Efficacy and Safety of Tifacogin (Recombinant Tissue Factor Pathway Inhibitor) in Severe Sepsis: A Randomized Controlled Trial

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Context The expression and release of tissue factor is a major trigger for the activation of coagulation in patients with sepsis. Tissue factor pathway inhibitor (TFPI) forms a complex with tissue factor and blood protease factors leading to inhibition of thrombin generation and fibrin formation.

Objectives To determine if administration of tifacogin (recombinant TFPI) provides mortality benefit in patients with severe sepsis and elevated international normalized ratio (INR) and to assess tifacogin safety in severe sepsis, including patients with low INR.

Design and Setting A randomized, double-blind, placebo-controlled, multicenter, phase 3 clinical trial conducted from March 21, 2000, through September 27, 2001, in 245 hospitals in 17 countries in North America, Europe, and Israel.

Patients The primary efficacy population consisted of 1754 patients (≥18 years) with severe sepsis and a high INR (≥1.2) randomly assigned to intravenous infusion of either tifacogin (0.025 mg/kg per hour for 96 hours, n=880) or placebo (arginine citrate buffer, n=874), and 201 patients with a low INR (<1.2) randomly assigned to receive the same dose of either tifacogin or placebo.

Main Outcome Measure All-cause 28-day mortality.

Results Overall mortality at 28 days in the tifacogin-treated group (n=880) vs the placebo group (n=874) for high INR was 34.2% vs 33.9%, respectively (P=.88, Pearson χ² test; P=.75, logistic regression model). None of the protocol-specified secondary end points differed between the tifacogin vs placebo groups. An analysis on the first 722 patients demonstrated a mortality rate of 38.9% for placebo vs 29.1% for tifacogin (P=.006, Pearson χ² test). Tifacogin significantly attenuated prothrombin fragment 1.2 and thrombin:antithrombin complex levels (P<.001, 2-sample t test) in patients with high and low INR. Overall mortality was lower in the tifacogin response in patients with low INR (12%; n=83) vs placebo (22.9%; n=118) (P=.051, Pearson χ² test; P=.03, logistic regression model). There was an increase in serious adverse events with bleeding in the tifacogin group in both cohorts (6.5% tifacogin and 4.8% placebo for high INR; 6.0% tifacogin and 3.3% placebo for low INR).

Conclusions Treatment with tifacogin had no effect on all-cause mortality in patients with severe sepsis and high INR. Tifacogin administration was associated with an increase in risk of bleeding, irrespective of baseline INR.

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For editorial comment see p 256.
ology with the cytokine-receptor family. A tissue factor pathway inhibitor (TFPI) is an endogenous serine protease inhibitor, synthesized and secreted by endothelial cells, which inhibits factor Xa directly and the factor VIIa/tissue factor catalytic complex in a Xa-dependent fashion. A significant portion of endogenous TFPI is bound to the microvasculature through low-affinity binding to glycosaminoglycans. This pool of TFPI is releasable into the circulation by exposure to heparin. A small pool of TFPI is stored in platelets and secreted on activation and degranulation. The majority of circulating TFPI is bound to lipoproteins. The circulating concentrations of TFPI vary widely in healthy volunteers and in patients with sepsis. A study by Shimura et al suggested that full-length TFPI was consumed in predisseminated intravascular coagulation conditions and that the truncated form of TFPI-antigen increased in patients with disseminated intravascular coagulation. The functional properties of circulating TFPI are not well delineated.

Endothelial damage is common in severe sepsis, as shown by elevations in endothelial derived factors, such as von Willebrand factor, and by the presence of coagulation abnormalities, including prolongation of prothrombin time, in more than 90% of patients who are severely ill and infected. It is hypothesized that in patients with severe sepsis, TFPI may protect the microvasculature endothelium from coagulation and sepsis-induced injury. This hypothesis is supported by several preclinical studies in which exogenous TFPI expressed in mammalian cells and/or Escherichia coli improved outcome in septic animals. The safety and bioactivity of tifacogin (recombinant TFPI) has been previously evaluated in healthy volunteers and in patients with sepsis. Tifacogin was found to be well tolerated with no clinically significant bleeding in healthy volunteers when administered as an infusion in doses of 0.5 to 1.8 mg/kg per hour for 72 hours. Phase 2 studies indicated that patients with severe sepsis were more sensitive to the anticoagulant action of TFPI than healthy volunteers. Tifacogin has been tested in 3 phase 2 studies. The most recent phase 2 study was a randomized, multicentered, placebo-controlled, single-blind trial with dose escalation in which 210 patients received a continuous infusion of either placebo or tifacogin at 0.025 mg/kg per hour or 0.05 mg/kg per hour for 96 hours. The findings of that study established the safety, tolerability, and bioactivity of tifacogin in patients with severe sepsis and suggested a possible interaction between treatment and international normalized ratio (INR) by logistic regression modeling. The objectives of the current phase 3 study was to evaluate the safety and efficacy of tifacogin in patients with severe sepsis with high INR (≥1.2), and to evaluate the safety of tifacogin in patients with severe sepsis with low INR (<1.2).

