High-Dose Antithrombin III in Severe Sepsis
A Randomized Controlled Trial

Brian L. Warren, MD
Alain Eid, MD
Pierre Singer, MD
Subramanion S. Pillay, MBChB, RCP, RCS
Peder Carl, MD
Ivan Novak, MD
Pavel Chalupa, MD, PhD
Alan Atherstone, MD, ChB, FRCS
Istvan Pénzes, DSc
Andrezej Kübler, MD, PhD
Sigurd Knaub, PhD
Heinz-Otto Keinecke
Hubert Heinrichs, MD
Fritz Schindel
Mathias Juers, MD
Roger C. Bone, MD†
Steven M. Opal, MD
for the KyberSept Trial Study Group

Context Activation of the coagulation system and depletion of endogenous anticoagulants are frequently found in patients with severe sepsis and septic shock. Diffuse microthrombus formation may induce organ dysfunction and lead to excess mortality in septic shock. Antithrombin III may provide protection from multiorgan failure and improve survival in severely ill patients.

Objective To determine if high-dose antithrombin III (administered within 6 hours of onset) would provide a survival advantage in patients with severe sepsis and septic shock.

Design and Setting Double-blind, placebo-controlled, multicenter phase 3 clinical trial in patients with severe sepsis (the KyberSept Trial) was conducted from March 1997 through January 2000.

Patients A total of 2314 adult patients were randomized into 2 equal groups of 1157 to receive either intravenous antithrombin III (30 000 IU in total over 4 days) or a placebo (1% human albumin).

Main Outcome Measure All-cause mortality 28 days after initiation of study medication.

Results Overall mortality at 28 days in the antithrombin III treatment group was 38.9% vs 38.7% in the placebo group ($P=.94$). Secondary end points, including mortality at 56 and 90 days and survival time in the intensive care unit, did not differ between the antithrombin III and placebo groups. In the subgroup of patients who did not receive concomitant heparin during the 4-day treatment phase (n=698), the 28-day mortality was nonsignificantly lower in the antithrombin III group (37.8%) than in the placebo group (43.6%) ($P=.08$). This trend became significant after 90 days (n=686; 44.9% for antithrombin III group vs 52.5% for placebo group; $P=.03$). In patients receiving antithrombin III and concomitant heparin, a significantly increased bleeding incidence was observed (23.8% for antithrombin III group vs 13.5% for placebo group; $P<.001$).

Conclusions High-dose antithrombin III therapy had no effect on 28-day all-cause mortality in adult patients with severe sepsis and septic shock when administered within 6 hours after the onset. High-dose antithrombin III was associated with an increased risk of hemorrhage when administered with heparin. There was some evidence to suggest a treatment benefit of antithrombin III in the subgroup of patients not receiving concomitant heparin.

JAMA. 2001;286:1869-1878 www.jama.com

SYSTEMIC ACTIVATION OF THE COagulation system is frequently observed in patients with severe sepsis and/or septic shock.[1,2] Endogenous anticoagulants and the fibrinolytic system are activated and function to regulate intravascular coagulation induced by the septic process. As the coagulation process continues, these clotting inhibitors are consumed,[3-6] and fibrinolysis is rapidly inhibited by the production of plasminogen activator inhibitor-1.[2-4] A procoagulant state develops in patients with sepsis, which has deleterious pathophysiological effects. The generation of diffuse thrombus formation throughout microcirculation compromises tissue perfusion to critical organs.[1-4,7]

For editorial comment see p 1894.

The notion that the uncontrolled activation of the coagulation system during sepsis contributes to the high mortality associated with septic shock has been speculated on for many years.[2,8-11] Antithrombin III is a hepatically synthesized, 58-kd plasma glycoprotein, which acts as a serine protease inhibitor affecting multiple components of the intrinsic, extrinsic, and common coagulation pathways.[2,12-16] Recent experimental evidence in several animal studies indicates that supraphysiological doses of antithrombin III possess substantial anti-inflammatory activity in addition to anticoagulant func-

Author Affiliations, Financial Disclosures, and Role of the Sponsor are listed at the end of this article.
†Deceased
Corresponding Author and Reprints: Steven M. Opal, MD, Brown University School of Medicine, Infectious Disease Division, Memorial Hospital of Rhode Island, 111 Brewster St, Pawtucket, RI 02860 (e-mail: Steven_Opal@brown.edu).
Caring for the Critically Ill Patient Section Editor: Deborah J. Cook, MD, Consulting Editor, *JAMA*.
Advisory Board: David Bihari, MD; Christian Brun-Buisson, MD; Timothy Evans, MD; John Heffner, MD; Norman Paradis, MD.

tions.[17] Antithrombin III binds to selected forms of glycosaminoglycans found on endothelial membranes resulting in an increase in prostacyclin synthesis. This limits interactions between endothelial cells and neutrophil, reduces platelet aggregation, and decreases proinflammatory cytokine production. This effect is abolished by heparin intake.[17-21]

Therapeutic doses of heparin[22] or antithrombin III[23] have been used clinically for more than 20 years for the prevention and treatment of disseminated intravascular coagulation and sepsis. Antithrombin III levels decrease precipitously in the early phases of severe sepsis,[3,5,24] and rapid depletion of antithrombin III in septic shock portends an unfavorable prognosis.[24] Numerous experimental studies in animals[25-27] and phase 2, placebo-controlled therapeutic trials of antithrombin III in patients with severe sepsis[28-31] have been conducted. Some of these trials have been analyzed in a recent meta-analysis.[31] The results suggested that antithrombin III may provide significant protection from multiorgan failure and a survival benefit in the most severely ill patients with severe sepsis and/or septic shock.

This phase 3 international trial of severe sepsis (the KyberSept Trial) was undertaken to determine the clinical efficacy of antithrombin III and the level of protection afforded by this endogenous human anticoagulant.

METHODS

The study was a randomized, double-blind, placebo-controlled trial, with 211 contributing centers in 19 countries worldwide. Randomization to the active study drug antithrombin III and a placebo group was 1:1.

An independent data safety and monitoring board oversaw risks and benefits during 2 formal interim analyses; in addition, safety assessments (with a focus on bleeding events) were performed at more frequent intervals.

Patient Characteristics

Adult hospitalized men and women (≥18 years) were admitted to the study if they gave informed consent and met the following criteria within a 6-hour period: clinical evidence of sepsis with a suspected source of infection, body temperature (rectal or core) higher than 38.5°C or lower than 35.5°C, and leukocyte count higher than $10 \times 10^3/\mu L$ or lower than $3.5 \times 10^3/\mu L$. Additionally, 3 of the following 6 signs had to be met within the same 6-hour period: tachycardia (heart rate >100/min); tachypnea (>24/min) or mechanical ventilation because of septic indication; hypotension with systolic blood pressure lower than 90 mm Hg despite sufficient fluid replacement or the need of vasoactive agents to maintain systolic blood pressure of 90 mm Hg or greater; thrombocytopenia with platelet counts of less than $100 \times 10^3/\mu L$; elevated lactate levels (above upper limit of normal range) or metabolic acidosis (pH <7.3 or base excess ≤ –10 mmol/L) not secondary to respiratory alkalosis; oliguria with urine output of less than 20 mL per hour despite sufficient fluid replacement.

Patients presenting with any of the following criteria were not to be included into the study: advanced directive to withhold life-sustaining treatment (except cardiopulmonary resuscitation); condition other than sepsis anticipated to be fatal within 28 days; pregnancy or breastfeeding; history of hypersensitivity to study medication; treatment with other investigational drugs within the last 30 days; treatment with an antithrombin III concentrate within the last 48 hours; treatment with heparin (except subcutaneous low dose or intravenous [IV] line flushing) or coumarin derivatives; nonsteroidal anti-inflammatory drug treatment within previous 2 days; known bleeding disorder or ongoing massive surgical bleeding; platelet count of less than $30 \times 10^3/\mu L$; immunocompromised status; acute myocardial infarction (within previous 7 days); third-degree burns (≥20% of total body area); incurable malignancy with documented metastases and life-expectancy of less than 3 months; hematologic neoplasia during cytostatic treatment; bone marrow aplasia; preexisting dialysis-dependent renal failure; end-stage liver disease; transplantation (postoperative state); history of stroke within the last year; severe cranial or spinal trauma within the last year; planned cranial or spinal surgery (except nontraumatic lumbar puncture) within the next 48 hours.

Study Medication

Patients were randomly assigned to receive 30 000 IU antithrombin III (Aventis Behring, Marburg, Germany) with a loading dose of 6000 IU (given over 30 minutes), followed by a continuous IV infusion of 6000 IU per day for 4 days, or an equivalent volume of placebo solution (1% of human albumin).

