

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

MAY 31, 2012

VOL. 366 NO. 22

Drotrecogin Alfa (Activated) in Adults with Septic Shock

V. Marco Ranieri, M.D., B. Taylor Thompson, M.D., Philip S. Barie, M.D., M.B.A., Jean-François Dhainaut, M.D., Ivor S. Douglas, M.D., Simon Finfer, F.R.C.P., Bengt Gårdlund, M.D., John C. Marshall, M.D., Andrew Rhodes, M.D., Antonio Artigas, M.D., Ph.D., Didier Payen, M.D., Ph.D., Jyrki Tenhunen, M.D., Ph.D., Hussein R. Al-Khalidi, Ph.D., Vivian Thompson, M.P.H., Jonathan Janes, M.B., B.Ch., William L. Macias, M.D., Ph.D., Burkhard Vangerow, M.D., and Mark D. Williams, M.D., for the PROWESS-SHOCK Study Group*

ABSTRACT

BACKGROUND

There have been conflicting reports on the efficacy of recombinant human activated protein C, or drotrecogin alfa (activated) (DrotAA), for the treatment of patients with septic shock.

METHODS

In this randomized, double-blind, placebo-controlled, multicenter trial, we assigned 1697 patients with infection, systemic inflammation, and shock who were receiving fluids and vasopressors above a threshold dose for 4 hours to receive either DrotAA (at a dose of 24 μg per kilogram of body weight per hour) or placebo for 96 hours. The primary outcome was death from any cause 28 days after randomization.

RESULTS

At 28 days, 223 of 846 patients (26.4%) in the DrotAA group and 202 of 834 (24.2%) in the placebo group had died (relative risk in the DrotAA group, 1.09; 95% confidence interval [CI], 0.92 to 1.28; $P=0.31$). At 90 days, 287 of 842 patients (34.1%) in the DrotAA group and 269 of 822 (32.7%) in the placebo group had died (relative risk, 1.04; 95% CI, 0.90 to 1.19; $P=0.56$). Among patients with severe protein C deficiency at baseline, 98 of 342 (28.7%) in the DrotAA group had died at 28 days, as compared with 102 of 331 (30.8%) in the placebo group (risk ratio, 0.93; 95% CI, 0.74 to 1.17; $P=0.54$). Similarly, rates of death at 28 and 90 days were not significantly different in other predefined subgroups, including patients at increased risk for death. Serious bleeding during the treatment period occurred in 10 patients in the DrotAA group and 8 in the placebo group ($P=0.81$).

CONCLUSIONS

DrotAA did not significantly reduce mortality at 28 or 90 days, as compared with placebo, in patients with septic shock. (Funded by Eli Lilly; PROWESS-SHOCK ClinicalTrials.gov number, NCT00604214.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Thompson at the Pulmonary and Critical Care Unit, Bullfinch Bldg., Rm. 148, Massachusetts General Hospital, 55 Fruit St., Boston, MA 02114, or at tthompson1@partners.org.

Drs. Ranieri and Thompson contributed equally to this article.

*Investigators in the Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis and Septic Shock (PROWESS-SHOCK) study group are listed in the Supplementary Appendix, available at NEJM.org.

This article (10.1056/NEJMoa1202290) was published on May 22, 2012, at NEJM.org.

N Engl J Med 2012;366:2055-64.

Copyright © 2012 Massachusetts Medical Society.

RECOMBINANT HUMAN ACTIVATED PROTEIN C, or drotrecogin alfa (activated) (DrotAA), was approved for the treatment of severe sepsis in 2001 on the basis of the Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study,¹ a phase 3 international, randomized, controlled trial that was stopped early for efficacy after the enrollment of 1690 patients with severe sepsis. Absolute mortality in the intention-to-treat population was reduced by 6.1 percentage points, a relative risk reduction of 19.4%. Subsequent subgroup analysis suggested that the mortality benefit was limited to patients with increased illness severity (i.e., those with more than one sepsis-related dysfunctional organ or with an Acute Physiology and Chronic Health Evaluation [APACHE] II score² of more than 24 [on a scale of 0 to 71, with higher scores indicating an increased risk of death]). The Food and Drug Administration limited its approval of the drug for use in patients with “a high risk of death” and requested additional trials involving less severely ill adults and children. These trials were terminated early for futility by independent data and safety monitoring committees.^{3,4} Moreover, subgroups of patients at increased risk for death within the adult trial did not appear to benefit from the use of DrotAA. The lack of confirmatory data from placebo-controlled trials⁵ called into question the results of the PROWESS study and thus the efficacy of the drug.⁶

DrotAA received marketing authorization from the European Medicines Agency for the treatment of adults with severe sepsis and multiple organ failure, but the approval was subject to annual review.⁷ In 2007, the agency concluded that sufficient doubt existed to warrant a new placebo-controlled trial.⁸ We conducted the PROWESS-SHOCK study to test the hypothesis that DrotAA, as compared with placebo, would reduce mortality in patients with septic shock.⁹

METHODS

STUDY PATIENTS

The study protocol has been published previously (www.springerlink.com/content/t3353213r20835ul/fulltext.pdf).⁹ The trial was approved by the institutional review board at each study center, and written informed consent was obtained from patients or their legally authorized surrogates in accordance with local requirements.