METHODS

The optimized phase 3 tifacogin in multicenter international sepsis trial (OPTIMIST) study was a randomized, double-blind, placebo-controlled trial, with 245 contributing centers in 17 countries in North America, Europe, and Israel. The institutional review boards at each center approved the study. Randomization to the active study drug (tifacogin) and to a placebo group occurred in a 1:1 fashion. The trial was performed in 2 stages: stage 1 recruited patients with high INR only with severe sepsis from March 21, 2000, through September 27, 2001, and stage 2 continued to enroll patients with high INR and initiated the recruitment of patients with low INR, which began January 19, 2001, and ended September 27, 2001.

An independent, unblinded data management committee evaluated the safety, futility, and efficacy of tifacogin during 4 formal prospectively defined interim analyses. The main safety assessment was the comparison of the incidence and severity of bleeding events as identified by the investigator and mortality between the tifacogin and placebo groups.

Patient Characteristics

Adult hospitalized men and women aged at least 18 years who met the entry criteria were enrolled in the study if they gave informed consent, had at least 2 signs of systemic inflammatory response syndrome, and at least 2 signs of organ dysfunction and/or hypoperfusion within 24 hours before the start of drug infusion. In addition, the baseline INR was determined within 24 hours before the start of drug infusion. The initial signs of systemic inflammatory response syndrome were allowed to have started or been intermittently present for more than 24 hours before drug infusion. The initial sign of organ dysfunction or hypoperfusion also was allowed to be present for more than 24 hours before the start of drug infusion. The onset of the second organ failure could not be present for more than 24 hours before the initiation of drug administration.

Study Entry Criteria

Stage 1 entry criteria included patients with a baseline INR of at least 1.2 not attributable to medications or conditions other than severe sepsis. Infection status was determined by using clinical signs of infection and documented by culture, gram stain, antigenic or nucleic acid assay of a body fluid, or a chest radiograph consistent with a diagnosis of pneumonia. These criteria were used to support the rationale for systemic therapy with antimicrobials (antimicrobial agents) and to provide a clear verifiable focus of infection. The patients also had to have at least 2 signs of organ dysfunction and/or hypoperfusion.

Study Medication

Tifacogin is produced in E coli and is distinguished from endogenous TFPI by an alanine at the N terminus and lack of glycosylation. Patients were randomly assigned to receive 0.025 mg/kg per hour of tifacogin (Chiron Corporation, Emeryville, Calif) as a continuous intravenous infusion for 96 hours or an equivalent volume of placebo (arginine citrate buffer). Patients were pro-
spective randomized by using random block sizes of 2, 4, or 6 within each center and INR cohort. The placebo and tifacogin vials were packaged identically to maintain blinding.

TFPI Levels
Blood samples for obtaining TFPI plasma concentrations were collected preinfusion (–2 hours to time 0) on days 1 (4 and 8 hours), 2, and 3, as well as at termination of dosing. Pharmacokinetic samples were measured with a validated electrochemiluminescent immunoassay by using monoclonal and polyclonal antibodies to TFPI. The monoclonal antibody was specific for the first Kunitz domain of TFPI. As a result, the assay measured endogenous TFPI as well as the recombinant form (tifacogin). The assay standards and quality controls were diluted in rabbit plasma because rabbit plasma does not contain TFPI, which cross reacts with the monoclonal antibody. The lower limit of quantitation was 5 ng/mL.