Randomization plans had been prepared in advance with a block size of 4 patients. When a patient qualified for enrollment, investigators called the randomization center (available on a 24-hour basis) and were told the medication package number to be used. Packages for individual patients consisted of vials and labels identical in appearance for antithrombin III and placebo.

Unfractionated or low molecular weight heparin for venous thrombosis prophylaxis (≤10 000 IU subcutaneous per day), and heparin flushes for vascular catheter patency (IV of ≤2 IU per kilogram of body weight per hour) were allowed.

Study Variables

The primary efficacy outcome was defined as 28-day all-cause mortality in the primary efficacy population, consisting of all patients randomized who had received any portion of study drugs and whose survival status after 28 days was known. Secondary efficacy criteria were survival time, length of intensive care unit stay, and occurrence of new organ dysfunction (according to Logistic Organ Dysfunction score[32]) within 7 days. The severity of sepsis was assessed via the Simplified Acute Physiology Score version II[33] (SAPS II). Circulatory shock was assumed if the shock index (ie, the ratio of heart rate [beats per minute] and systolic blood pressure [millimeters of mercury]) exceeded the value of 1.5. Sur-

gical interventions and bleeding events were recorded for 28 days. Bleeding was classified as major if it was intracranial or required a transfusion of at least 3 units of blood. Other serious adverse events were recorded for 14 days. Antithrombin III plasma concentrations (functional) at baseline and after 24 hours were assessed by a central laboratory (Medinet, Breda, the Netherlands). The activated partial thromboplastin time and prothrombin time values were assessed at baseline and 3 times daily for days 1 through 5 and on day 7.

Subpopulations of special interest, as mentioned in the protocol for secondary analyses, were patients treated according to protocol, severity of sepsis (moderate, high, or very high risk), patients with baseline antithrombin III below 60%, and use of concomitant heparin.

Statistical Methods

The initial sample size of 2000 patients was based on an assumed placebo mortality of 45%, a relative risk reduction of 15% with antithrombin III (toward a mortality of 38%, which was considered a clinically relevant difference), and a power of 85%, as derived from the Casagrande formula.[37] A reassessment of sample size[38] was foreseen in the study protocol after enrollment of 500 patients, to maintain power above 85%, and resulted in the final target sample size of 2300 patients.

The difference in 28-day all-cause mortality between antithrombin III and placebo treatment for the primary efficacy population was assessed by a stratified Mantel-Haenszel test with continuity correction[34] accepting an adjusted overall 2-sided type I error of 5% ($\alpha = .05$). Three strata were defined in a protocol amendment according to predicted mortality[35] from baseline SAPS II (moderate risk, <30%; high risk, 30%-60%; very high risk, >60%). Two interim analyses took place after recruitment of 33% ($\alpha = .0005$) and 67% ($\alpha = .014$) of the target sample size; the nominal α level for the final analysis was .045, corresponding to the O'Brien/Fleming scheme.[36]

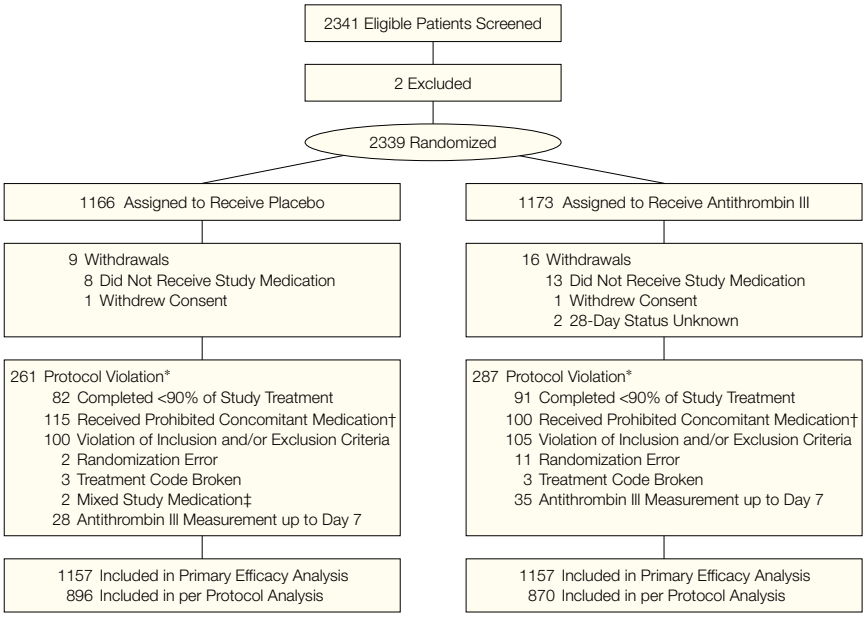
The comparability of patients at baseline was assessed by clinical and laboratory parameters. The 28-day mortality and adverse outcomes (eg, bleeding) were also expressed as relative risks of antithrombin III vs placebo treatment, together with asymptotic 95% confidence intervals.[34] A per protocol population (FIGURE 1) and various subgroups of the primary efficacy population were also defined. These included baseline antithrombin III levels, microbial type of infection, heparin exposure, sex, age, SAPS II stratum, ethnic group (a priori-defined subgroups), shock at baseline, and surgical status (defined post-hoc). A multifactorial logistic regression analysis was performed to test simultaneously sets of predefined possible prognostic variables for their impact on the 28-day survival status; depending on their additional contribution to prognosis of survival, the variables were entered into ($P<.10$) or removed from the model by a forward selection technique[39]; within this analysis all subgroup variables were tested for an interaction with the treatment group. The predefined subgroup of patients who received or did not receive heparin was made slightly more precise during analysis so that "no concomitant heparin" was taken as "no overlap of heparin and study medication during day 1-4." Any further analyses and subpopulations (eg, elderly patients, male or female patients, or patients with shock at baseline), including length of intensive care unit stay (Kaplan-Meier curves) were of descriptive and exploratory nature.

RESULTS

Characteristics of the Study Population

Details of study conduct, randomization, and resulting populations are given in Figure 1. The primary efficacy population consisted of 2314 adult patients randomly assigned in equal numbers of 1157 to the antithrombin III treatment group and to the placebo group. Patients were well matched at study entry for age, sex, SAPS II score, body weight, and race (TABLE 1). The most common underlying diseases in patients were the respiratory system (35%), followed by intra-abdominal in-

Figure 1. Trial Profile



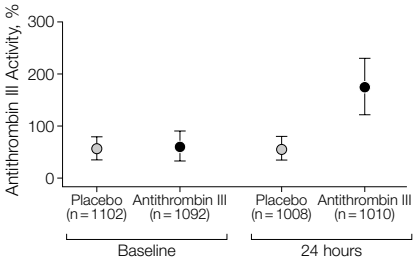
Asterisk indicates a patient may have more than 1 protocol violation; dagger, high-dose nonsteroidal anti-inflammatory drug, high-dose heparin, coumarin, or additional antithrombin III; double dagger, placebo vials were accidentally switched with antithrombin III vials during 96-hour treatment phase.

Table 1. Patient Characteristics of Primary Efficacy Population*

	Placebo (n = 1157)	Antithrombin III (n = 1157)
Age, mean (SD), y	58 (17)	57 (17)
Men	61	62
Simplified Acute Physiology Score version II, mean (SD)	49 (16)	49 (17)
Body weight, mean (SD), kg	77 (20)	77 (19)
Race		
White	83	85
Black	8	7
Other	9	9
Underlying problem or site of infection†		
Respiratory system	34	35
Intra-abdominal infection	28	27
Genitourinary system	8	6
Injury	6	7
Other	24	24
Blood culture results		
Gram-negative	16	15
Gram-positive	17	15
Other/mixed	2	4
Not done/not verified	64	66
Surgical status		
No	53	54
Yes	47	46
Baseline antithrombin III <60%	55	52
Circulatory shock‡	47	49

*Values are expressed as percentages unless otherwise indicated.
†*International Classification of Diseases, Ninth Revision*.
‡See "Methods" section for definition.

Figure 2. Antithrombin III Activity Levels



Circles indicate mean values and error bars, SDs.

fections (28%), genitourinary tract infections (8%), and miscellaneous sites of infection (31%). A total of 810 patients (35%) had positive blood cultures at the time of study enrollment. These were gram-positive bacterial pathogens in 45% of positive blood isolates; gram-negative pathogens in 46%; fungal pathogens in 4%; and polymicrobal, parasites, or viruses in 5% of positive blood cultures. The antithrombin III and placebo groups were well matched with respect to source of infection, frequency of bacteremia, and type of infecting microorganism(s).