Adult patients were eligible for inclusion if they had sepsis (infection and two or more signs of systemic inflammation), shock, and clinical evidence of hypoperfusion. We defined hypoperfusion as metabolic acidosis (base deficit, ≥ 5.0 mmol per liter; venous bicarbonate, < 18 mmol per liter; or lactate, > 2.5 mmol per liter) or renal or hepatic dysfunction. (Case definitions are provided in the protocol.) We defined shock as the need for treatment with norepinephrine at a dose of at least 5 μg per minute or an equivalent dose of another vasopressor for 4 hours or more, provided that at least 30 ml per kilogram of body weight of crystalloid or an equivalent volume of colloid was administered during the 8-hour interval surrounding the start of vasopressor treatment. We required that patients remain refractory to reasonable attempts to wean vasopressors and begin study treatment within 24 hours after the first dose of a vasopressor. (Full details regarding inclusion and exclusion criteria are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

Patients with coexisting illnesses with a high risk of death (e.g., metastatic cancer) were excluded. The clinical coordinating center confirmed the eligibility of each patient before randomization.

STUDY TREATMENTS

A centralized system randomly assigned patients to receive an intravenous infusion of DrotAA (Xigris, Eli Lilly) at a dose of 24 μg per kilogram of body weight per hour for 96 hours or matching placebo dissolved in 0.9% saline solution. Study-group assignments were concealed from patients, investigators, treating clinicians, and the sponsor. Temporary interruptions of the study infusion were mandated for invasive procedures; in such cases, the infusion was extended through day 6 (the treatment period) so that the 96-hour infusion could be completed wherever possible. All other treatments were at the discretion of treating clinicians.

EVALUATION OF PATIENTS

We assessed baseline demographic characteristics, preexisting conditions, organ function, sites of infection, microbiology results, and hematologic and laboratory measurements within 24 hours before the administration of a study drug. Blood samples for the measurement of protein C levels were collected on days 1 through 7. Assays

to assess protein C activity were performed on an STA Compact coagulation analyzer with the use of the STA-Staclot protein C kit (Diagnostica Stago). Patients were followed until either 90 days or death.

PRIMARY AND SECONDARY OUTCOMES

The primary outcome was death at 28 days. Secondary outcomes included 28-day mortality in patients with severe protein C deficiency (plasma concentration, $\leq 50\%$ of the lower limit of the normal range), 90-day mortality, measures of organ dysfunction, and safety. We examined heterogeneity of the treatment effect on mortality at 28 and 90 days in prespecified subgroups, as defined by the following baseline characteristics: APACHE II score (< 25 or ≥ 25), number of organs that had failed, presence or absence of the acute respiratory distress syndrome (ARDS), the quartile of time from the onset of shock to the initiation of study treatment, plasma protein C level, glucocorticoid treatment, prophylactic heparin administration, recent surgery, and platelet count.

We assessed organ function using Sequential Organ Failure Assessment (SOFA) scores (on a scale of 0 to 4 for each organ system, with higher scores indicating more severe organ dysfunction). We used the SOFA score to measure the change from baseline to study day 7, using the mean arterial pressure and vasopressor dose to measure cardiovascular function, the ratio of the partial pressure of oxygen in arterial blood to the fraction of inspired oxygen to measure respiratory function, and the serum creatinine level to measure renal function.

STUDY OVERSIGHT

The steering committee designed the study in collaboration with the sponsor, Eli Lilly, as reported previously.⁹ Coauthors from the Duke Clinical Research Institute performed the analysis. The steering committee wrote the first draft of the manuscript, and the two first coauthors made the decision to submit the manuscript for publication. All authors had full and independent access to all the data and vouch for the integrity, accuracy, and completeness of the analysis and its fidelity to the study protocol.¹⁰

STATISTICAL ANALYSIS

We determined that the planned enrollment of 1500 patients would provide a power of 80% at a significance level of 0.05 to detect an absolute difference of 7 percentage points (20% relative

risk reduction) in the primary outcome of 28-day mortality from the placebo rate of 35%. An independent data and safety monitoring board conducted interim analyses, as described previously.⁹ The protocol specified an increase in sample size if the 28-day mortality for 750 patients was less than 30%.