End Points, Monitoring, and Enrollment
The primary efficacy end point was death from any cause occurring within the 28 days following the initiation of drug infusion in patients with high INR at the time of randomization. Patients who received any amount of study drug were included in the safety and efficacy analyses and were analyzed according to the treatment group to which they were randomized.

An external data management committee assessed the safety, futility, and efficacy of the trial at 4 prospectively defined interim analyses. The data management committee recommended including up to an additional 400 patients having a baseline INR of at least 1.2 to maintain the power of the trial at 90% to detect a relative decrease in mortality of 25%.

The planned enrollment for the trial was 1550 patients: 1350 patients with high INR and 200 patients with low INR at the time of randomization. An additional 400 patients were enrolled to maintain trial power, per the protocol. Consequently, 1987 patients were enrolled into the trial (Figure 1). Of these, 30 patients were randomized but not subsequently infused with study drug and 2 patients withdrew consent. A total of 1955 patients were therefore included in the primary and secondary efficacy and safety analyses: 1754 patients with high INR and 201 patients with low INR at the time of randomization.

Statistical Methods
The difference between the tifacogin and placebo groups in 28-day all-cause mortality was assessed by using a prespecified logistic regression model having factors for treatment group, baseline Acute Physiology and Chronic Health Evaluation (APACHE) II score, and baseline log10 IL-6 (both covariates treated as continuous variables). P values were computed for the Wald $\chi^2$ statistic with respect to a $\chi^2$ distribution with 1 degree of freedom. The presence of treatment by covariate interaction effects was assessed separately. To explore the robustness of the primary analysis, a simple Pearson $\chi^2$ test comparing tifacogin with placebo was also performed. Additionally, Kaplan-Meier method curves illustrating the unadjusted difference between the tifacogin and placebo groups in time to death were produced.

Exploratory analyses to investigate the association between baseline covariates and 28-day all-cause mortality and to identify treatment by covariate interactions were performed by using forward-stepwise logistic regression. Because treatment groups were well balanced with respect to prognostic baseline covariates, P values presented for these ex-
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RESULTS

Characteristics of the Study Population

Details of study conduct, randomization, and resulting patient population are shown in Figure 1. The study population consisted of 1955 adult patients aged at least 18 years randomly distributed between 2 patient cohorts: patients with severe sepsis with high INR or low INR. Within each cohort, patients were randomly assigned to the placebo group or tifacogin group. All patients were analyzed as randomized. The primary efficacy population consisted of 1754 patients with high INR randomly assigned to the placebo group (n = 874) or tifacogin group (n = 880).

Patients were well matched at study entry for age, sex, APACHE II score, body weight, and race (Table 1). The most common sites of infection were respiratory, followed by intrabdominal, genitourinary, skin and soft tissue, and infections due to intravascular devices. The patients were similar at study entry with respect to culture results, surgical status (having had a major surgical procedure requiring spinal or general anesthesia within 5 days before drug infusion), and shock at baseline.

TFPI Levels in Treatment Groups

The mean (SE) baseline TFPI level concentration in patients with high INR was 71 (1.5) ng/mL in the placebo group. Patients randomized to the tifacogin group rapidly achieved mean circulating TFPI levels that were approximately twice the mean endogenous circulating levels observed in the placebo group (147 [16] ng/mL). The increase in mean TFPI levels in the tifacogin group with high INR was observed throughout the conduct of the trial. A similar increase in mean TFPI levels was also observed in patients with low INR. Mean baseline TFPI levels in patients with low INR were comparable with patients with high INR (data not shown).

Efficacy of Tifacogin in Patients With High INR

The observed 28-day all-cause mortality for patients receiving tifacogin did not significantly differ from the placebo group in the primary study population (34.2% for the tifacogin group vs 33.9% for the placebo group; P = .75, Pearson chi^2 test; P = .75, logistic regression model). The Kaplan-Meier method survival curves are shown in Figure 2A. There was no difference in the mortality rate between the tifacogin and the placebo groups in any of the prospectively defined study subpopulations (Table 2).

A trend in favor of tifacogin was present for the first 9 months of enrollment into the trial, but was then reversed in favor of placebo in the last 7 months of enrollment. This finding is demonstrated in the 3-month moving average (Figure 3). The second interim analysis was performed on the first 722 patients enrolled in the study. At the time of that analysis, which was...
performed by the data management committee, the mortality rate was 38.9% in the placebo group and 29.1% in the tifacogin group (P = .006, Pearson χ² test). However, a decrease in placebo mortality and an increase in tifacogin mortality were observed in the later part of the study, leading to a complete reversal of the initial favorable results and final neutral trial outcome.