Antithrombin III Levels in Treatment Groups

Baseline antithrombin III levels were below 60% of normal functional levels in more than 50% of patients randomized to either the antithrombin III or the placebo group. These levels were unchanged after 24 hours of treatment in those patients in the placebo group. In contrast, the patients randomized to the antithrombin III group had their mean antithrombin III levels elevated by 115% on average to approximately 180% of normal circulating blood levels (FIGURE 2).

Efficacy of Antithrombin III in the Study Population

The SAPS II score—originally created as a predictor for hospital mortality—was a strong predictor of outcome yet overestimated observed 28-day all-cause mortality in each risk stratum (TABLE 2). The antithrombin III group's mortality rate did not significantly differ from the placebo group in any SAPS II risk stratum or in the overall study population (38.9% for antithrombin III group vs 38.7% for placebo group; $P = .94$). The Kaplan-Meier plot of survival function over the 90-day study period is given for both the antithrombin III group and placebo group in FIGURE 3. No significant differences were observed between the 2 treatment groups at any period over the course of the study. However, a trend toward a reduction in 90-day mortality in the antithrombin III group was seen in the high-risk SAPS II stratum (predicted mortality 30%-60%; $P = .07$ with Fisher exact test). An analysis of prespecified subgroups and the relative survival benefit between the antithrombin III and placebo groups after 28 days from study entry (with corresponding 95% confidence intervals) is depicted in FIGURE 4A. No subgroup outcome differed significantly between antithrombin III treatment and placebo ($P > .05$). A comparison between treatment groups of incidence of new organ dysfunction as described in the Logistic Organ Dysfunction score is presented in TABLE 3. New cardiovascular dysfunction within 7 days of study entry was significantly more likely to occur in the antithrombin III group than in the placebo group in the primary efficacy population. One possible explanation for this finding is an association with bleeding events: 24.7% of patients with new cardiovascular dysfunction had a hemorrhage (34.5% for antithrombin III and 11.9% for placebo) compared with 11.3% of patients without this dysfunction (14.9% for antithrombin III and 8.1% for placebo); and most patients with new cardiovascular dysfunction had hypotension (18.8% for antithrombin III and 13.2% for placebo) or tachycardia (10.8% for antithrombin III and 9.0% for placebo).

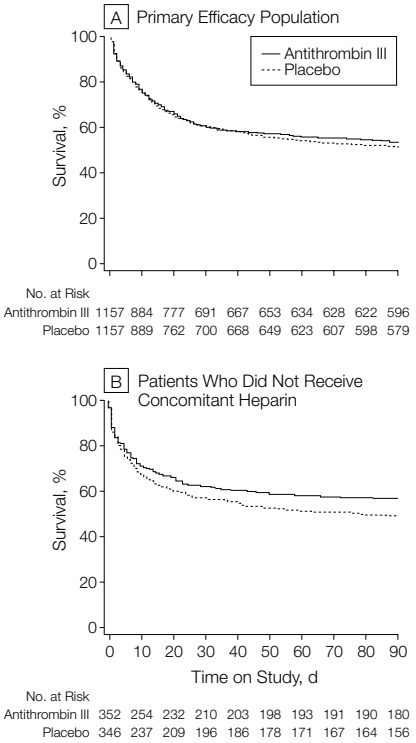
This difference favoring the placebo group is no longer significant when the patient population without protocol violations and with full study drug administration is analyzed (per protocol population). In the per protocol popu-

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

Population	No. of Patients	28-Day Mortality, %		RR (95% CI)
		Placebo	Antithrombin III	
Primary efficacy	2314	38.7	38.9	1.01 (0.91-1.11)†
Per protocol	1766	36.8	37.1	1.01 (0.90-1.14)†
Sex				
Male	1414	36.6	38.9	1.06 (0.93-1.22)
Female	900	42.0	38.9	0.93 (0.79-1.09)
Age, y				
≥65	912	46.4	49.3	1.06 (0.93-1.22)
<65	1402	33.5	32.3	0.97 (0.83-1.12)
Baseline antithrombin III, %				
<60	1171	47.5	46.2	0.97 (0.86-1.10)
≥60	1023	28.5	29.1	1.02 (0.84-1.24)
Shock at baseline				
No	1191	34.8	34.2	0.98 (0.84-1.15)
Yes	1118	43.2	43.5	1.01 (0.88-1.15)
Simplified Acute Physiology Score version II stratum‡				
Moderate risk (<30%)	652	19.2	21.9	1.14 (0.88-1.54)
High risk (30%-60%)	1008	40.7	36.9	0.91 (0.78-1.06)
Very high risk (>60%)	654	54.8	58.9	1.07 (0.94-1.23)
Surgical status				
No	1246	38.8	36.8	0.95 (0.82-1.09)
Yes	1068	38.6	41.4	1.07 (0.93-1.24)
Microbial type				
Gram-negative	362	35.3	37.6	1.07 (0.81-1.40)
Gram-positive	375	41.8	37.9	0.91 (0.71-1.17)
Other/mixed	73	46.2	38.3	0.83 (0.47-1.46)
Not done/not verified	1504	38.5	39.4	1.03 (0.90-1.16)
Race				
White	1941	37.1	37.7	1.02 (0.91-1.14)
Black	175	45.1	54.8	1.22 (0.90-1.64)
Other	198	48.1	37.2	0.77 (0.56-1.07)
Concomitant heparin administration§				
No heparin	698	43.6	37.8	0.86 (0.73-1.02)
Heparin (within or above limits)	1616	36.6	39.4	1.08 (0.96-1.22)

*RR indicates risk ratio; CI, confidence interval.
†Values are stratified.
‡Risk to die according to LeGall et al.[35]
§During 4-day study treatment.

Figure 3. Survival Rates for 90 Days



A, The placebo group had 603 patients censored and the antithrombin III group had 630 censored. B, The placebo group had 168 patients censored and the antithrombin III group had 199 censored.

lation there is also a trend toward less severe renal and pulmonary dysfunction in the antithrombin III group compared with the placebo group. Among survivors, time spent in the intensive care unit did not differ between treatment groups at any point (FIGURE 5).

Heparin Interactions With Antithrombin III

Among the predefined subgroups, an important treatment interaction between antithrombin III and heparin use was noted. Patients who received any heparin (n=1616) at any time during the initial 4-day administration of the study drug did not respond to antithrombin III as favorably as patients who did not receive heparin. This treatment interaction was observed even when relatively low doses of unfractionated or low molecular weight heparin were given for venous thrombosis prophylaxis (≤10 000 IU subcutaneous per day), and also with heparin flushes for vascular catheter patency (IV of ≤2 IU per kilogram of body weight per hour). Therapeutic doses of heparin at levels intended to provide systemic anticoagulation (>10 000 units per day) were not permitted during study drug infusion. A total of 698 patients received no concomitant heparin in the first 4 days of study entry (30% of the primary efficacy population). The 28-day mortality in patients who did not receive concomitant heparin was 37.8% of the antithrombin III group and 43.6% of the placebo group (P=.08); for patients who received concomitant heparin, the corresponding figures were 39.4% and 36.6%. Statistical evidence for the interaction between antithrombin III and heparin was provided from the multiple logistic regression analysis in which heparin exposure was the only variable with a significant (P=.02) interaction effect. Antithrombin III levels at baseline, although strongly predictive for 28-day mortality, did not interfere with the main treatment effect of antithrombin III vs placebo. The 90-day

Kaplan-Meier plot of patients who did not receive concomitant heparin treatment and who were randomized to either antithrombin III (n=352) or placebo (n=346) is presented in Figure 3B.

