**Background:** Heparin-induced thrombocytopenia (HIT) is an intensely prothrombotic syndrome managed by discontinuation of heparin therapy and substitution of an alternative inhibitor of thrombin. We describe our experience with argatroban, a direct thrombin inhibitor, in patients with HIT or HIT with thrombosis (HITTS).

**Methods:** In this multicenter, nonrandomized prospective study, 418 patients with HIT were administered intravenous argatroban, 2 µg/kg per minute, adjusted to maintain the activated partial thromboplastin time at 1.5 to 3 times the baseline value for a mean of 5 to 7 days. Comparisons were made with a historical control cohort (n=185). The prospectively defined, primary efficacy end point was a composite of all-cause death, all-cause amputation, or new thrombosis in 37 days. Other end points included the components of the composite, death due to thrombosis, increased platelet count, and bleeding.

**Results:** In the HIT arm, the composite end point was significantly reduced in argatroban-treated patients vs controls (28.0% vs 38.8%; P=.04). In the HITTS arm, the composite end point occurred in 41.5% of argatroban-treated patients vs 56.5% of controls (P=.07). By time-to-event analysis of the composite end point, argatroban therapy was significantly better than historical control therapy in HIT (P=.02) and HITTS (P=.008). Argatroban therapy also significantly reduced new thrombosis in HIT and HITTS and death due to thrombosis in HITTS. There were no significant between-group differences in all-cause death or amputation. Platelet counts recovered more rapidly in argatroban-treated patients than in controls. Bleeding rates were similar between groups.

**Conclusion:** Argatroban therapy, compared with historical control, improves outcomes, particularly new thrombosis and death due to thrombosis, in patients with heparin-induced thrombocytopenia.

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**HEPARIN-INDUCED thrombocytopenia (HIT) is a potentially catastrophic, generalized thrombotic disorder that is triggered by heparin therapy.**

During the past decade, there has been an explosion in our understanding of the clinical and pathophysiologic features of HIT. This information, in turn, has lead to the introduction of novel treatments. Clinical studies in patients with HIT have shown that most patients will have a decrease in their platelet count, which typically becomes less than 100 to 150 x 10^9/L. Approximately half to two thirds of all patients with HIT will have a simultaneous or subsequent thromboembolic event. It is the thromboembolic events that account for the overall mortality of 20% to 30% reported in patients with HIT.

Laboratory studies have shown that HIT is caused by immune complexes composed of IgG bound to a complex of heparin and platelet factor 4. These immune complexes activate platelets and endothelial cells. The activated platelets release procoagulant microparticles that initiate thrombin generation and trigger the thrombotic complications that characterize the syndrome. Antibody-mediated endothelial injury may also contribute to the development of thrombosis. Further evidence of the prothrombotic nature of the syndrome comes from clinical observations: when patients with isolated HIT are treated by cessation of heparin therapy alone, at least 50% will progress to a thrombotic event, typically within a week.

Complications of HIT span a spectrum of venous and arterial thromboembolic events, including deep venous thrombosis, pulmonary embolism, myocardial infarction, thrombotic stroke, and limb artery occlusion requiring amputation.

These clinical and laboratory observations have led most clinicians to conclude that patients with HIT should be treated by discontinuation of heparin therapy and rapid initiation of an alterna-
A thrombin-specific anticoagulant that does not resemble heparin or react with HIT antibodies. During the past several years, a variety of approaches to anticoagulation of patients with HIT have been reported in retrospective studies. Although the design of these studies has not been optimal, several observations have been made. First, heparin and low-molecular-weight heparins should not be used because they often cross-react with the antibodies that cause HIT, which frequently worsens the syndrome. Second, warfarin sodium is contraindicated as an acute treatment because it can paradoxically worsen the thrombosis and cause venous gangrene. A heparinoid called danaparoid sodium has been used successfully in some patients, but danaparoid cross-reacts with approximately 10% of HIT antibodies.

