the intention-to-treat principle. Continuous data were descriptively summarized as medians and percentiles with differences judged by Mann–Whitney test. Discrete variables were described in terms of frequencies and percentages. Fisher exact test or chi-square test, in quartile groups with linear-by-linear association, judged differences in proportions. Study end-points were depicted graphically as cumulative relative frequencies over time using the Kaplan–Meier method. Multiple logistic regression analyses were performed evaluating predictors of high activated partial thromboplastin time levels, and the influence of activated partial
Results

There were no significant differences between the heparin or any of the three inogatran groups concerning the composite of death, myocardial infarction or refractory angina at 7 days in the main TRIM study. An insignificant trend was noticed when there was a favourable outcome with heparin. However, no significant differences were detected between the three inogatran groups concerning the composite end-point, but there was a trend towards unfavourable outcome in the highest inogatran dose group.[14]

During the inogatran infusion there was a good dose–response relationship concerning median activated partial thromboplastin time in the low, medium and high dose groups and the activated partial thromboplastin time levels were fairly stable throughout the infusion period (Fig. 1). Reductions in infusion rate were only carried out in 4% or less of the patients in each group. However, a wide dispersion in activated partial thromboplastin time levels between the individual patients within each of the randomized treatment groups was noticed. Because of this overlap in activated partial thromboplastin time between the three groups and in the absence of significant differences in clinical outcome, all inogatran patients were combined into one group in the further analyses of the relationships between activated partial thromboplastin time levels and clinical outcome.

The heparin-treated patients had a clearly different pattern in activated partial thromboplastin time response (Fig. 1), in part because of the high initial infusion rate and frequent dose reductions, but presumably also because of differences in the mechanism of action of these two drugs. Therefore, in the further analyses the heparin treated patients are presented separately.

Inogatran treatment

Activated partial thromboplastin time samples were collected from at least 868 (96%) of the 904 inogatran treated patients at each sample time — baseline, 6, 24 and 48 h. Activated partial thromboplastin time medians for the combined inogatran group were 29 s at baseline and during infusion 44, 44 and 45 s at 6, 24 and 48 h, respectively.

Adverse ischaemic events, i.e. death, myocardial infarction or refractory angina, were more frequent in the group of patients with activated partial thromboplastin time above the median at 6 h. This difference in clinical outcome was already evident after the 72 h of infusion therapy (Table 1). A clustering of ischaemic events was observed after cessation of treatment and to a similar degree in patients with activated partial thromboplastin time above or below the median at 6 h (Fig. 2). Analysis of activated partial thromboplastin time samples after 24 h infusion showed similar results: 46 (10.4%) of 442 patients with activated partial thromboplastin time above the median died or experienced a myocardial infarction or refractory angina during the first 7 days, compared to only 27 (6.3%) of 426 patients with activated partial thromboplastin time below the median (P=0.03).

Dividing the group of inogatran treated patients in four groups according to quartiles of activated partial thromboplastin time together with all relevant baseline characteristics on the end-points of the study.

Figure 1  Distribution of activated partial thromboplastin times at different time-points before and during infusion in the four randomized treatment groups — low, medium, high dose inogatran and heparin — and for the combined group of all inogatran patients. Box-plots contain median, 1st and 3rd quartiles and in the whiskers 10th and 90th percentiles.
thromboplastin time at 6 h indicated a direct relationship between higher activated partial thromboplastin time and deteriorating clinical outcome, with an approximately doubled event rate in the top quartile as compared to the bottom quartile (Fig. 3). A similar trend was seen for the relation between activated partial thromboplastin time at 24 h and clinical outcome.

A minority of inogatran treated patients achieved activated partial thromboplastin time values above 70 s at sometime during the infusion. Almost a quarter of them (13 of 55) died or experienced a myocardial infarction or refractory angina during the first 7 days.

An activated partial thromboplastin time ratio in the supposed therapeutic range during inogatran treatment was also related to adverse outcome. Fifty-two (11·0%) of the 472 patients with an activated partial thromboplastin time ratio ≥1·5 at 6 h had an adverse ischaemic event within 7 days, compared to 30 (7·7%) of the 390 patients with an activated partial thromboplastin time ratio below 1·5 (P=0·10). Correspondingly, only 27 (6·6%) of the 407 patients with an activated partial thromboplastin time ratio below 1·5 at 24 h had an adverse ischaemic event during the first 7 days, compared to 46 (10·6%) of the 435 patients with an activated partial thromboplastin time ratio ≥1·5 (P=0·04).