**Bioactivity of Tifacogin**

Because there was no apparent survival benefit in the primary efficacy population (patients with INR ≥ 1.2) and in the prespecified subgroups, we investigated whether or not tifacogin exhibited in vivo bioactivity in the patients who were treated. In vitro, preclinical, and clinical studies⁵,¹⁰,¹¹ have previously demonstrated that TFPI is a potent thrombin-generation inhibitor. Therefore, differences in plasma levels of prothrombin fragment 1.2 and thrombin:antithrombin complex in the placebo and tifacogin groups were assessed. The geometric mean (SE) ratio of prothrombin fragment 1.2 and thrombin:antithrombin complex plasma levels during treatment (24 and 96 hours) for the placebo group as a percentage of baseline were 120 (5) at 24 hours and 137 (8) at 96 hours, and 87 (7) at 24 hours and 84 (8) at 96 hours, respectively. The geometric mean (SE) ratio of prothrombin fragment 1.2 and thrombin:antithrombin complex plasma levels for the tifacogin group were 101 (5) at 24 hours and 126 (7) at 96 hours, and 65 (5) at 24 hours and 60 (6) at 96 hours, respectively. Tifacogin treatment was associated with lower prothrombin fragment 1.2 and thrombin:antithrombin complex levels at 24 and 96 hours postinitiation of treatment (P < .001, 2-sample t test vs placebo). This finding demonstrates that tifacogin exhibited biological activity in patients with severe sepsis. Similar decreases in thrombin:antithrombin complex levels had been previously observed in the phase 2 clinical trial.¹³ Tifacogin administration also resulted in decreased thrombin:antithrombin complex and prothrombin fragment 1.2 levels in patients with low INR (data not shown).

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**Table 2. 28-Day Mortality Overall and in Prespecified Subpopulations**

<table>
<thead>
<tr>
<th>Population</th>
<th>No. of Patients</th>
<th>28-Day Mortality Rate, No. (%)</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy (baseline INR ≥ 1.2)</td>
<td>Placebo 874, Tifacogin 880</td>
<td>Placebo 296 (33.9), Tifacogin 301 (34.2)</td>
<td>1.01 (0.89-1.15)</td>
</tr>
<tr>
<td>Baseline INR ≥1.5 and coagulation organ dysfunction score &lt;4</td>
<td>Placebo 149, Tifacogin 125</td>
<td>Placebo 68 (45.6), Tifacogin 52 (41.6)</td>
<td>0.91 (0.69-1.20)</td>
</tr>
<tr>
<td>Baseline INR &lt;1.5 or coagulation organ dysfunction score ≥4</td>
<td>Placebo 724, Tifacogin 753</td>
<td>Placebo 228 (31.5), Tifacogin 248 (32.9)</td>
<td>1.05 (0.90-1.21)</td>
</tr>
</tbody>
</table>

**Notes:**
- Shock at baseline: No 208, Yes 666
- Baseline APACHE II score <20 207, ≥20 665
- Baseline PaO₂/FiO₂ ratio <300 767, ≥300 107

**Abbreviations:** APACHE, Acute Physiology and Chronic Health Evaluation; INR, international normalized ratio.

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**Analysis of Tifacogin Response in Patients With Low INR**

Two hundred and one patients with low INR were randomized and treated, of which 118 received placebo and 83 received tifacogin. The Kaplan-Meier method plot of survival during the 28-day period is shown for both tifacogin and placebo groups (Figure 2B). Overall, 28-day all-cause placebo mortality was 22.9% compared with 12.0% for patients receiving tifacogin (P = .051, Pearson χ² test). A prespecified logistic regression analysis was also performed, adjusting for treatment, baseline APACHE II score, and log₁₀ IL-6 variables. The adjusted analysis dem-
onstrated significant benefit for the low INR group ($P = .03$).

**Post-hoc Analyses of Factors Contributing to the Primary Patient Population Outcome**

Because of the changes in the 28-day mortality observed during the course of the trial (Figure 3) and the observation that the findings from the tifacogin-attenuated coagulation were abnormal in the patient populations with both high and low INR (but only provided a mortality benefit in patients with low INR), post hoc analyses were conducted to identify confounding factors that could have contributed to the final outcome of the study in the primary population with high INR.