Recently, 2 novel thrombin-specific inhibitors have become available in the United States for use in patients with HIT: argatroban (Argatroban; GlaxoSmithKline), which is a small synthetic molecule (molecular weight 527), and recombinant hirudin (lepirudin; molecular weight 6980), which is a polypeptide of nonhuman origin. These direct thrombin inhibitors offer significant advantages in the treatment of HIT: both neutralize clot-bound and soluble thrombin (albeit the agents have different relative efficiencies against these forms of thrombin) and, because the agents are chemically distinct from heparin, cross-reactivity with HIT antibodies does not occur. In 1 of 2 historical controlled studies of lepirudin in patients with HIT, lepirudin therapy significantly reduced a combined end point of new thromboembolic complications, limb amputation, and death. In a prospective study of argatroban use in patients with HIT (Argatroban-911), argatroban therapy significantly reduced the primary composite end point of death, amputation, or new thrombosis in patients with isolated HIT.

In this article, we describe, to our knowledge, the largest prospective study of patients with HIT reported to date. This multicenter trial of argatroban therapy extends our knowledge of patients with HIT and confirms the importance of thrombin inhibition in this patient population.

**METHODS**

We conducted a multicenter prospective study of argatroban therapy for HIT between November 1, 1996, and August 31, 1998. The study allowed continued availability of argatroban to patients requiring the drug during its regulatory review process, and hence no sample size was prospectively defined. The institutional review board at each of 86 participating medical centers approved the study before initiation, and written informed consent was obtained from patients. Many of the researchers had participated in the previous study of argatroban therapy in HIT and, for patient recruitment purposes, used educational initiatives in their institutions to maintain (or increase) awareness of HIT and the availability of the agent. No single medical center enrolled more than 11% of the treated patients.

**TREATMENT GROUP**

Eligible patients were men and nonpregnant women 18 years or older who had clinically diagnosed HIT (defined as a platelet count <100×10^9/L or a 30% reduction in platelet count relative to the preheparin treatment value after heparin therapy with no explanation besides HIT). Patients were assigned to 1 of 2 study arms according to their initial presentation: isolated HIT or HIT with thrombosis (HITTS).

Exclusion criteria were an unexplained activated partial thromboplastin time (aPTT) greater than 2 times the control value at baseline; documented coagulation disorder or bleeding diathesis unrelated to HIT; a lumbar puncture in the past 7 days; a history of previous aneurysm, hemorrhagic stroke, or recent (within 6 months) thrombotic stroke unrelated to HIT; a known bleeding site, unless the risk of thrombosis outweighed the potential bleeding risk; current pregnancy or breastfeeding; and a terminal illness with a life expectancy of less than 2 weeks. A patient was permitted entry of 1 data set only.

Heparin therapy was discontinued and continuous intravenous Argatroban therapy was initiated at 2 µg/kg per minute. A lower starting dose was allowed if needed owing to the patient’s medical condition (eg, the presence of hepatic impairment). The aPTT was determined 2 hours later, and the dose was adjusted (up to 10 µg/kg per minute maximum) until the aPTT was 1.5 to 3 times the baseline aPTT value (not to exceed 100 seconds). The aPTT was measured daily and 2 hours after each dose adjustment. Patients received argatroban until the underlying condition was clinically resolved, appropriate anticoagulation was provided with other agents, or treatment was continued for 14 days. For patients transferred to warfarin therapy (63% of patients), the method for the transition was not legislated.

**CONTROL GROUP**

Historical control subjects were from our previous study and were typically seen within 4 years before initiation of that study (or 5 years before initiation of the present study). Controls met the same inclusion and exclusion criteria as in our previously reported study (Argatroban-911), with their selection as described. Controls had the same eligibility criteria as the patients described in this study and were treated according to the local practice at that particular hospital, with typical treatments being heparin therapy discontinuation or oral anticoagulant therapy. There was no attempt to modify or legislate therapy for any of the controls.

**ASSESSMENTS**

Argatroban-treated patients were followed up from baseline (ie, the date that argatroban therapy was initiated) during treatment, and for 30 days after therapy cessation. Controls were followed for 37 days after their baseline date (ie, the date that heparin therapy was discontinued after the platelet count met inclusion criteria or the date that the platelet count met inclusion criteria after initiation of heparin therapy). Death from all causes, death due to thrombosis, amputation from all causes, new thrombosis, and bleeding events were recorded. Major bleeding was defined as overt and associated with a hemoglobin concentration decrease of 20 g/L or greater, leading to a transfusion of 2 or more units, or as intracranial, retroperitoneal, or into a major prosthetic joint. Bleeding not meeting these criteria was considered minor.