Percutaneous transluminal coronary angioplasty or coronary artery bypass surgery was performed in only seven patients within 48 h of the start of the study drug infusion. The study drug infusion was discontinued before the procedure. Exclusion of those patients from analysis did not alter the relationships between activated partial thromboplastin time and ischaemic events described above.

There was a positive correlation between plasma-concentration of inogatran and activated partial thromboplastin time at 6 and 48 h (Fig. 4). However, there was no relationship between inogatran concentrations and death, myocardial infarction or refractory angina at any time during the study. Thrombin time had, as compared to activated partial thromboplastin time, a better and more linear correlation to plasma concentrations of inogatran at 6 h (Fig. 5).

### Table 1: Activated partial thromboplastin time (APTT) levels after 6 h inogatran infusion in relation to clinical outcome

<table>
<thead>
<tr>
<th>APTT, s</th>
<th>Number of patients</th>
<th>&lt;44</th>
<th>≥44</th>
<th>p</th>
</tr>
</thead>
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<tr>
<td>423</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>464</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death, MI or refractory angina, 72 h</td>
<td>15 (3·5%)</td>
<td>33 (7·1%)</td>
<td>0·02</td>
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</tr>
<tr>
<td>Death, MI or refractory angina, 7 days</td>
<td>28 (6·6%)</td>
<td>54 (11·6%)</td>
<td>0·01</td>
<td></td>
</tr>
<tr>
<td>Death, MI or refractory angina, 30 days</td>
<td>44 (10·4%)</td>
<td>68 (14·7%)</td>
<td>0·06</td>
<td></td>
</tr>
</tbody>
</table>

MI=myocardial (re-)infarction.

Figure 2 → Probability of death, myocardial (re-)infarction or refractory angina over 7 days in inogatran treated patients, in relation to activated partial thromboplastin time at 6 h ≥44 s (n=464) solid line, and <44 s (n=423) broken line. Vertical line indicates cessation of study drug.

Baseline characteristics and inclusion diagnose

Patients with activated partial thromboplastin time above the median after 6 h of inogatran infusion had, as expected, a lower median body weight. These patients were older and had a slightly higher baseline activated partial thromboplastin time (Table 2). Congestive heart failure was also more common in patients with a high...
activated partial thromboplastin time, but there were no significant differences concerning gender, inclusion diagnosis (unstable angina or non-Q wave myocardial infarction), diabetes mellitus, hyperlipidaemia, hypertension, previous myocardial infarction, angioplasty or bypass surgery. There were, except for treatment with ACE inhibitors and digitalis, no differences recorded in medical treatment on admission.

**Multivariate logistic regression models**

Low weight, higher baseline activated partial thromboplastin time, high baseline serum-creatinine and previously known congestive heart failure were, in multivariate analysis, identified as independent predictors of high activated partial thromboplastin time during inogatran infusion. A multivariate logistic regression...
analysis, which included all relevant baseline characteristics — age, activated partial thromboplastin time at baseline and at 6 h, congestive heart failure, diabetes mellitus, hypertension, previous myocardial infarction, serum creatinine and weight — demonstrated that age and activated partial thromboplastin time above the median at 6 h remained independent predictors of death, myocardial (re-)infarction or refractory angina up to 7 days in patients treated with inogatran.

### Heparin treatment

The heparin treated patients had a peak in activated partial thromboplastin time after 6 h of infusion with a median activated partial thromboplastin time of 69 s, and a much larger dispersion of activated partial thromboplastin time levels than among the inogatran treated patients (Fig. 1). The dispersion diminished and the median activated partial thromboplastin time decreased to 54 and 49 s at 24 and 48 h, respectively, in part because of frequent dose reductions, which were carried out in 41% of the patients. However, the median activated partial thromboplastin time in patients without any dose reduction also decreased by almost 20% between 6 and 24 h.

The event rate during heparin infusion was low and only three (2.0%) of 151 patients with activated partial thromboplastin time above, and five (3.4%) of 151 patients with activated partial thromboplastin time below the median at 6 h had an adverse event during the first 72 h ($P=0.50$). However, activated partial thromboplastin time above the median at 24 h was related to favourable outcome during infusion (Table 3). This benefit was lost after cessation of treatment, because of clustering of events within 24 h, and no difference in clinical outcome was seen at 7 days (Fig. 6). An activated partial thromboplastin time ratio at 6 or 24 h within 1.5 to 2.5 times the pre-treatment level was not related to any improvement in clinical outcome as compared to activated partial thromboplastin time ratios below or above this interval.