**Tifacogin Interaction With Heparin in Patients With High and Low INR**

In vitro and preclinical studies indicate that the third Kunitz domain and C terminus of TFPI bind heparin with low affinity. Similarly, heparin displaces TFPI from binding to glycosaminoglycans on the surface of endothelial cells.

Patients who received at least 1 dose of unfractionated heparin or low molecular-weight heparin during the period beginning 24 hours before dosing through the end of the dosing period (heparin) were compared with patients who did not receive heparin during that time (no heparin). Mortality was examined in patients with high INR and low INR, stratified by heparin use. The mortality of patients receiving tifacogin who did not receive heparin before or during dosing was 34.6% compared with 42.7% in the placebo group ($P = .05$) (TABLE 3). In contrast, the mortality of patients receiving tifacogin with high INR who received heparin under similar conditions was 34.0%, although the mortality rate was 29.8% for the placebo group. There was no increase in bleeding or other nonsepsis-related serious adverse events in patients receiving tifacogin and heparin. Despite the small numbers, improved survival was observed in patients receiving tifacogin with low INR both with and without concomitant heparin use, although the improvement in outcome was more apparent in patients receiving no heparin. Mortality was lower in patients receiving placebo and heparin compared with those who did not. However, the patients who received heparin were not as severely ill as determined by APACHE II scores, INR value, and mean organ dysfunction score compared with patients who did not receive heparin (data not shown).

**Safety Findings in Patients With High and Low INR**

The incidence of investigator-identified adverse events and serious adverse events (those that were life-threatening or prolonged hospitalization) in patients with high and low INR was similar in both the tifacogin and placebo groups (TABLE 4). The majority of patients experienced at least 1 adverse event during the 28-day trial period (INR $\geq$1.2: tifacogin group, 91% and placebo group, 92%; INR <1.2: tifacogin group, 94% and placebo group, 92%). Approximately half of the patients had at least 1 serious adverse event (tifacogin group, 51%; placebo group, 51%) in the high INR group. Slightly fewer patients experienced at least 1 serious adverse event in the low INR group (tifacogin group, 36%; placebo group, 43%).

There was an increase in the incidence of adverse events with bleeding in the tifacogin group compared with the placebo group (INR $\geq$1.2: tifacogin group, 24% and placebo group, 19%; INR <1.2: tifacogin group, 24% and placebo group, 21%). The most common events with bleeding were from the gastrointestinal and respiratory tracts (data not shown).

There was an increase in the overall incidence of serious adverse events with bleeding in the tifacogin group (6.5%) compared with the placebo group (4.8%) for high INR. In patients with low INR, serious adverse events with bleeding occurred in 5 (6.0%) of 83 patients in the tifacogin group and 4 (3.3%) of 118 patients in the placebo group. In the patients with high INR, there were more events with bleeding in the central nervous system (CNS) in the tifacogin group (9 events) compared with the placebo group (3 events). In the patients with low INR, there were 2 events with CNS bleed-
ing in the tifacogin group and none in the placebo group.

The β half-life of tifacogin in the blood is relatively short (8 hours); therefore, tifacogin safety was best evaluated during dosing and up to 2 days after stopping the infusion. More than half of the serious adverse events with bleeding in patients with high INR occurred during dosing or within 2 days of stopping the infusion in both the tifacogin and placebo groups (tifacogin group, 34 [60%] of 57 events; placebo group, 22 [52%] of 42 events). During this period, 5 of the 9 events with CNS bleeding occurred in the tifacogin group and no events occurred in the placebo group.

Six patients experienced a serious adverse event with bleeding during dosing or in the 2 days following the completion of dosing in the group with low INR (tifacogin group, 3.6% [3 of 83 patients]; placebo group, 2.5% [3 of 118 patients]). One patient receiving tifacogin experienced an event with CNS bleeding within 2 days of dosing.

The administration of heparin at baseline and/or during dosing did not appear to increase the overall risk of events with investigator-identified bleeding or serious events with bleeding for either the tifacogin or the placebo groups (Table 5). The risk of events with CNS bleeding in the high INR group was not increased in patients receiving both tifacogin and heparin (6 [1%] of 600 patients) compared with those receiving tifacogin alone (3 [1%] of 280 patients). The risk of events with CNS bleeding in the low INR group also did not appear to increase in patients receiving heparin.