The prospectively defined end point was a composite of all-cause death, all-cause amputation, or new thrombosis within 37 days of baseline. Secondary efficacy assessments included the individual components of the composite end point and death due to thrombosis. Additional outcomes were the anticoagulant(s) used by the patient during the study, the maximum dose achieved, and the aPTT at the time of dose adjustment. The time of the aPTT measurement was also recorded.
lant effect of argatroban therapy as assessed by aPTT and the change in platelet count by study day 3.

STATISTICAL ANALYSIS

Although sample size was not prospectively defined, we previously estimated for a similarly designed study (Argatroban-911) \(^{17}\) that 150 argatroban-treated patients per study arm, at least 60 controls with HIT, and 50 controls with HITTS would allow detection of a significant treatment effect (absolute difference in composite end point rate of ≥20%).

Analyses were conducted separately for the study arms on the intent-to-treat population using statistical software (SAS version 6.12; SAS Institute Inc, Cary, NC). Hypothesis testing was 2-sided and 2-tailed. Between-group analyses were performed using the t test (age, weight, and baseline platelet count) or the Fisher exact test (sex, race, and clinical outcomes). The odds ratios and associated 95% confidence intervals (CIs) were estimated for the primary end points using contingency table analyses. Between-group analysis was also performed on the primary efficacy end point using the time-to-event method (Kaplan-Meier life tables), with significance assessed using the log-rank test. Individuals were censored on their last day of follow-up or on day 37, whichever came first. Hazard ratios and 95% CIs were estimated by proportional hazards regression analysis. The model included only a treatment term, and the assumption of proportionality was met. An analysis of covariance was performed on the change in platelet count by study day 3, with baseline platelet count as the covariate.

RESULTS

This analysis included 418 patients with HIT (189 with isolated HIT and 229 with HITTS) who received argatroban therapy and 185 historical controls (139 with isolated HIT and 46 with HITTS). The treatment and control groups were comparable with respect to demographic and baseline characteristics in each study arm except that baseline platelet counts in the isolated HIT arm were significantly lower in argatroban-treated patients than in controls (P < .001) (Table 1).

Patients with HIT received argatroban at a mean (SD) dose of 1.7 (1.0) µg/kg per minute over a mean (SD) duration of 5.1 (4.2) days, and patients with HITTS received argatroban at a mean (SD) dose of 1.9 (1.1) µg/kg per minute over a mean (SD) duration of 7.1 (6.5) days. The protocol-specified treatment period was completed by 317 (76%) of 418 patients. Fifty-four patients (13%) prematurely discontinued infusion because of surgery (n = 12), an elevated aPTT or international normalized ratio (n = 10), a negative HIT antibody test result after initiation of drug therapy (n = 9), transfer to another study evaluating argatroban use during coronary interventions (n = 8), patient or family request (n = 4), or other reasons (n = 7). Forty-seven patients (11%) were withdrawn because of adverse events. Events leading to withdrawal of more than 1 patient were gastrointestinal tract bleeding (n = 5), multisystem organ failure leading to death (n = 3), and thrombocytopenia (n = 2).

PRIMARY EFFICACY OUTCOME

In the HIT study arm, the primary efficacy end point—a composite of all-cause death, all-cause amputation, or new thrombosis—was significantly reduced in argatroban-treated patients compared with controls (odds ratio, 0.61; 95% CI, 0.39-0.98; P = .04) (Table 2). For those with HITTS, the composite end point occurred in 95 argatroban-treated patients (41.5%) and 26 controls (56.5%) (odds ratio, 0.55; 95% CI, 0.36-0.87; P < .008) (Table 2). By time-to-event analysis of the composite end point, argatroban therapy was significantly favored over control therapy in participants with HIT (hazard ratio, 0.64; 95% CI, 0.43-0.93; P = .02) (Figure 1) or HITTS (hazard ratio, 0.56; 95% CI, 0.39-0.87; P = .002) (Figure 2).