The final primary analysis used a P value of less than 0.05 with adjustment for interim analyses of the cumulative data. The 28-day primary efficacy analysis was conducted according to the intention-to-treat principle and documented in the statistical analysis plan, as described previously.⁹⁻¹¹ Patients with unknown survival status at 28 days or 90 days were excluded from the landmark analyses. In the time-to-event analyses, data for patients with unknown survival status were censored on the last day that patients were known to be alive.

We used a Cox proportional-hazards model to estimate the hazard ratio for death with the use of DrotAA versus placebo. We used a log-rank test to assess differences in survival curves between the two groups in the time-to-event analysis through 28 days and 90 days. Survival estimates were calculated with the use of the Kaplan-Meier method. We used the Wilcoxon rank-sum test to assess between-group differences in SOFA scores. Similarly, we used ranked analysis of variance to assess the change in protein C level from baseline to day 7 and to compare the two study groups. We used the Breslow-Day test for homogeneity of odds ratios to determine differences in the treatment effect across categories for each of the prespecified subgroups at 28 days. All safety analyses were conducted in the population of treated patients.

RESULTS

STUDY PATIENTS

Aggregate mortality after recruitment of 750 patients was 27.6%. Therefore, we increased the sample size to 1696 on May 12, 2010. Patients were enrolled from March 2008 through August 2011 at 208 sites in Europe, North and South America, Australia, New Zealand, and India (for details, see the Supplementary Appendix). From 27,816 potential patients, we recruited 1697, with 852 assigned to receive DrotAA and 845 assigned to receive placebo. We were able to evaluate the primary outcome in 1680 patients (99.0%) (Fig. 1).