**COMMENT**

In this study, there was no survival benefit provided by tifacogin in the primary study population of patients with severe sepsis with high INR. The change in trial outcome after the enrollment of more than 700 patients with high INR is unusual and distinct from that observed in previous severe sepsis studies, including those examining 2 other endogenous coagulation inhibitors. For example, a decrease in mortality rates among patients treated with activated protein C was observed after 720 patients were enrolled during the later stages of the recombinant human activated protein C worldwide evaluation in severe sepsis (PROWESS) trial. However, unlike this study, the mortality rate in the placebo group of the PROWESS trial was relatively constant throughout the duration of the study. Large changes in mortality rates over time were not observed in the Kybercept trial for either patients treated with antithrombin III or the placebo group (S. Opal, MD, written communication, March 5, 2003).

Several hypotheses were evaluated to determine possible variables that could account for the time-dependent changes observed in the outcome of the current trial. Among the hypotheses evaluated were changes in study operational variables, changes in the enrolled patient population, changes in standard of care, and changes in tifacogin activity or toxicity. Although the recruitment at new sites and the simultaneous enrollment of patients with high and low INR in the second stage of the trial occurred at the same time as the change in mortality rates in the tifacogin and placebo groups, these operational issues did not explain the reversal in study outcome. An extensive audit of clinical trial procedures excluded a process error (eg, randomization error) and confirmed that patients were correctly analyzed according to the treatment received. The population pharmacokinetic data support the

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**Table 4. Summary of Patients With Adverse Events**

<table>
<thead>
<tr>
<th>Baseline INR ≥1.2</th>
<th>Placebo (n = 874)</th>
<th>Tifacogin (n = 880)</th>
<th>P Value†</th>
<th>Placebo (n = 118)</th>
<th>Tifacogin (n = 83)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>802 (92)</td>
<td>801 (91)</td>
<td>.58</td>
<td>108 (92)</td>
<td>78 (94)</td>
<td>.52</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>443 (51)</td>
<td>447 (51)</td>
<td>.96</td>
<td>51 (43)</td>
<td>30 (36)</td>
<td>.31</td>
</tr>
<tr>
<td>Adverse event with bleeding</td>
<td>168 (19)</td>
<td>215 (24)</td>
<td>.008</td>
<td>25 (21)</td>
<td>20 (24)</td>
<td>.63</td>
</tr>
<tr>
<td>Serious adverse event with bleeding</td>
<td>42 (4.8)</td>
<td>57 (6.5)</td>
<td>.13</td>
<td>4 (3.3)</td>
<td>5 (6.0)</td>
<td>.37</td>
</tr>
<tr>
<td>Bleeding in central nervous system</td>
<td>3 (0.3)</td>
<td>9 (1)</td>
<td>.08</td>
<td>0</td>
<td>2 (2)</td>
<td>.09</td>
</tr>
</tbody>
</table>

Abbreviation: INR, international normalized ratio.
*Data are presented as No. (%).
†Comparing tifacogin with placebo from Pearson χ² test.

**Table 5. Summary of Patients Experiencing Adverse Events With Bleeding and Serious Adverse Events With Bleeding by Concomitant Heparin Use**

<table>
<thead>
<tr>
<th>Heparin</th>
<th>Placebo</th>
<th>Tifacogin</th>
<th>P Value†</th>
<th>Placebo</th>
<th>Tifacogin</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline INR ≥1.2</td>
<td>114 (19)</td>
<td>138 (23)</td>
<td>.09</td>
<td>54 (20)</td>
<td>77 (28)</td>
<td>.03</td>
</tr>
<tr>
<td>No. of patients</td>
<td>600</td>
<td>600</td>
<td>274</td>
<td>280</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse event with bleeding, No. (%)</td>
<td>29 (5)</td>
<td>39 (7)</td>
<td>.21</td>
<td>13 (5)</td>
<td>18 (6)</td>
<td>.39</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline INR &lt;1.2</th>
<th>No. of patients</th>
<th>81</th>
<th>65</th>
<th>37</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event with bleeding, No. (%)</td>
<td>16 (20)</td>
<td>16 (25)</td>
<td>.48</td>
<td>9 (24)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Serious adverse event with bleeding, No. (%)</td>
<td>2 (2)</td>
<td>5 (8)</td>
<td>.14</td>
<td>2 (5)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviation: INR, international normalized ratio.
*Patients receiving any heparin during the period beginning 24 hours before dosing through the end of the dosing period (heparin); those patients who did not receive heparin during that time (no heparin).
†Comparing tifacogin with placebo from Pearson χ² test.
randomization code. The TFPI levels were consistent over time in the tifacogin group.