### Bleeding complications

The overall incidence of bleedings in the TRIM study was low.[14] Over 7 days 13 patients (1.1%) suffered a major bleeding and 87 patients (7.2%) had a minor
bleeding, and no relationship between activated partial thromboplastin time levels and bleeding complications could be observed.

**Discussion**

Activated partial thromboplastin time, easily available and currently the most widely used method for monitoring of treatment with antithrombin agents, has considerable disadvantages. It is an in-vitro method that reflects surface-induced activation of the coagulation system and is therefore mainly sensitive to factors of the intrinsic pathway. However, in-vivo coagulation activation in unstable coronary artery disease is triggered by the Tissue Factor/factor VII-pathway\[15\]. The relationship between activated partial thromboplastin time and plasma concentrations of heparin or recombinant hirudin, currently the best evaluated direct thrombin inhibitor, is non-linear\[16–18\]. There are also differences in activated partial thromboplastin time levels at different laboratories, as there is a considerable variation in available reagents, giving widely different results\[17,19\]. A batch-to-batch variation of a particular activated partial thromboplastin time reagent may also occur\[20\]. In-vivo, r-hirudin infusion induces dose-dependent predictable activated partial thromboplastin time prolongation in patients with chronic stable coronary artery disease\[21\]. In contrast, large inter-individual variations in the activated partial thromboplastin time response were seen in healthy volunteers at identical plasma levels of r-hirudin measured by anti-IIa-concentration\[18\].

Despite the long experience of activated partial thromboplastin time-monitoring during heparin treatment, data on the desirable interval for an optimal anticoagulant effect in the treatment of unstable coronary artery disease are limited. In the AHCPR guidelines\[22\] it is recommended that the activated partial thromboplastin time is maintained at 1.5 to 2.5 times control, corresponding to heparin plasma concentrations of 0.2–0.4 U . ml\(^{-1}\) by protamine titration\[23\]. This recommendation is mainly based on results by Théroux et al.\[7\] which are similar to the recommendations for treatment of venous thrombosis\[23\]. Activated partial thromboplastin time has been used to monitor treatment in recent large-scale clinical trials with direct thrombin inhibitors in patients with acute myocardial infarction or unstable coronary artery disease. However, there have been differences in dosing regimens as well as in the target activated partial thromboplastin time ranges\[10,11,14,24–26\].

<table>
<thead>
<tr>
<th>APTT, s</th>
<th>&lt;54</th>
<th>≥54</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>145</td>
<td>155</td>
<td></td>
</tr>
<tr>
<td>Death, MI or refractory angina, 72 h</td>
<td>7 (4.8%)</td>
<td>1 (0.6%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Death, MI or refractory angina, 7 days</td>
<td>13 (9.9%)</td>
<td>12 (7.7%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Death, MI or refractory angina, 30 days</td>
<td>16 (11.0%)</td>
<td>20 (12.9%)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

MI = myocardial (re-)infarction.

**Figure 6** Probability of death, myocardial (re-)infarction or refractory angina over 7 days in heparin-treated patients, in relation to activated partial thromboplastin time at ≥54 s (n=154) solid line, and <54 s (n=145) broken line. Vertical line indicates cessation of study drug.
Direct thrombin inhibitors have some theoretical advantages over unfractionated heparin, e.g. better effect on clot-bound thrombin and independence of antithrombin \[27,28\]. Nevertheless, despite promising results in animal models, they have failed to prove superiority over unfractionated heparin in several clinical trials of unstable coronary artery disease, acute myocardial infarction (adjunctive to thrombolysis) or angioplasty, calling into question the optimal dose and duration of therapy \[29\].

This was the first large-scale clinical trial of inogatran, a low molecular mass, selective, rapidly binding competitive inhibitor of thrombin \[12,13\]. Inogatran did not improve the clinical outcome compared to unfractionated heparin. Moreover, the randomized low, medium and high doses of inogatran, with dose adjustments aiming at activated partial thromboplastin time levels in the low to medium range, failed to identify any dose-effect relationship. The rather low overall activated partial thromboplastin time levels achieved in the study, in combination with the lack of correlation between plasma concentrations of inogatran and clinical outcome, raised questions about inappropriate low dosages of inogatran, especially as the protocol prohibited dose increments. The result of the present analysis, with a positive correlation between activated partial thromboplastin time levels and adverse events, was therefore completely unexpected.