A total of 71.7% of patients were recruited at

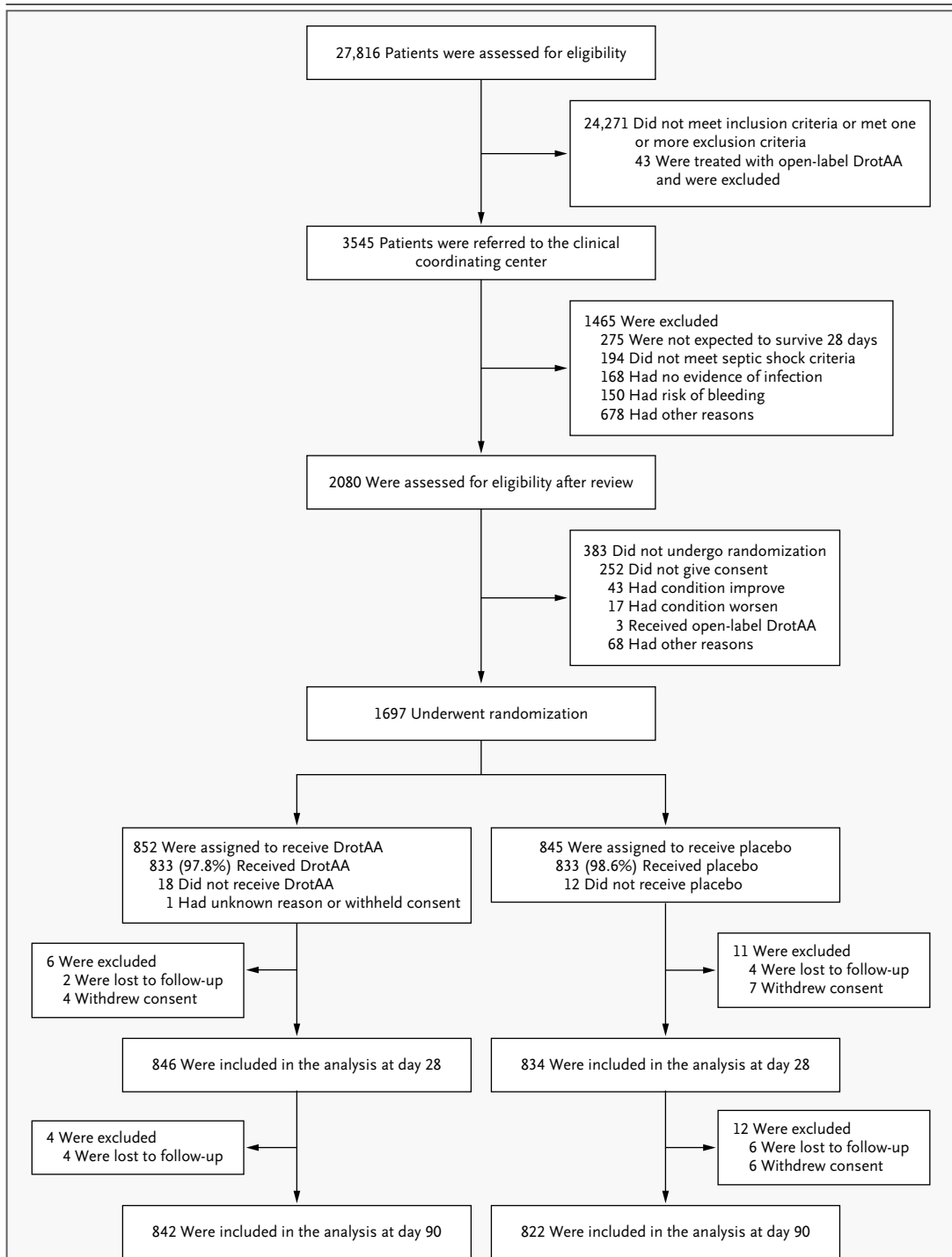


Figure 1. Screening, Randomization, and Follow-up of the Study Patients.

Screening procedures for all sites were not standardized, and not all sites returned screening logs. To screen for eligibility, sites were encouraged to identify all patients receiving vasopressors. If patients appeared to meet all inclusion and no exclusion criteria or if sites requested clarification, the clinical coordinating center was contacted. If the center confirmed eligibility, the site was authorized to randomly assign the patients. The reasons for exclusion are provided in Table S1 in the Supplementary Appendix. All patients who underwent randomization are included in the survival analysis for 28 and 90 days; data for patients with unknown survival status (i.e., those who were lost to follow-up or withdrew) were censored on the last day the patient was known to be alive. DrotAA denotes drotrecogin alfa (activated).

Table 1. Site and Cause of Infection.*

Variable	Drotrecogin Alfa (Activated)	Placebo
Primary site of infection — no./total no. (%)		
Lung	369/851 (43.4)	375/845 (44.4)
Abdomen	263/851 (30.9)	246/845 (29.1)
Urinary tract	97/851 (11.4)	112/845 (13.3)
Skin	48/851 (5.6)	45/845 (5.3)
Other site†	74/851 (8.7)	67/845 (7.9)
Positive blood culture — no./total no. (%)	270/851 (31.7)	239/845 (28.3)
Community-acquired infection — no./total no. (%)	654/850 (76.9)	654/845 (77.4)
Identification of infectious organism — no./total no. (%)	623/851 (73.2)	575/845 (68.0)‡
Sensitivity of infectious organism to administered antibiotics — no./total no. (%)§	514/611 (84.1)	481/571 (84.2)
Time from initiation of antibiotics to initiation of vasopressor — hr		
Median	2.5	2.5
Interquartile range	0–7.1	0–8.6
Source control of infection — no./total no. (%)¶	275/303 (90.8)	264/295 (89.5)

* There was no significant difference between the two study groups, except as indicated.

† Other sites included the central nervous system, blood, heart, pleura, reproductive tract, bone, and head.

‡ P=0.02

§ Drugs in this category are all antimicrobial agents that were administered before infusion of a study drug.

¶ Included in this category are patients who were treated for source control of infection (e.g., surgery, drainage, or removal of an infected central venous catheter) in the subgroup of patients for whom source control was deemed to be necessary. The type and frequency of organisms recovered from blood are provided in Table S3 in the Supplementary Appendix.

European sites and 14.1% at North American sites, with 14.2% recruited from other countries. Baseline characteristics were similar in the two groups (Table S2 in the Supplementary Appendix): 56.4% of the patients were men, and the mean (\pm SD) ages were 63.4 \pm 15.4 years in the DrotAA group versus 62.7 \pm 16.4 years in the placebo group. The mean APACHE II scores were 25.2 \pm 8.1 and 25.5 \pm 8.1 in the DrotAA and placebo groups, respectively; 84.1% of the patients had dysfunction of three or more organs.

The site of infection, cultured organisms, and antimicrobial treatments were similar in the two groups (Table 1, and Table S3 in the Supplementary Appendix). The most common sites of infection were the lung, abdomen, and urinary tract. A causative pathogen was identified before starting study treatment in 1198 of 1696 patients (70.6%); 509 of 1696 patients (30.0%) had positive blood cultures. The median time from the initiation of antibiotics to initial vasopressor therapy was 2.5 hours (interquartile range, 0 to 7.1) in the DrotAA group and 2.5 hours (interquartile range, 0 to 8.6) in the placebo group (P=0.98).

The control of infection at the presumed source was accomplished in 275 of 303 patients (90.8%) in the DrotAA group and 264 of 295 (89.5%) in the placebo group (P=0.60).