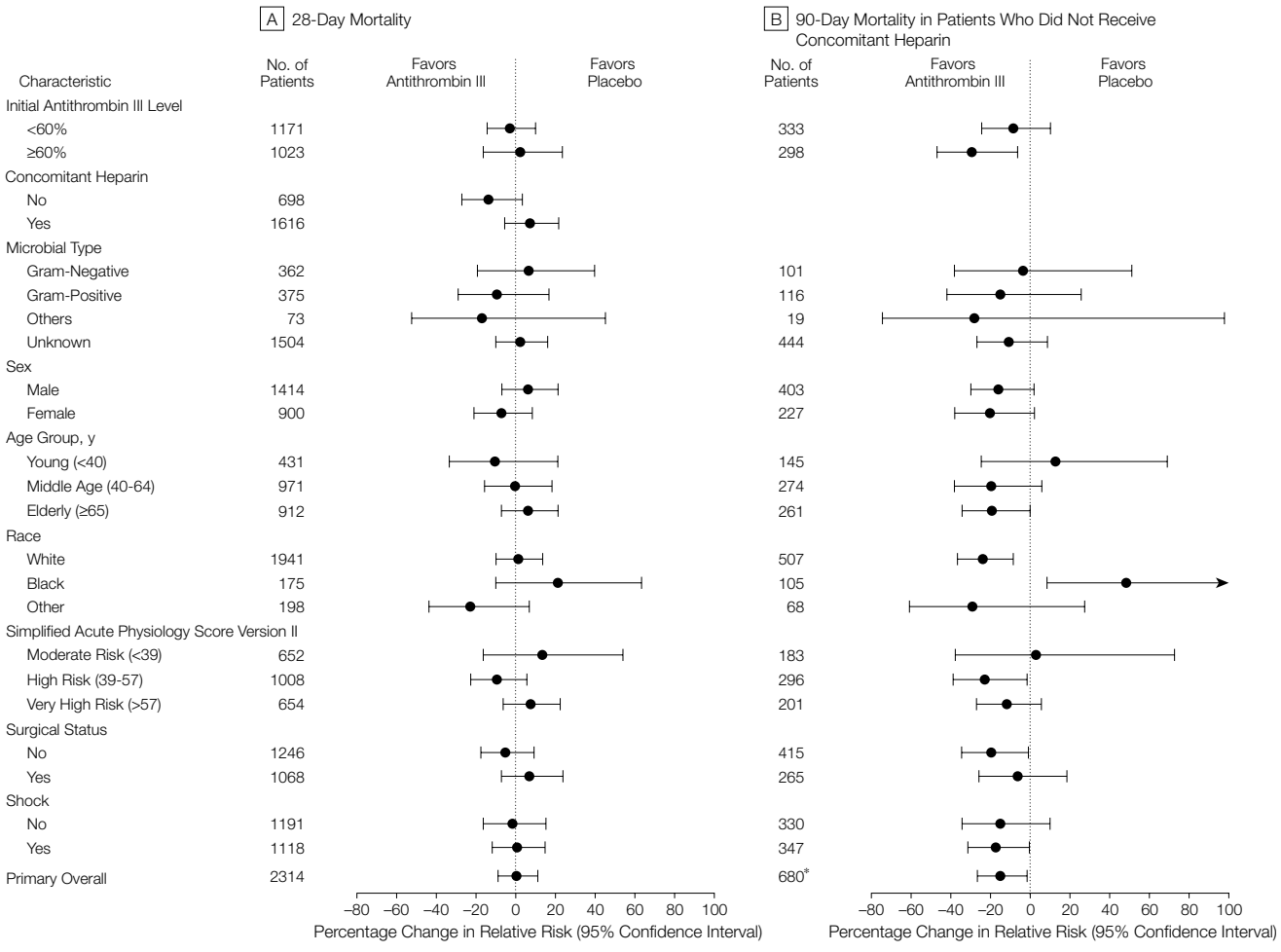
Antithrombin III resulted in a 15% absolute improvement in 90-day mortality in this subgroup of patients (n=680; 44.9% for antithrombin III group vs 52.5% for placebo group; $P=.03$). An analysis of other subgroups within the population of patients who received no concomitant heparin administration is shown in Figure 4B. This analysis demonstrates that the antithrombin III treatment effect is in the same direction consistently for almost all subgroups.

Safety Analysis of High-Dose Antithrombin III Treatment

The total percentage of patients with adverse events and serious adverse events was high (46%) as expected in this critically ill population of intensive care unit patients with severe sepsis and septic shock. Except for bleeding events, these adverse events did not differ significantly in type or overall frequency between the 2 treatment groups. The hemoglobin concentrations, activated partial thromboplastin time, prothrombin time, and fibrinogen concentrations were not significantly different between the antithrombin III group or placebo group during the first 7 days of the study (data not shown).

The overall incidence of bleeding complications was significantly more common in the high-dose antithrombin III treatment group (255 events [22.0%]) than in the placebo group (148 events [12.8%]) ($P<.001$). This difference was most marked in those patients who received concomitant heparin therapy either in low doses allowed in the protocol or in large therapeutic doses (ie, as deviations from protocol) (TABLE 4). Intracranial bleeding was rare with 5 (0.4%) events in the placebo group and 8 (0.7%) events in the antithrombin III group ($P=.58$). Bleeding events were more common in both the antithrombin III and placebo groups in patients undergoing sur-

Figure 4. Mortality Rates for 28 and 90 Days



Asterisk indicates 18 patients were lost to follow-up.

gery during the first 7 days of the study than in medical patients. However, the relative risk of bleeding between treatment groups did not increase in surgical patients (data not shown). Hemorrhagic episodes were not related to higher antithrombin III levels in the antithrombin III treatment group. Antithrombin III activities were comparable in patients with bleeding episodes and those without bleeding complications (FIGURE 6). Among patients with bleeding incidents, 28-day mortality was 50.7% in the placebo group and 51.4% in the antithrombin III group. For the majority of nonbleeding patients, the corresponding figures were 36.9% in the placebo group and 35.4% in the antithrombin III group.

Table 3. Incidence of New Organ Dysfunction According to Limit of Detection Within 7 Days After Admission by Treatment Groups, Primary Efficacy Population

Body System of Dysfunction	No. of Patients*	Incidence of New Organ Dysfunction, No. (%)		Relative Risk (95% Confidence Interval)†
		Placebo	Antithrombin III	
Neurologic (Glasgow Coma scale score <14)	1013	94 (9.3)	67 (6.8)	0.75 (0.49-1.15)
Cardiovascular‡	751	167 (22.2)	222 (29.6)	1.33 (1.04-1.70)
Renal§	413	164 (39.6)	155 (37.6)	0.94 (0.74-1.20)
Pulmonary‖	361	96 (26.6)	81 (22.5)	0.84 (0.58-1.21)
Hematologic¶	1992	227 (11.4)	205 (10.3)	0.92 (0.71-1.18)
Hepatic#	1805	312 (17.3)	325 (18.0)	1.04 (0.86-1.27)

*Only patients without the dysfunction on admission.
†Overall stratified estimate and 2-sided 95% confidence interval according to Mantel-Haenszel.
‡Heart rate of less than 30/min or greater than 139/min or systolic blood pressure of less than 90 mm Hg or greater than 239 mm Hg.
§Serum urea of 0.36 g/L (6 mmol/L) or higher; blood urea nitrogen level of 17 mg/dL (6 mmol/L) or higher; serum creatinine of 1.2 mg/dL (106 mmol/L) or higher; or urine output of less than 0.75 L/d or 10 L/d or higher.
‖Mechanically ventilated, under continuous positive airway pressure or under inspiratory postive airway pressure.
¶White blood cell count of less than $2.5 \times 10^3/\mu L$ or $50 \times 10^3/\mu L$ or platelet count of less than $50 \times 10^3/\mu L$.
#Bilirubin level of 2.0 mg/dL (34.2 µmol/L) or higher or prothrombin time of less than 25% (Quick test) or greater than 3 multiplied by prothrombin time of standard plasma (seconds) or prothrombin time (international normalized ratio) of greater than 3 on the International Sensitivity Index.

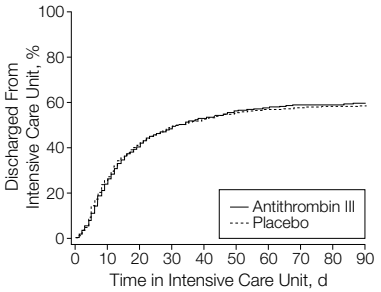
COMMENT

The results of the KyberSept Trial of high-dose antithrombin III treatment in severe sepsis joins a long list of promising experimental agents for sepsis that failed to show a significant benefit in a multicenter, randomized phase 3 clinical trial.[40] The results of this large international trial are particularly disappointing since antithrombin III has extensive preclinical[20,21,25-27] and prospective phase 2 clinical evidence of efficacy in sepsis.[10,28-31] Despite a compelling series of controlled and uncontrolled clinical trials with antithrombin III in human sepsis (performed with various dosages and different heparinization regimens),[10] the use of antithrombin III in high doses in this large, carefully conducted multicenter clinical trial failed to achieve efficacy in the primary study end point of 28-day, all-cause mortality.