In contrast, during ongoing heparin infusion there was an association between higher activated partial thromboplastin time and improved clinical outcome. This clinical benefit was lost within the first 24 h after cessation of treatment because of reactivation with clustering of events. It is unknown whether the peak in activated partial thromboplastin time at the beginning of the heparin infusion is advantageous, and whether the tapering of plasma levels of heparin in the later phase might reduce the reactivation after cessation of treatment \[25\]. However, in the GUSTO-I trial, which included almost 30 000 patients receiving intravenous heparin adjunctive to thrombolysis, a direct relationship was found between higher activated partial thromboplastin time levels during the first 12 h and death or myocardial reinfarction \[30\].

The results in the present study might be related to the differences in the mechanisms of action between heparin and direct thrombin inhibitors. Heparin exerts multiple effects on the coagulation system mainly by amplifying the effects of the natural anticoagulant antithrombin. Antithrombin, besides inactivation of and binding to thrombin, also inhibits several coagulation factors such as XIIa, XIa, IXa, Xa, all of which can alter the activated partial thromboplastin time. Direct thrombin inhibitors, on the other hand, have a selective inhibitory effect on thrombin (f IIa). Therefore, at comparable activated partial thromboplastin time levels the thrombin activity is probably much lower during treatment with a direct thrombin inhibitor than during heparin treatment. Considering the multiple and complex effects of thrombin, with both procoagulative and anticoagulative activity, an unsuitable dose of a direct thrombin inhibitor could alter this balance too far and in an unexpected and negative way, and thereby even impair the prognosis.

A similar experience of the antithrombotic efficacy of inogatran infusion associated with only a moderate activated partial thromboplastin time increase has been made in a porcine model of copper-coil-induced coronary artery thrombosis. Inogatran dosages resulting in an activated partial thromboplastin time prolongation of as little as 1·3 times baseline proved more effective in inhibiting thrombotic occlusion than heparin in dosages resulting in activated partial thromboplastin time-ratios 2·0–5·0 \[31\].

No correlation was detected between bleeding complications and activated partial thromboplastin time levels, probably because of the limited number of episodes. However, a number of studies have demonstrated a relationship between higher activated partial thromboplastin time and bleeding complications during treatment with heparin \[30\] and direct thrombin inhibitors \[24,32,33\].

Thrombin time, another method with which to assess the anticoagulant effect during thrombin inhibition, showed a more linear relationship with plasma concentrations of inogatran in the present study. Nevertheless, the small number of samples made it impossible to relate the thrombin times to clinical outcome. An alternative sensitive assay for monitoring the efficacy of direct thrombin inhibitors is the Ecarin clotting time \[34\]. This method is insensitive to heparin, has a low inter-individual variability and a strong linear correlation to plasma concentrations of r-hirudin in healthy volunteers \[35\]. Further evaluation of this method in clinical trials of direct thrombin inhibitors seems thereby warranted.

Inogatran is a dipeptide that, in contrast to r-hirudin, reversibly binds only to the catalytic site of thrombin. The differences in thrombin binding and molecular masses of direct thrombin inhibitors could be a limitation in the interpretation of the results from our study and make them less generally applicable for the whole range of low and high molecular mass direct thrombin inhibitors.

Although a high activated partial thromboplastin time response, together with older age, was identified in multivariate analysis as an independent predictor of adverse outcome, it cannot be ruled out that this high activated partial thromboplastin time might be a sign of another underlying condition impairing the prognosis. The absence of a correlation between the inogatran level and clinical outcome supports this idea that an ‘abnormal’ response to inogatran treatment might be related to an increased risk for new events. Another limitation is that patients were not randomized to different target activated partial thromboplastin time intervals in this trial. To perform such a trial would obviously be very difficult, especially with unfractionated heparin, because of the large inter-individual variation in activated partial thromboplastin time, despite cautious dosing regimens with weight adjusted doses.
Conclusion
This study emphasizes the poorly defined optimal activated partial thromboplastin time range during thrombin inhibition, especially with direct thrombin inhibitors, in unstable coronary artery disease. Higher activated partial thromboplastin times during inogatran treatment are, even in the expected therapeutic range, related to increased risk of death, myocardial infarction or refractory angina. This might indicate a narrow therapeutic window, yet to be defined, for direct thrombin inhibitors. These findings could also be the result of a methodological problem in the monitoring of the anticoagulant efficacy with activated partial thromboplastin time, which at least in part might be explained by the differences in anticoagulant mechanisms between direct thrombin inhibitors and heparin. The results raise the issue that less favourable results in clinical trials with other direct thrombin inhibitors might have been related to dosing regimens wrongly indicated by the use of activated partial thromboplastin time in the monitoring of anticoagulant efficacy.

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