SECONDARY EFFICACY OUTCOMES

There were no significant between-group differences in all-cause mortality (Table 2). However, argatroban therapy, compared with control therapy, significantly reduced the incidence of death due to thrombosis in participants with HITTS (2.6% vs 15.2%; P = .002).

There were no significant differences in the frequency of amputation in argatroban-treated patients com-

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**Table 1. Demographic and Baseline Characteristics of 418 Argatroban-Treated Patients and 185 Historical Controls by Study Arm**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Isolated HIT</th>
<th>HIT With Thrombosis</th>
<th>Isolated HIT</th>
<th>HIT With Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control Group (n = 139)</td>
<td>Argatroban Group (n = 189)*</td>
<td>Control Group (n = 46)</td>
<td>Argatroban Group (n = 229)*</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>66 ± 12</td>
<td>64 ± 15</td>
<td>66 ± 11</td>
<td>64 ± 14</td>
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<tr>
<td>Sex, No. (%)</td>
<td>M 80 (58)</td>
<td>97 (51)</td>
<td>28 (61)</td>
<td>115 (50)</td>
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<td></td>
<td>F 59 (42)</td>
<td>92 (49)</td>
<td>18 (39)</td>
<td>114 (50)</td>
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<tr>
<td>Race, No. (%)</td>
<td>Black 8 (6)</td>
<td>16 (9)</td>
<td>6 (13)</td>
<td>14 (6)</td>
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<td></td>
<td>White 116 (83)</td>
<td>163 (86)</td>
<td>38 (83)</td>
<td>205 (90)</td>
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<tr>
<td></td>
<td>Other 15 (11)</td>
<td>10 (5)</td>
<td>2 (4)</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Weight, mean ± SD, kg</td>
<td>81 ± 22 (n = 109)</td>
<td>79 ± 22 (n = 178)</td>
<td>84 ± 25 (n = 34)</td>
<td>82 ± 21 (n = 220)</td>
</tr>
<tr>
<td>Baseline platelet count, mean ± SD, ×10(^9) /L</td>
<td>123 ± 72 (n = 123)</td>
<td>84 ± 66 (n = 187)</td>
<td>106 ± 83 (n = 37)</td>
<td>88 ± 83 (n = 225)</td>
</tr>
</tbody>
</table>

Abbreviation: HIT, heparin-induced thrombocytopenia.

\(^*P > .20\) vs controls for each variable except baseline platelet count in the HIT study arm, where \(P < .001\).
pared with controls (Table 2). The most common site of amputation in both groups was the knee (above, through, or below), occurring overall in 28 (6.7%) of 418 argatroban-treated patients (including 6 who underwent bilateral amputation) and 6 (3.2%) of 185 historical controls (including 2 who underwent bilateral amputation).

Argatroban therapy, compared with control therapy, resulted in significant reductions in new thrombosis in patients with HIT (5.8% vs 23.0%; P < .001) or HITTS (13.1% vs 34.8%; P < .001) (Table 2). Arterial thrombosis was less frequent than venous thrombosis in the treatment and control groups, with myocardial infarction secondary to HIT or thrombotic stroke occurring in 11 (27%) of 41 argatroban-treated patients and 13 (27%) of 48 controls who experienced new thrombosis.

**ADDITIONAL EFFICACY OUTCOMES**

**Figure 3** presents the mean aPTT responses during the first 72 hours of argatroban therapy. The mean aPTT was within the target aPTT range (1.5–3 times the baseline value) typically by first assessment (overall mean of 3.8 hours after initiation of argatroban therapy), and it remained generally constant throughout the infusion. Similar, predictable responses occurred in patients with HIT or HITTS.

Mean platelet counts through study day 7 are shown in **Figure 4** for the treatment and control groups. Argatroban-treated patients, compared with controls, had more rapid recovery of platelet counts (P < .001 for each arm).