The lower than expected frequency of reduced levels of circulating antithrombin III at study entry may have accounted for the less than expected therapeutic benefits of high-dose administration of antithrombin III. The levels of antithrombin III attained in the blood after 24 hours in recipients of antithrombin III was also lower than expected as well. It was hypothesized that a blood level of approximately 200% to 250% of normal levels would be necessary to derive maximum benefits of antithrombin III in the severely septic population.[41,42] In a previously conducted pharmacokinetic trial with antithrombin III in patients with severe sepsis, the same dosage regimen of antithrombin III was administered and mean antithrombin III plasma levels of about 200% were achieved over 4 days of treatment.[43] In the phase 3 trial, mean measured levels of antithrombin III 24 hours after the start of treatment were approximately 180% of normal. Antithrombin III levels decrease rapidly in sepsis as a result of lowered hepatic synthesis, enhanced use, and increased degradation by elastase from activated neutrophils.[41] The continuous infusion of antithrombin III in this study may have been insufficient to keep up with excess loss in many of these severely septic patients.

Additionally, antithrombin III must bind to glycosaminoglycans on endothelial surfaces and/or to inflammatory cells like polymorphonuclear leukocytes to promote local anticoagulant activity and anti-inflammatory activities as a number of recent in vitro and in vivo experiments showed.[44,45] It has been demonstrated that heparin competitively inhibits the binding of antithrombin III to other glycosaminoglycans.[41] This finding is consistent with the observation that the subgroup without heparin benefits from the high-dose antithrombin III therapy. An arbitrary level of antithrombin III was given (total of 30 000 IU) to each patient randomized to the antithrombin III group and it is unclear if this provided optimal antithrombin III levels in each patient with sepsis.

Figure 5. Intensive Care Unit Discharge



No. at Risk

Antithrombin III	1157	872	673	579	525	491	472	460	458	452
Placebo	1157	855	671	577	533	508	488	480	473	468

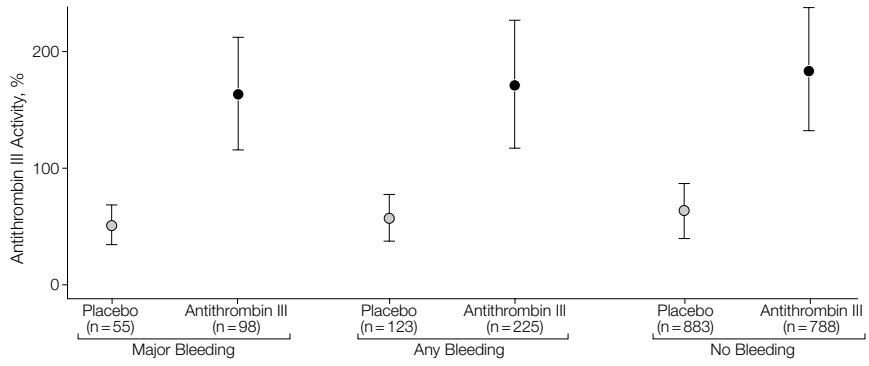
The placebo group had 496 patients censored and the antithrombin III group had 488 censored.

An independent data and safety monitoring board analyzed the frequency of hemorrhagic events throughout the study. While it was observed that the bleeding episodes were more common in the antithrombin III group, the absence of excess deaths attributable to hemorrhage between the 2 treatment groups and the lack of fulfillment of the priori stopping rules allowed the study to continue to completion. Excess of

Table 4. Bleeding Events

Outcome	Placebo, %	Antithrombin III, %	Relative Risk (95% Confidence Interval)
		Overall	
	(n = 1155)	(n = 1161)	
Any bleeding	12.8	22.0	1.71 (1.42-2.06)
Major bleeding	5.7	10.0	1.75 (1.31-2.33)
Minor bleeding	7.8	14.3	1.83 (1.45-2.33)
		Without Concomitant Heparin	
	(n = 345)	(n = 354)	
Any bleeding	11.3	17.8	1.58 (1.10-2.28)
Major bleeding	4.6	7.9	1.71 (0.95-3.07)
Minor bleeding	7.0	12.7	1.83 (1.15-2.91)
		With Concomitant Heparin	
	(n = 810)	(n = 807)	
Any bleeding	13.5	23.8	1.77 (1.43-2.18)
Major bleeding	6.2	10.9	1.77 (1.27-2.45)
Minor bleeding	8.2	15.0	1.84 (1.39-2.43)

Figure 6. Antithrombin III Levels According to Bleeding Status for 24-Hours



Circles are means and error bars are SDs.

major bleeding had not been observed in previously conducted controlled phase 2 studies with high-dose antithrombin III.[28,43]

Conclusion

The results of this study indicate that high-dose administration of antithrombin III in combination with heparin in this setting of a severely septic patient population offers no mortality advantage over standard care for sepsis. However, in the predefined subgroup of patients not receiving concomitant heparin, there is a trend toward reduced 28-day and 90-day mortality with antithrombin III, based on the following, generally accepted criteria: subgroups were few in number, defined a priori, and the heparin interaction has a biological rationale (antithrombin III is a cofactor of heparin). The possible survival benefit of antithrombin III in this specific subgroup of patients with severe sepsis may be worthy of further investigation.

However, hemorrhagic complications were more likely even when low doses of heparin were administered in this patient population in combination with high-dose antithrombin III. This clinically important safety concern must be considered when using high-dose antithrombin concentrates. Furthermore, the effect of selectively applied heparin on 28-day mortality cannot be reliably interpreted since heparin was not a randomized study factor. With regard to safety, the treatment interaction with heparin was expected but the magnitude of adverse events attributable to interactions between heparin and antithrombin III was not expected. During 2 interim analyses, the risk benefit assessment of the data safety and monitoring board did not lead to recommendations for the further conduct of the study.

It is notable that potential differences in outcome were most apparent after long-term follow-up (90 days after study entry). This finding suggests that prolonged follow-up may be worthwhile in future sepsis studies rather than the standard mortality end point of 28 days after study entry. Another phase 3 sepsis trial with a similar anticoagulant strategy (recombinant human activated protein C) resulted in a statistically significant survival benefit.[46] The explanation(s) for the disparity in outcome between antithrombin III and recombinant human activated protein C trials are not entirely clear at this time but may relate to trial design issues, dosing, differences in anti-inflammatory properties, and differential effects of concomitant heparin administration. This topic will be the focus of a separate article with a detailed analysis of similarities and differences between antithrombin III and recombinant human activated protein C and the design of these 2 clinical trials.

Author Affiliations: Department of Surgery, Tygerberg Hospital and the University of Stellenbosch, Tygerberg, South Africa (Dr Warren); Critical Care Division, University of Oklahoma Health Science Center, Oklahoma City (Dr Eid); Critical Care Medicine, Rabin Medical Center, Beilinson Campus, Petach Tikva, Israel (Dr Singer); Department of Surgery, Livingston Hospital, Port Elizabeth, South Africa (Dr Pillay); Critical Care Medicine, Hvidovre University Hospital, Hvidovre, Denmark (Dr Carl); Intensive Care Unit, Charles University Hospital, Pilsen, Czech Republic (Dr Novak); Clinic of Infectious Diseases, Brno-Bohunice, Czech Republic (Dr Chalupa); Department of Surgery, Frere Hospital, East London, South Africa (Dr Atherstone); Department of Anaesthesiology and Intensive Care, Semmelweiss Medical University, Budapest, Hungary (Dr Pénzes); Department of Anaesthesiology and Intensive Therapy, Wroclaw University of Medicine, Wroclaw, Poland (Dr Kübler); Aventis Behring, Marburg, Germany (Drs Knaub, Heinrichs, Juers, and Messrs Keinecke and Schindel); Critical Care Division, Rush Medical Center, Chicago, Ill (Dr Bone); and Infectious Disease Division, School of Medicine, Brown University, Providence, RI (Dr Opal).
Author Contributions: Dr Opal, as principal investigator of the KyberSept Trial, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

Study concept and design: Knaub, Keinecke, Heinrichs, Bone, Opal.
Acquisition of data: Warren, Eid, Singer, Pillay, Carl, Novak, Chalupa, Atherstone, Pénzes, Kübler, Schindel, Juers, Opal.
Analysis and interpretation of data: Knaub, Keinecke, Heinrichs, Schindel, Juers, Opal.
Drafting of the manuscript: Knaub, Opal.
Critical revision of the manuscript for important intellectual content: Warren, Eid, Singer, Pillay, Carl, Novak, Chalupa, Atherstone, Pénzes, Kübler, Knaub, Heinrichs, Schindel, Juers, Opal.
Statistical expertise: Keinecke, Schindel.
Obtained funding: Opal.
Administrative, technical, or material support: Knaub, Juers.
Study supervision: Opal, Knaub, Heinrichs,

Financial Disclosures Aventis Behring provided funding for this article. Mr Keinecke owns stocks and stock options in Aventis Behring.