The possibility that the patient population enrolled in the current study changed over time was also examined. There were no detectable temporal changes in the degree of disease severity. The mean APACHE II scores of the patients receiving placebo enrolled in the first stage of the study were 25.0 for the tifacogin group and 25.1 for the placebo group, and those for the second stage of the study were 25.0 and 24.8, respectively. An increase in tifacogin levels was not observed in the placebo group. Additionally, patient characteristics in this trial were examined by using the APACHE III database. Baseline mortality risk by day 28 was well balanced between treatment groups and did not change over time (W. A. Knaus, MD, written communication, April 15, 2002).

Possible changes in the standard of care and the adoption of emerging treatment modalities were also evaluated by polling the clinical sites involved in the study and by the review of the hospital records of the patients enrolled in the study. There were no apparent changes in patient management that correlated with patient outcome. Although heparin appeared to be a confounding factor, changes in heparin use did not explain the reversal in study outcome.

The increase in mortality with tifacogin could have been the result of a decrease in tifacogin in vivo activity or an increase in toxicity. This hypothesis was not substantiated by the in vivo anticoagulant measures of tifacogin bioactivity, such as extent of decrease in thrombin:antithrombin complex, prothrombin fragment 1.2, prolongation of INR, and activated partial thromboplastin time. There also was no evidence of decreased drug activity by in vitro parameters to match the increase in mortality in the tifacogin group in the second stage of the study. The tifacogin safety profile, measured by frequency of adverse events and serious adverse events, was similar in the first and second stage of the trial. A change in tifacogin potency or toxicity, if such an event occurred, would only explain alterations in mortality for 1 group of the trial (ie, the tifacogin group) and would not address the simultaneous decline in placebo mortality observed in the second half of the study.

Post hoc analyses suggested that there was an interaction between heparin and tifacogin in which patients who did not receive concomitant heparin appeared to benefit from treatment with tifacogin. Interactions with heparin were also observed in clinical trials with 2 other endogenous anticoagulants, activated protein C and antithrombin III. Specifically, both the PROWESS and Kybersept trials noted an apparent attenuation of activated protein C and antithrombin III efficacy in patients who received heparin.16-18 The biological basis for this interaction is more evident for antithrombin III, which is a cofactor of heparin, and for TFPI, which has heparin-binding domains and is reported to be displaced by heparin from the endothelium.19,20 The nature of the activated protein C and heparin interaction is not well understood. Optimal use of low-dose heparin and activated protein C is being investigated.20 In addition to the observation of an interaction between heparin and the endogenous anticoagulants, the PROWESS, Kybersept, and OPTIMIST studies also showed that 28-day all-cause mortality was lower in patients receiving placebo who also received low-dose prophylactic heparin. Patients who received prophylactic heparin were found to be less severely ill in the OPTIMIST study than the corresponding group of patients who did not receive heparin (evaluated by APACHE II score, INR value, and mean organ dysfunction score). The patients were not randomized to receive heparin in all 3 endogenous anticoagulant severe sepsis trials. Hence, it is difficult to assess the true effect of heparin on mortality of patients with severe sepsis from these trials.

Activation of the coagulation cascade has been postulated to contribute to organ system dysfunction and mortality in patients with sepsis. Three known endogenous anticoagulants (antithrombin III, activated protein C, and TFPI) have been evaluated for the treatment of severe sepsis. Only treatment with recombinant activated protein C demonstrated benefit in the more severely ill patients with sepsis. The lack of benefit with antithrombin III and tifacogin may have been due to differences in biological activities unrelated to coagulation or insufficient dosing to overcome the procoagulant environment. Other potential factors that may have influenced the outcome of these studies include differences in trial design and the confounding effect of concomitant heparin. Additional studies with all 3 agents in the absence of heparin may be warranted.

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REFERENCES


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