STUDY TREATMENT AND COINTERVENTIONS

Study treatment was administered to 1666 of 1696 patients (98.2%) and was interrupted at least once in 593 of 1666 patients (35.6%). The mean total duration of study treatment was 83.3 \pm 26.7 hours in the DrotAA group and 85.1 \pm 25.1 hours in the placebo group. The major reason for interrupting a study treatment was an invasive procedure (in 215 of 306 patients with interruptions [70.3%] in the DrotAA group vs. 238 of 287 [82.9%] in the placebo group). Study treatment was stopped prematurely in 216 of 833 patients (25.9%) in the DrotAA group and 191 of 833 (22.9%) in the placebo group. In the two groups, the most common reason for premature discontinuation was the patient's death (Table S4 in the Supplementary Appendix). The proportions of patients receiving glucocorticoids and anti-coagulants were also similar in the two groups,

as were the number and site of surgical procedures performed during the treatment period (Table S4 in the Supplementary Appendix).

OUTCOMES

The status of patients at 28 days is provided in Table S5 in the Supplementary Appendix. At 28 days, 223 of 846 patients (26.4%) in the DrotAA group and 202 of 834 (24.2%) in the placebo group had died (relative risk in the DrotAA group, 1.09; 95% confidence interval [CI], 0.92 to 1.28; $P=0.31$). At 90 days, 287 of 842 patients (34.1%) in the DrotAA group and 269 of 822 (32.7%) in the placebo group had died (relative risk, 1.04; 95% CI, 0.90 to 1.19; $P=0.56$) (Table 2). In addition, the time-to-event analysis at 90 days showed similar results (hazard ratio, 1.07; 95% CI, 0.91 to 1.26; $P=0.43$ by the log-rank test) (Fig. 2A). There was no significant heterogeneity in the treatment effect on mortality at 28 days and 90 days in the prespecified subgroups (Fig. 2B, and Fig. S1 in the Supplementary Appendix). Changes in organ function during the 7-day study period

Figure 2 (facing page). Probability of Survival and Odds Ratios for Death, According to Subgroup.

Panel A shows Kaplan–Meier estimates for the probability of survival, which at 90 days did not differ significantly between patients receiving drotrecogin alfa (activated) (DrotAA) and those receiving placebo (hazard ratio, 1.07; 95% confidence interval, 0.91 to 1.26; $P=0.43$ by the log-rank test). Panel B shows the odds ratios and 95% confidence intervals for death from any cause among all patients in the predefined subgroups. The size of the symbols indicates the relative number of deaths. Although the odds ratio for death at 28 days was a specified outcome in the predefined statistical analysis plan (Fig. S1 in the Supplementary Appendix), odds ratios at 90 days are shown because the outcome at 90 days was deemed to be more relevant to clinicians and patients. The Acute Physiology and Chronic Health Evaluation (APACHE) II score ranges from 0 to 71 points, with higher scores indicating greater disease severity. Sequential Organ Failure Assessment (SOFA) scores range from 0 to 4 for each organ system, with higher scores indicating more severe organ dysfunction. Organ failure was defined as a SOFA score of 3 or 4 for any individual organ system. The protein C class indicates the percentage of normal protein C activity. ARDS denotes acute respiratory distress syndrome.

Table 2. Study Outcomes and Adverse Events.*

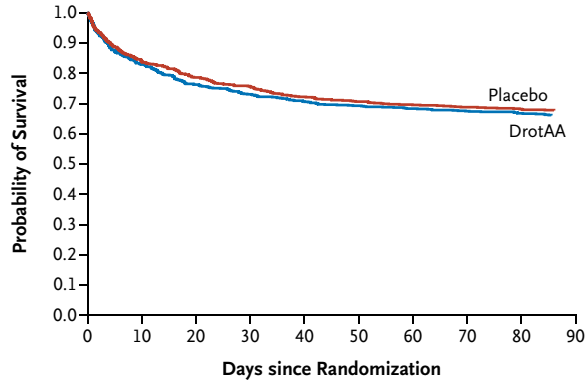
Outcome	Drotrecogin Alfa (Activated)	Placebo	Relative Risk (95% CI)	P Value
Death — no./total no. (%)				
At 28 days	223/846 (26.4)	202/834 (24.2)	1.09 (0.92–1.28)	0.31
At 90 days	287/842 (34.1)	269/822 (32.7)	1.04 (0.90–1.19)	0.56
Change in SOFA score by day 7†				
Cardiovascular	−2.61±1.72	−2.69±1.70		0.44
Respiratory	−0.71±1.23	−0.70±1.19		0.84
Renal	−0.64±1.34	−0.64±1.34		0.99
Coagulation	−0.03±1.18	−0.04±1.15		0.92
Liver	−0.03±0.96	−0.03±0.91		0.63
At least one serious adverse event by day 28 — no./total no. (%)‡	119/833 (14.3)	96/833 (11.5)	1.23 (0.96–1.59)	0.11
At least one bleeding event during treatment period — no./total no. (%)				
Nonserious	72/833 (8.6)	40/833 (4.8)	1.80 (1.23–2.61)	0.002
Serious	10/833 (1.2)	8/833 (1.0)	1.25 (0.49–3.15)	0.81
Cerebral hematoma, cerebral or subarachnoid hemorrhage, or hemorrhagic stroke by day 28 — no./total no. (%)	3/833 (0.4)	3/833 (0.4)	1.00 (0.20–4.90)	1.00

* Plus–minus values are means ±SD.