PPD Development (Austin, Tex; a contract research organization): We thank Madeline Ducate, global project leader, for her continuous commitment and dedication. We also thank the whole PPD Development team responsible for monitoring, data management, central randomization, and the medical hotline.

Role of the Sponsor: Drs Bone and Opal and the steering committee developed the study design in close cooperation with the study sponsor. The study conduct and data collection were monitored by the contract research organiztion (PPD Development) along with the study sponsor and steering committee. All the primary data and statistical analyses were reviewed by Dr Opal, the corresponding author, on behalf of the coauthors and the investigative team. Data interpretation was conducted by the statistical group of the sponsor (Messrs Keinecke and Schindel) in collaboration with the statistical consultant (Dr Wittes). The manuscript was prepared by Dr Opal along with the study sponsor and reviewed by each of the coauthors.

Steering Committee: S. M. Opal, (chair), Memorial Hospital of Rhode Island, Pawtucket; J. Cohen, Hammersmith Hospital, London, England; F. Fourrier, Hôpital B, Lille, France; C. Kessler, Lobardy Cancer Center, Washington, DC; M. Lamy, Centre Hospitalier Universitaire de Liège, Liège, Belgium; S. F. Lowry, University of Medicine and Dentistry of New Jersey, New Brunswick; W. Schramm, Ludwig-Maximilians-Universität, Munich, Germany; C. L. Sprung, Hadassah Hebrew University, Jerusalem, Israel; and L. G. Thijs, Free University of Amsterdam, Amsterdam, the Netherlands.

Data and Safety Monitoring Board: Janet Wittes, PhD, Statistics Collaborative, Washington, DC; Eugen Faist, Ludwig-Maximilians-Universität, Munich, Germany; H. Wiedemann, Cleveland Clinic Foundation, Cleveland, Ohio; and G. Ramsay, University Hospital Maastricht, Maastricht, the Netherlands.

Study Group: *Australia:* Footscray: C. French, Western Hospital; Geelong: C. Corke, Geelong Hospital; Heidelberg: R. Bellomo, Austin and Repatriation Medical Centre; Hobart: A. Turner, Royal Hobart Hospital; Perth: G. Dobb, Royal Perth Hospital; Woodville: S. Peake, Queen Elizabeth Hospital; Woolongong: S. Rachakonda, Woolongong and Port Kembla Hospitals. *Austria:* Graz: W. List, Universitätsklinik für Anaesthesiologie und Intensivmedizin; I. C. Hiotakis, Landeskrankenhaus Graz; Innsbruck: C. Wiedermann, Universitätsklinik für Innere Medizin; Salzburg: G. Pauser, Allgemeines Öffentliches Landeskrankenhaus; Vienna: W. Ilias, Krankenhaus der Barmherzigen Brüder; and C. Weinstabl, Abt für Allgemeine Anästhesie und Intensivmedizin. *Belgium:* Braine L'Alleud: H. Lignian, Braine L'Alleud Hospital; Brussels: H. Spapen, Intensive Geneeskunde; Genk: R. De Jongh, Ziekenhuis Oost Limburg; Gent: J. Decruyenaere, University Hospital Gent; Ottignies: T. Dugernier, Clinique Saint-Pierre; Yvoir: E. Installe, Cliniques Universitaires UCL de Mon-Godinne. *Brazil:* Sao Paulo: M. Boulos, Univeridade De Sao Paulo. *Czech Republic:* Brno: R. Kraus, Faculty Hospital; Brno-Bohunice: P. Chalupa, Clinic of Infectious Diseases; Havlickuv Brod: P. Longin, Verge Hospital; Hradec Kralove: V. Dostal, Faculty Hospital; Kadan: J. Nygryn, NsP Kadan; Mlada Boleslav: I. Herold, Claudian Hospital; Olomouc: O. Marek, Faculty Hospital Olomouc; and P. Pokorny, Military Hospital; Opava: P. Kumpel, Slezska Hospital; Ostrava-Poruba: P. Kudrna, University Hospital; Plzen: I. Novak, Charles University Hospital Pilsen; Plzen-Vory: E. Kasal, Faculty Hospital Plzen-Vory; Usti nad Labem: J. Svejda and R. Splechtna, Masaryk Hospital. *Denmark:* Aalborg: S. Jensen, Aalborg Hospital South; Aarhus: P. Toft, Aarhus Kommune Hospital; Copenhagen: A. Engquist, Bispebjerg Hospital; Esbjerg: B. Dilling-Hansen, Centralsygehuset; Glostrup: J. Strom, Amtsygehuset; Hillerod: S. Elkjaer, Hillerod Hospital; Hvidovre: P. Carl, Hvidovre University Hospital; Naestved: B. Fogh, Centralsygehuset; Slagelse: C. Laerkholm, Centralsygehuset; Viborg: J. J. Jensen, Viborg Hospital. *England:* Cambridge: G. Park, Addenbrookes Hospital; Leeds: Y. Young, St James' University Hospital; Leicester: M. Pepperman, Leicester Royal Infirmary; London: R. Beale, Guys Hospital; D. Treacher, St Thomas' Hospital; A. Webb, Middlesex Hospital; and S. Withington, Royal London Hospital; Manchester: G. Brear, Wythenshawe Hospital; R. Kishen, Hope Hospital; P. Nigthingale, Withington Hospital; and J. Eddleston, Manchester Royal Infirmary; Nottingham: R. Winter, Queens Medical Centre; Plymouth: M. Walker, Derriford Hospital; Southampton: M. Nielsen, Southampton General Hospital. *Finland:* Jyvaskyla: R. Laru-Sompa, Keski-Suomen Keskussairaala; Kokkola: M. Kuusela, Keski-Pohjanmaan Keskussairaala; Lahti: M. Heino, Paijat-Hameen Keskussairaala; Oulu: J. Laurila, University of Oulu; Turku: J. Klossner, Turku University Central Hospital. *Germany:* Augsburg: H. Forst, Krankenhauszweckverband Augsburg; Berlin: M. Welte, Universitätsklinikum Benjamin-Franklin; Bonn: P. Walger, Medizinische Universitätspoliklinik; Dresden: K. Rothe, Anästhesie des Städtischen Klinikums Dresden-Friedrichstadt; Gera: W. Schirrmeister, Anästhesie des Klinikums der Stadt Gera; Greifswald: M. Gründling, Ernst-Moritz-Arndt-Universität; Jena: K. Reinhart, Klinik für Anästhesiologie und Intensivtherapie; Kiel: A. Bastian, I. Medizinische Klinik der Christian-Albrecht-Universität; Leipzig: L. Engelmann, Medizinische Klinik und Poliklinik; Lübeck: H. Bruch, Medizinische Universität zu Lübeck; and H. Djonlagic, Medihzinische Universitätsklinik; Munich: R. Gärtner, Klinikum Innenstadt der LMU; and C. Peckelsen, Städtisches Krankenhaus München-Harlaching; Schwerin: P. Lazarus, Klinik für Innere Medizin des Klinikums Schwerin; Tübingen: K. Unertl, Universität Tübingen. *Hungary:* Budapest: I. Pénzes and L. Flautner, Semmelweiss Medical University; Debrecen: J. Aranyosi, Intenziv Osztaly; and P. Sapy, Medical University School of Debrecen; Miskolc: J. Karaszi, Semmelweiss Hospital; Szeged: A. Balogh, Szentgyorgyi Albert Medical University. *Israel:* Afula: A. Lev, Emek Medical Center; Haifa: U. Taitelman, Rambam Medical Center; Jerusalem: C. Sprung, Hadassah (Ein Karem) Medical Center; Kfar-Saba: R. Jedeikin, Meir Hospital; Petach Tikva: P. Singer, Rabin Medical Center; Tel Hashomer: E. Segal, Sheba Medical Center; Tel Aviv: P. Sorkine, Ichilov Medical Center; Zrifin: G. Lewinsohn, Assaf Harofeh Hospital. *the Netherlands:* Amsterdam: B. Van der Hoven, Acute Inwendige Geneeskunde; Apeldoorn: J. Bakker, Ziekenhuis Centrum Apeldoorn; Bennekom: A. R. H. Van Zanten, Ziekenhuis Gelderse Vallei Bennekom; Groningen: J. E. Tulleken, University Hospital Groningen (AZG); Leeuwarden: R. Gerritsen, Medisch Centrum Leeuwarden; Nijmegen: S. J. Van Leeuwen, University Hospital Nijmegen (AZN); Rotterdam: A. D. Dees, Ikazia Ziekenhuis; The Hague: J. A. M. De Haas, Ziekenhuis Leyenburg Den Haag; Utrecht: W. Hustinx, Diaconessenhuis Utrecht; and J. C. A. Joore, Universitair Medisch Centrum Utrecht. *New Zealand:* Auckland: S. Streat, Auckland Healthcare; Christchurch: S. Henderson, Canberbury Health Ltd; Hawke's Bay: R. Freebairn, Whakawateatia Healthcare Hawke's Bay; Otahuhu: D. Galler, South Auckland Health; Palmerston North: G. McHugh, Mid Central Health; Whangarei: F. Muller, Northland Health Ltd. *Poland:* Gdansk: J. Suchorzewska, Katedra i Klinika Anestezjologii i Intensywnej Terapii AM; Krakow-Nowa Huta: T. Zelazny, Szpital im Rydygiera; Poznan: R. Szulc, Medical Academy; Sosnowiec: L. Krawczyk, Szpital Gorniczy w Sosnowcu; Warszawa: J. Jastrzebski, Klinika Anestezjologii i Intensywnej Terapii CMKP; and B. Kaminski, Centralny Szpital Kliniczny; Wroclaw: A. Kuebler, Department of Anaesthesiology and Intensive Therapy. *Scotland:* Aberdeen: N. Webster, Aberdeen Royal Infirmary; Edinburgh: I. Grant, Western General Hospital; Glasgow: A. Binning, Western Infirmary. *South Africa:* Auckland Park: P. Williams, Helen Joseph Hospital; Bloemfontein: S. Smit, University of the Orange Free State; East London: A. Atherstone, Frere Hospital; Johannesburg: C. Clinton, Johannesburg Hospital; Kimberley: E. Theron, Kimberley Hospital; Krugersdorf: A. de Kock, Krugersdorp Private Hospital; Port Elizabeth: S. Pillay, Livingstone Hospital; Pretoria: J. Kilian, Wilgers Hospital Consulting Rooms; and J. Pretorius, Pretoria Academic Hospital; Somerset West: E. Blaine, Vergelegen Medi-Clinic; Tygerherg: B. L. Warren, Department of Surgery, Tygerberg Hospital and the University of Stellenbosch. *Spain:* Alicante: P. Marco, Hospital General de Alicante del SVS; Badalona-Barcelona: M. Sabria, Hospital Germans Trias i Pujol; Barcelona: J. Boveda, Hospital General de la Vall d'Hebron; La Comfia: A. Santos, Hospital Xeral Basico de Conxo, Santiago de Compostela; Madrid: J. E. Guerrero, Hospital Gregorio Maranon; Pamplona (Navarra): J. Ramos, Hospital Virgen del Camino; Sevilla: C. Leon, Hospital Universitario; and C. Ortiz, Hospital Virgen del Rocio; Vitoria (Alava): M. Hernandez, Hospital Txagorritxu. *Sweden:* Gavle: J. Malstam, Gavle County Hospital; Helsingborg: K. Olofsson, Helsingborg Hospital; Jonkoping: P. Nordlund, Ryhov County Hospital; Karlstad: L. A. Johansson, Central Hospital; Kristianstad: T. Nolin, Central Hospital; Linkoping: M. Golster, Linkoping University Hospital; Skövde: K. Lofving, Karn Hospital; Stockholm: B. Gardlund, Karolinska Hospital; and J. Hulting, Soder Hospital; Uppsala: H. Stiernstrom, Uppsala Academic Hospital. *Switzerland:* Basel: A. P. Perruchoud, Kantonsspital Basel; Geneva: P. Suter, Hôpital Cantonal. *Wales (United Kingdom):* Cardiff: M. Smithies, University Hospital of Wales. *United States: Alabama:* Birmingham: J. Kennedy Jr, University of Alabama. *Arizona:* Tucson: S. Camhi, VA Medical Center; and A. Camilli, University of Arizona Medical Center. *California:* Los Angeles: H. Belzberg, LAC/USC Medical Center; Orange: A. Wilson, University of California Medical Center; San Francisco: C. Brown, California Pacific Medical Center; and H. Lampiris, VA Medical Center. *Colorado:* Denver: M. Fliegelman, Colorado Pulmonary Associates; and M. Mogyoros, Kaiser Permanente. *Washington, DC:* M. Seneff, George Washington University Hospital. *Delaware:* Newark: G. Fulda, Medical Research Institute of Delaware. *Florida:* Jacksonville: B. Venus, Columbia Memorial Hospital. *Georgia:* Atlanta: M. Foreman, Morehouse School of Medicine. *Illinois:* Chicago: J. Dematte, Michael Reese Hospital; and L. Zun, Mount Sinai Hospital Medical Center; North Chicago: R. Gazmuri, North Chicago VA Medical Center. *Iowa:* Iowa City: J. Sum-Ping, University of Iowa Hosptials and Clinics. *Kansas:* Kansas City: S. Pingleton, University of Kansas Medical Center; Topeka: L. Rumans, St Francis Hospital; Witchita: S. Smith, University of Kansas Medical School. *Ken-*