**BLEEDING**

In the HIT and HITTS study arms, major bleeding rates were not different between argatroban-treated patients and controls (Table 3). There was a single fatal bleeding event in the treatment group. A patient with lupus erythematosus and nephrotic syndrome was hospitalized with rectal bleeding and recurrent deep venous
thrombosis; she received heparin and urokinase and then, after a diagnosis of HIT, argatroban. The rectal bleeding persisted, her condition deteriorated (metabolic acidosis and respiratory failure), and the family requested no resuscitation. No argatroban-treated patient experienced an intracranial hemorrhage. In the historical control group, 2 fatal bleeding events, including an intracranial hemorrhage, occurred.17 Minor bleeding rates were also not different between the groups (Table 3).

**COMMENT**

Heparin-induced thrombocytopenia is the most serious and potentially catastrophic hematologic complication of drug therapy that physicians manage today. Although the recognition and understanding of HIT are relatively recent, its importance continues to grow. This relates to the fact that heparin therapy is increasingly used in a variety of arterial and venous indications. Furthermore, the current atmosphere of litigation often means that patients who have an adverse reaction to a medicinal agent are likely to seek legal advice.

The clinical manifestations and impact of HIT have been well studied, and recently its pathogenesis has become better understood. Heparin-induced thrombocytopenia typically begins 5 to 12 days after starting heparin therapy,19 and, although it can be associated with any heparin given at any dose and by any route, it has its greatest frequency when full-dose, standard (unfractionated) heparin is given to surgical patients. For these patients, the risk of HIT is 2% to 5%.20 The thrombocytopenia is typically moderately severe, with platelet counts of 50 to $75 \times 10^9$/L, but it is the resultant thrombotic complications that give rise to the severe morbidity and mortality. The thrombi most frequently occur in the venous circulation (ratio of 4:1), but arterial thrombotic events are well described.1,8 Results of early studies21 suggested that thromboembolic complications may be relatively uncommon, but we now recognize that depending on the clinical situation, one half to two thirds of patients with HIT can have thromboembolic complications.1-4 Furthermore, the previously accepted therapy of discontinuing heparin administration with no anticoagulant substitution has now been shown to be unacceptable in 2 studies,1,3 both of which documented that 50% of patients progress to a thrombotic event after discontinuation of heparin therapy for HIT.

The pathogenesis of HIT has been resolved. Patients at risk form an IgG antibody that binds to a conformationally induced site on platelet factor 4 when it is bound to heparin. These IgG–platelet factor 4–heparin immune complexes bind to platelets and endothelial cells, triggering activation of the coagulation cascade that presumably is responsible for the thrombotic complications.5,6

| Outcome† | Isolated HIT | | | HIT With Thrombosis | | | P Value | | | P Value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Control Group | Argatroban Group | | Control Group | Argatroban Group | | | | | | |
| Major bleeding | 12 (8.6) | 10 (5.3) | .27‡ | 1 (2.2) | 14 (6.1) | .48§ |
| Minor bleeding | 57 (41.0) | 59 (31.2) | .08 | 19 (41.3) | 87 (38.0) | .74 |

Abbreviation: HIT, heparin-induced thrombocytopenia.
*Data are given as number (percentage).
†Patients with more than 1 event are counted only once; patients with major and minor bleeding are counted as having major bleeding.
‡Odds ratio, 0.59; 95% confidence interval, 0.25-1.41.
§Odds ratio, 2.93; 95% confidence interval, 0.38-22.8.
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A better understanding of the pathogenesis of HIT has led to insights into the optimal treatment. In vitro studies and clinical experience have demonstrated that virtually any heparin or low-molecular-weight heparin cross-reacts with HIT antibodies and can cause worsening or progression of the thromboembolic process. The exception is the heparinlike anticoagulant danaparoid, which has been used successfully in patients with HIT. Two recently introduced thrombin-specific inhibitors, lepirudin and argatroban, offer promise as effective alternate anticoagulant therapeutic agents for patients with HIT. Distinguishing features between these agents include their routes of elimination and relative immunogenicity. Lepirudin, which is renally excreted, requires dose adjustments in patients with renal insufficiency and should be avoided in patients with acute renal failure or those undergoing hemodialysis. Argatroban, which is heptatically metabolized, requires dose adjustments in patients with hepatic impairment but not in patients with renal impairment. Approximately 50% of patients with HIT treated with lepirudin generate antibodies that may enhance its anticoagulant activity, and careful monitoring is important to avoid bleeding complications. Antibodies that alter the anticoagulant activity of argatroban have not been detected in patients with HIT on prolonged or repeated administration of argatrobe.
ban. The agents are similar in that both are generally monitored using aPTT and both lack a specific antidote. However, their anticoagulant effects generally return to baseline rapidly on drug discontinuation (elimination half-life in healthy individuals is 1.3 hours for lepirudin and 39-51 minutes for argatroban).