† Sequential Organ Failure Assessment (SOFA) scores range from 0 to 4 for each organ system, with higher scores indicating more severe organ dysfunction. P values were calculated with the use of the Wilcoxon rank-sum test.

‡ A complete list of serious adverse events is provided in Table S6 in the Supplementary Appendix.

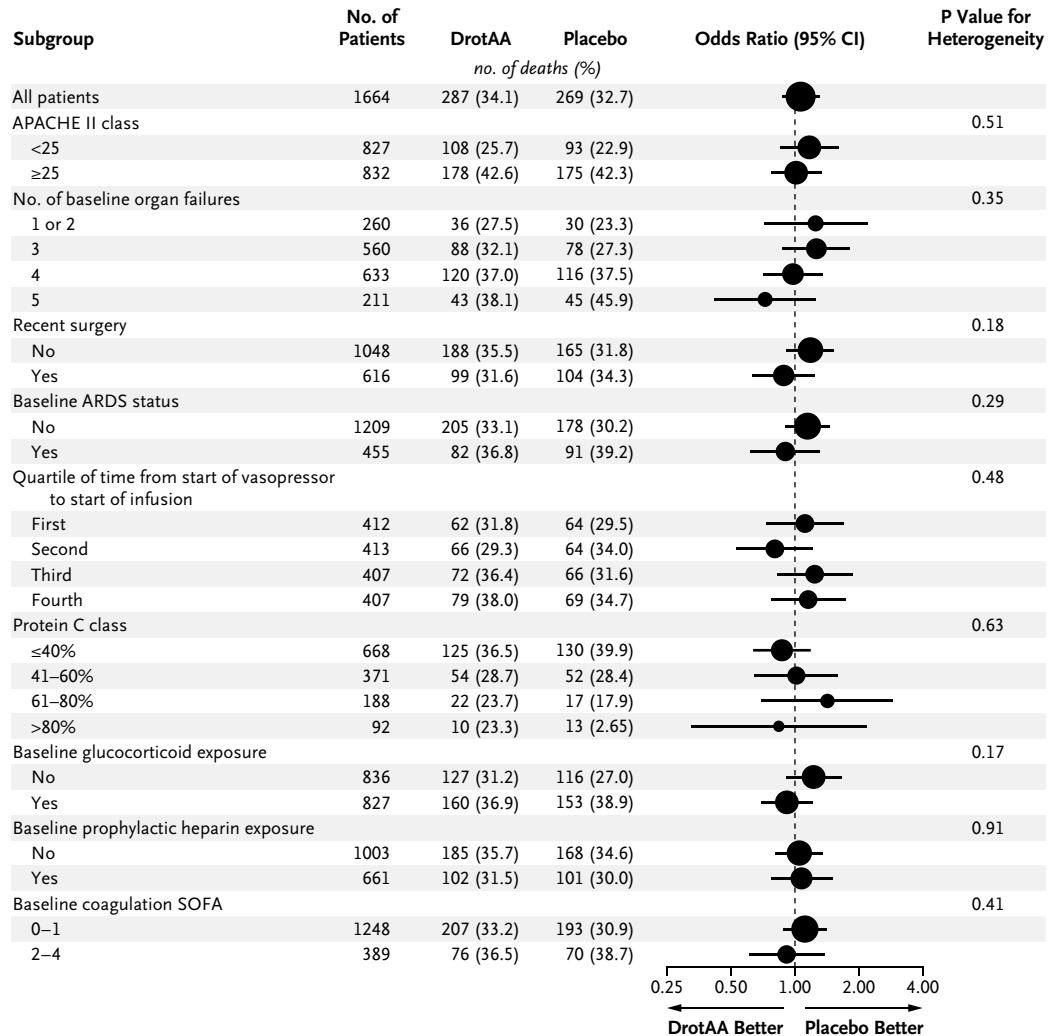
A Probability of Survival



No. at Risk

Placebo	845	703	656	622	593	579	569	563	557	553
DrotAA	851	701	645	616	596	584	576	567	561	555

B Odds Ratio for Death



did not differ significantly in the two groups (Table 2). Protein C activity increased from baseline during the first 6 days in both groups; the mean increase was significantly greater in patients in the DrotAA group than in the placebo group on each of the first 4 study days ($P < 0.001$) (Fig. S2 in the Supplementary Appendix).