tucky: Louisville: L. Collins, VA Medical Center; and E. Fletcher, University of Louisville. *Maryland:* Baltimore: E. Shepard, St Agnes Health Care. *Massachusetts:* Springfield: J. Steingrub, Bay State Medical Center; Worcester: P. Marik, St Vincent's Hospital. *Michigan:* Detroit: M. Dahn, Detroit VA Medical Center; and M. Simoff, Henry Ford Hospital and Medical Center. *Missouri:* Kansas City: D. Dark, St Luke's Hospital; and T. Smith, St Joseph Health Center; Springfield: S. Daugherty, Cox Medical Plaza II. *New Jersey:* Camden: S. Monk, Cooper Hospital; Morristown: K. Kelly, Morristown Memorial Hospital. *New York:* New York: A. Leibowitz, Mount Sinai Medical Center; Rochester: T. Evans, Rochester General Hospital; and D. Kauffman and P. Thorborg, University of Rochester Medical Center. *Ohio:* Cleveland: A. DiMarco, Metro Health Medical Center; J. Renston, Mt Sinai Medical Center; and R. Salata, University Hospitals of Cleveland; Columbus: P. Escobar and R. St John, Remington-Davis. *Oklahoma:* Oklahoma City: G. Kinasewitz, University of Oklahoma Health Science Center. *Oregon:* Portland: R. Maunder, Oregon Clinic; and B. Sperley, Health First Medical Group. *Pennsylvania:* Harrisburg: N. Gantz, Pinnacle Health Care at Polyclinic; Pittsburgh: A. Miro, Clinical Trials Program; and J. Wilberger, Allegheny General Hospital; Upland: J. Huffman, Crozer Chester Medical Center. *Puerto Rico:* San Juan: C. Ramirez-Rhonda, VA Medical Center. *Rhode Island:* Pawtucket: S. Opal, Memorial Hospital of Rhode Island; Providence: J. Klinger, Rhode Island Hospital. *Tennessee:* Knoxville: B. Daley, Volunteer Research Group; Nashville: R. Light, St Thomas Hospital. *Texas:* El Paso: H. Ho, Texas Technical University Health Sciences Center; Fort Worth: D. Ziegler, John Peter Smith Hospital; Houston: R. Lodato, University of Texas Health Sciences Center; and P. Manian, VA Medical Center; San Antonio: H. Gaskill, University of Texas Health Sciences Center. *Wisconsin:* Milwaukee: E. Cheng, Froedtert West Hospital. *Wyoming:* Casper: M. Dowell, Wyoming Medical Center.

Acknowledgment: We thank Vincent Benn, PhD, for being the clinical project manager for the United States and Brazil; Sabine Blank, Benita Braun, Ralf Edling, Daniele Egger, Penny Fatato, Jean Fishel, Christine Hirtz, Brad Krueger, Claudia Nolte, Christine Piasek, and Gabriele Porzner for their committed monitoring assistance; Martina Gorys, Michelle Miller, and Katrin Rühl for their administrative assistance; Silke Kuhl and Bianka Plogmann for their data checking assistance; and Eva Schüssler for her careful data management and programming.