Although HIT is relatively common, the experience in clinical trials with thrombin-specific inhibitors has been modest. In 2 prospective studies including a total of 166 patients compared with 120 historical controls, lepirudin therapy was significantly effective in one study but not the other. Recently, we described a prospective study in which argatroban was effective at reducing the composite end point of death, amputation, or new thrombosis in 160 patients with isolated HIT. Although benefit was also seen in 144 patients with HITTS, it did not achieve significant levels, possibly related to the smaller patient numbers. Hence, we chose to continue to study patients with HIT who were treated with argatroban. In the study reported herein and our previous study of argatroban therapy in HIT, the eligibility criteria, dosing regimen, and outcomes assessed were the same. The studies differed in that they were conducted sequentially and sample size was not limited in the second study.

The present study describes an additional 418 adults with acute HIT. The effectiveness of argatroban therapy in this population was compared with historical control patients who also had active HIT. Several interesting observations were made. First, there was a significant reduction in the composite end point (all-cause death, amputation, or new thrombosis) in patients with HIT vs controls. Furthermore, by time-to-event analysis of the composite end point, significantly more argatroban-treated patients with HIT or HITTS remained event free vs controls. In addition, we observed that argatroban therapy significantly reduced new thrombosis and death due to thrombosis vs controls. Also, platelet counts recovered more rapidly in patients receiving argatroban vs historical controls. Indeed, mean platelet counts for the control group, but not the treatment group, continued to decrease, perhaps representing ongoing platelet consumption in the absence of an effective thrombin inhibitor.

Because argatroban is a direct thrombin inhibitor, its concomitant use with warfarin prolongs the prothrombin time and international normalized ratio beyond those produced by warfarin alone. Guidelines for monitoring this transition have been recently described. Nevertheless, there was no apparent overdosing or underdosing of warfarin.

During the design phase of this study, the researchers believed that it was not ethical to use placebo for patients with HIT because of its catastrophic nature. Similarly, other available agents, including heparin and low-molecular-weight heparin, were not believed to be ideal, and no alternative agent was available for use as an active comparator. Any study that uses a historical control population is less ideal than a true randomized trial. For example, different methods may be used to ascertain events for historical controls and treated patients, the diagnosis may not be as secure in the past owing to advances in disease awareness, and clinical practices may change over time (eg, initiating warfarin therapy during HIT is not recommended now until anticoagulation has been provided with an alternative agent and platelet counts have recovered). Our efforts to minimize possible sources of bias in the control group have been described previously. We suggest that the antithrombotic benefit in the argatroban-treated group is unlikely to be related to differences in the controls compared with the drug-treated patients because the groups met the same eligibility criteria and were generally well matched at baseline. Indeed, one difference between the groups was the lower platelet count in argatroban-treated patients compared with controls (significant in the HIT arm). We recently reported that a lower platelet count is associated with a worse outcome in patients with HIT. Hence, any difference between the groups would be that argatroban-treated patients had more severe HIT than controls.

Including the 304 patients with HIT from our previously reported study, a total of 722 patients with HIT (with or without thrombosis) treated with argatroban have been described, representing the largest population of patients with HIT reported to date treated with a direct thrombin inhibitor. There is a remarkable consistency in outcome between the 2 studies. The results of this study further support the conclusion that argatroban therapy, compared with control therapy, improves the outcomes of heparin-induced thrombocytopenia, particularly thrombosis and death due to thrombosis, without increasing bleeding risk.

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