During the first 28 days, one or more serious adverse events were recorded in 119 of 833 patients (14.3%) in the DrotAA group versus 96 of 833 patients (11.5%) in the placebo group ($P = 0.10$) (Table 2, and Table S4 in the Supplementary Appendix). During the treatment period, non-serious bleeding events were more common among patients receiving DrotAA than among those receiving placebo (in 72 of 833 patients [8.6%] vs. 40 of 833 [4.8%], $P = 0.002$), as were serious bleeding events (in 10 of 833 patients [1.2%] vs. 8 of 833 [1.0%], $P = 0.81$), although the latter difference was not significant.

DISCUSSION

In this large international study involving critically ill adults with septic shock, DrotAA did not reduce mortality at either 28 or 90 days, as compared with placebo. The lack of benefit was consistent across predefined subgroups.

The strengths of the trial lie in both its design and its execution. From the results of previous randomized trials, we identified a clinically relevant population of patients who were likely to benefit from treatment with DrotAA, and we predefined a limited number of relevant subgroups within this population.^{1,3,12-18} The characteristics of the patients we recruited matched the population we targeted. The baseline characteristics indicated a high degree of disease severity: 97.5% had multiple organ dysfunction, 90.2% had metabolic acidosis, and more than half had an elevated lactate level that persisted after fluid resuscitation. The baseline protein C level was markedly reduced in many patients. All patients remained dependent on vasopressors at study entry; most were treated with norepinephrine, with a median dose of 21 to 24 μg per minute at the start of study treatment. The baseline APACHE II score (which was designed to estimate the risk of death among critically ill patients rather than to assess the eligibility of individual patients for particular treatments) was somewhat lower than expected. Similar APACHE II scores

have been reported in a trial of treatments for septic shock,¹⁹ and such scores may reflect improved early resuscitation, since they are sensitive to lead-time bias.^{20,21}

We used an adaptive design²² that allowed us to increase the sample size to maintain adequate statistical power, since some trials involving patients with severe sepsis showed lower-than-expected mortality.^{19,23,24} To reduce the risk of assignment bias, we concealed study-group assignments before and after randomization, and to minimize crossovers, we used a standardized process to select hospitals and intensive care units that did not regularly treat patients with DrotAA. The success of these processes is evident in the excellent compliance with study treatment and the minimal crossover observed in the study. We achieved near complete follow-up and followed a predefined, published statistical analysis plan. We used mortality as an outcome that is less subject to biased ascertainment than other outcomes.²⁵ We focused on mortality at 90 days,¹⁸ since 45% of the patients were still hospitalized at 28 days, a percentage similar to that reported in the PROWESS study.

Our trial also has some limitations. We did not collect comprehensive data to study the coagulation or inflammatory responses during infusion of the study drugs, although such data exist from previous trials.^{1,3,12,13,17,26} The between-group difference in protein C activity in our trial was similar to that seen in the PROWESS study,^{27,28} and this finding combined with the expected increase in nonserious bleeding events in the DrotAA group^{5,13} indicates that the patients received the intended treatment; both are indirect markers of the biologic activity of DrotAA. Mortality in the placebo group was low, as compared with historical data,^{1,29-31} but consistent with that observed in more recent observational studies^{32,33} and trials.^{34,35}

Our findings are consistent with results of the Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) and the Resolution of Organ Failure in Pediatric Patients with Severe Sepsis (RESOLVE) trials, which showed that DrotAA did not reduce mortality in children or adults with severe sepsis who had a low risk of death.^{3,4} Our results are consistent with the finding in the ADDRESS trial in that DrotAA was not effective in patients with an increased disease severity.⁴ We cannot explain

the inconsistency between our findings and the reduction in mortality at 28 days that was observed in the PROWESS study.¹ Our findings of similar mortality at 90 days are consistent with those of the PROWESS study at 3 months, at which time mortality was not significantly reduced by DrotAA.³⁶

Our study showed that DrotAA was not beneficial when administered to a population of patients for which it was an approved treatment. The fact that we found no benefit in any of the prespecified subgroups should reassure clinicians who no longer have DrotAA available to treat patients with septic shock.³⁷

Supported by Eli Lilly.