REFERENCES

1. Gando S, Kamene T, Nanzaki S, Nakanishi Y. Disseminated intravascular coagulation is a frequent complication of systemic inflammatory response syndrome. *Thromb Haemost.* 1996;75:224-228.
2. Vervloet MG, Thijs LG, Hack CE. Derangements of coagulation and fibrinolysis in critically ill patients with sepsis and septic shock. *Semin Thromb Hemost.* 1998;24:33-44.
3. Lorente JA, García-Frade LJ, Landin L, et al. Time course of hemostatic abnormalities in sepsis and its relation to outcome. *Chest.* 1993;103:1536-1542.
4. Levi M, ten Cate H, van der Poll T, van Deventer SJH. Pathogenesis of disseminated intravascular coagulation in sepsis. *JAMA.* 1993;270:975-979.
5. Fourrier F, Chopin C, Goudemand J, et al. Septic shock, multiple organ failure, and disseminated intravascular coagulation: compared patterns of antithrombin III, protein C, and protein S deficiencies. *Chest.* 1992;101:816-823.
6. Gando S, Smanzaki S, Sasaki S, Aoi K, Kemmotsu O. Activation of the extrinsic coagulation pathway in patients with severe sepsis and septic shock. *Crit Care Med.* 1998;26:2005-2009.
7. Hinshaw LB. Sepsis/septic shock: participation of the microcirculation: an abbreviated review. *Crit Care Med.* 1996;24:1072-1078.
8. Van Deventer SJH, Btiller HR, ten Cate JW, Aarden LA, Hack CE, Sturk A. Experimemal endotoxin in humans: an analysis of cytokine release and coagulation, fibrinolytic and complement pathways. *Blood.* 1996;88:2520-2528.
9. Van der Poll T, Bullet HR, ten Cate HT. Activation of coagulation after administration of TNF in normal subjects. *N Engl J Med.* 1990;322:1622-1627.
10. Eisele B, Lamy M. Clinical experience with antithrombin III concentrates in critically ill patients with sepsis and multiple organ failure. *Semin Thromb Haemost.* 1998;24:71-80.
11. Murano G, Williams L, Miller-Andersson MX, Aronson DL, King C. Some properties of antithrombin III and its concentrations in human plasma. *Thromb Res.* 1980;18:259-262.
12. Mammen EF. Clinical relevance of antithrombin deficiencies. *Semin Hematol.* 1995;4(suppl 2):2-6.
13. Pixley RA, De La Cadena R, Page JD, et al. The contact system contributes to hypotension but not to disseminated intravascular coagulation in lethal bacteremia. *J Clin Invest.* 1993;91:61-70.
14. Mammen EF. Antithrombin III: its physiologic importance and role in DIC. *Semin Thromb Haemost.* 1998;24:19-25.
15. Jesty J, Lorenz A, Rodriguez J, Wun TC. Initiation of tissue factor pathway of coagulation in the presence of heparin: control by antithrombin III and tissue factor pathway inhibitor. *Blood.* 1996;15:2301-2307.
16. Hamamoto T, Kisiel W. The effect of heparin on the regulation of factor VIIa-tissue factor activity by tissue factor pathway inhibitor. *Blood Coagul Fibrinolysis.* 1996;7:470-476.
17. Harada N, Okajima K, Kushimoto S, Isobe H, Tanaka K. Antithrombin reduces ischermia/reperfusion injury of rat liver by increasing the hepatic level of prostacyclin. *Blood.* 1999;93:157-164.
18. Yamauchi T, Umeda F, Inoguchi T, Nawata H. Antithrombin III stimulates prostacyclin production by cultured aortic endothelial cells. *Biochem Biophys Res Commun.* 1989;163:1404-1411.
19. Horie S, Ichii H, Kazama M. Heparin-like glycosaminoglycan is a receptor for antithrombin III-dependent but not thrombin-dependent prostacyclin production in human endothelial cells. *Thromb Res.* 1990;59:899-904.
20. Uchiba M, Okajima K, Murakami K, Okabe H, Takatsuki K. Attenuation of endotoxin-induced pulmonary vascular injury by antithrombin III. *Am J Physiol.* 1996;270:L921-L930.
21. Uchiba M, Okajima K, Mumkami K. Effects of various doses of antithrombin III on endotoxin-induced endothelial cell injury and coagulation abnormalities in rats. *Thromb Res.* 1998;89:233-241.
22. Corrigan JJ. Heparin therapy in bacterial septicemia. *J Pediatr.* 1977;91:695-700.
23. Schipper HG, Jenkins CSP, Kahl LH, ten Cate JW. Antithrombin III transfusion in disseminated intravascular coagulation. *Lancet.* 1978;1:854-856.
24. Mesters RW, Mannucci PW, Coppola R, Keller T, Ostermann H, Kienast J. Factor VII and antithrombin III activity during sepsis and septic shock in neutropenic patients. *Blood.* 1996;88:881-886.
25. Ostrovsky L, Woodman RC, Payne D, Teoh D, Kubes P. Antithrombin III prevents and rapidly reverses leukocyte recruitment in ischemia/reperfusion. *Circulation.* 1997;96:2302-2310.
26. Dickneite G. Antithrombin III in animal models of sepsis and organ failure. *Semin Thromb Haemost.* 1998;24:61-69.
27. Giebler R, Schmidt U, Koch S, Peters J, Scherer R. Combined antithrombin III and C1-esterase inhibitor treatment decreases intravascular fibrin deposition and attenuates cardiorespiratory impairment in rabbits exposed to *Escherichia coli* endotoxin. *Crit Care Med.* 1999;27:597-604.
28. Fourrier F, Chopin C, Huart J-J, Runge I, Caron C, Goudemand J. Double-blind, placebo-controlled trial of antithrombin III concentrates in septic shock with disseminated intravascular coagulation. *Chest.* 1993;104:882-888.
29. Inthorn D, Hoffmann JM, Hartl WH, Muhlbayer D, Jochum M. Antithrombin III supplementation in severe sepsis: beneficial effects on organ dysfunction. *Shock.* 1997;8:328-334.
30. Baudo F, Caimi TM, deCataldo F, et al. Antithrombin III (AT III) replacement therapy in patients with sepsis and/or post surgical complications: a double-blind, randomized, multicenter trial. *Intensive Care Med.* 1998;24:336-342.
31. Eisele B, Lamy M, Thijs LG, et al. Anti-thrombin III in patients with severe sepsis: a randomized, placebo-controlled, double-blind, multicenter trial plus a meta-analysis on all randomized-placebo-controlled, double-blind trials with antithrombin III in severe sepsis. *Intensive Care Med.* 1998;24:663-672.
32. Le Gall JR, Klar J, Lemeshow S, et al. The logistic organ dysfunction system: a new way to assess organ dysfunction in the intensive care unit. *JAMA.* 1996;276:802-810.
33. Le Gall JR, Lemeshow S, Saulnier F. Simplified acute physiology score (SAPS II) based on a European/North American multicenter study. *JAMA.* 1993;270:2957-2963.
34. Kleinbaum DG, Kupper LL, Morgenstem H. *Epidemiologic Research: Principles and Quantitative Methods.* London, England: Life time Learning Publication; 1982.
35. Le Gall JR, Lemeshow S, Leleu G, et al. Customized probability models for early severe sepsis in adult intensive care patients. *JAMA.* 1995;273:644-650.
36. Pocock SJ, Geller NL. Interim analyses in randomized clinical trials. *Drug Inf J.* 1986;20:263-269.
37. Casagrande JT, Pike MC, Smith PG. An improved approximate formula for calculation of sample sizes for comparing two binomial distributions. *Biometrics.* 1978;34:483-486.
38. Herson J, Wittes J. The use of interim analyses for sample size adjustment. *Drug Inf J.* 1993;27:753-760.
39. Collett D. *Modelling Binary Data.* London, England: Chapman and Hall; 1991.
40. Opal SM, Cross AS. Clinical trials for severe sepsis: past failures and future hopes. *Infect Dis Clin North Am.* 1999;13:285-298.
41. Opal SM. Therapeutic rationale for antithrombin in sepsis. *Crit Care Med.* 2000;28:S34-S37.
42. Fourrier F, Joudain M, Tournoys A. Clinical trial results with antithrombin III in sepsis. *Crit Care Med.* 2000;28:S38-S43.
43. Ilias W, List W, Decruyenaere J, et al. Antithrombin III in patients with severe sepsis: a pharmacokinetic study. *Intensive Care Med.* 2000;26:704-715
44. Hoffman JN, Vollmar B, Inthorn D, Schildberg FW, Menger MD. Antithrombin reduces leukocyte adhesion during chronic endotoxemia by modulation of the cyclooxygenase pathway. *Am J Physiol Cell Physiol.* 2000;279:C98-C107.
45. Leithauser B, Bratm H, Jaecks S, Matthias FR. Binding of antithrombin to endothelial surface is crucial for its antiinflammatory effects after LPS-challenge. *Intensive Care Med.* 2000;26(suppl B):257.
46. Bernard GR, Vincent J-L, Laterre P-F, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med.* 2001;344:699-709.