Dr. Ranieri reports serving as a member of a data and safety monitoring board for Biotest and an advisory board member for Hemodec and Maquet; Dr. Thompson, serving as the chair of a data and safety monitoring board for AstraZeneca and as an advisory board member for Hemodec, receiving consulting fees from Abbott, Sanofi-Aventis, Immunetrics, US Biotest, Sirius Genomics, and Eli Lilly; Dr. Barie, receiving consulting fees from Eisai and lecture fees from Eli Lilly; Dr. Douglas, receiving grant support from Eli Lilly, Eisai, and Agennix and serving as cochair for the International Guidelines Committee for the 2012 Surviving Sepsis Campaign; Dr. Finfer, receiving consulting fees from Eisai, being a member of the International Sepsis Forum (ISF), and receiving travel support from ISF corporate sponsors; Dr. Marshall, receiving consulting fees from Eisai, Idaho Technology, Roche Diagnostics, Bayer, Vertex Technologies, Pfizer, Daiichi Sankyo, and Hoffmann-La Roche, receiving grant support and travel expenses from BioMérieux, serving as a member of the ISF and receiving travel support from ISF corporate sponsors, serving as a member of the Center for Sepsis Control and Care at the University of Jena and as a member of the data and

safety monitoring board for Artisan Pharma, Leo Pharma, Celgene Therapeutics, and Therapeutic Monitoring Systems, and serving as a steering committee member for Spectral Diagnostics and Eisai; Dr. Rhodes, serving on advisory boards for LIDCO and BioMérieux and receiving lecture fees from Edwards, LiDCO, and Covidien; all the preceding authors, or their institutions, received financial support from Eli Lilly for time spent performing committee activities and for travel; Dr. Artigas, receiving travel support and lecture fees and grant support and support for patient recruitment (through his institution) from Eli Lilly, serving on advisory boards for Gambro and Hemodec, and receiving consulting fees from Brahms; Dr. Payen, serving on an advisory board for Homeostasie Consulting and receiving consulting and lecture fees from Homeostasie Consulting and institutional grant support from Naturalia et Biologia; Dr. Tenhunen, receiving institutional grant support for lectures, travel expenses, and data analysis from Eli Lilly; Dr. Al-Khalidi and Ms. Thompson, being employees of the Duke Clinical Research Institute, which received financial support for statistical analysis, preparation of study reports, manuscript review and writing, and travel from Eli Lilly; and Drs. Janes, Macias, Vangerow, and Williams, being current or former employees of and having an equity interest in Eli Lilly. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the study patients, their families, and surrogate decision makers for their participation; Arthur Wheeler, Todd Rice, Wes Ely, and Gordon Bernard and their staff at the Vanderbilt Clinical Coordinating Center; Rebecca Bailey, Sheila Calderon, Joan Gottesman, Cindy Pastern, Monica Schultz, Mary Stroud, Bridget Swindell, and Kimberly Warren for coordinating the clinical trial; Robinette Angle, DeNada E.S. Campbell, Elvira Coca, Timothy L. Costigan, Sandra Donaldson, Frederique Fillon, Darell Heiselman, Annick Schatteman, Douglas Schlichting, Stefano Telara, Mariano Alejandro Mignini, and Lucio Varanese of Eli Lilly for providing assistance to the steering committee; and Vivian Thompson and the Duke Clinical Research Institute for their analyses of study data and assistance in the preparation of the manuscript.

APPENDIX

The authors' affiliations are as follows: Ospedale S. Giovanni Battista-Molinette, Università di Torino, Turin, Italy (V.M.R.); the Pulmonary and Critical Care Unit, Massachusetts General Hospital, Boston (B.T.T.); the Departments of Surgery and Public Health, Weill Cornell Medical College, New York (P.S.B.); Cochin Port Royal Hospital-Paris Descartes University (J.-F.D.), University Paris Diderot, Sorbonne Paris Cité, and the Department of Anesthésie-Réanimation-SMUR, Hôpital Lariboisière, AP-HP (D.P.) — all in Paris; Denver Health and University of Colorado School of Medicine — both in Denver (I.S.D.); Royal North Shore Hospital and the George Institute for Global Health, University of Sydney — both in Sydney (S.F.); the Department of Infectious Diseases, Karolinska University Hospital, Stockholm (B.G.); the Departments of Surgery and Critical Care Medicine, Keenan Research Institute, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto (J.C.M.); Intensive Care Medicine, St. George's Healthcare NHS Trust and St. George's University of London — both in London (A.R.); Critical Care Center, Hospital de Sabadell, CIBER Enfermedades Respiratorias, Corporació Sanitària Universitària Parc Taulí, Universitat Autònoma de Barcelona, Sabadell, Spain; (A.A.); the Department of Surgical Sciences/Anaesthesiology and Intensive Care, Uppsala University, Uppsala, Sweden (J.T.); Duke Clinical Research Institute, Duke University Medical Center, Durham, NC (H.R.A.-K., V.T.); and Lilly Research Laboratories, Eli Lilly, Indianapolis (J.J., W.L.M., B.V., M.D.W.).

REFERENCES

- 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.
- Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818-29.
- Abraham E, Laterre P-F, Garg R, et al. Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. *N Engl J Med* 2005;353:1332-41.
- Nadel S, Goldstein B, Williams MD, et al. Drotrecogin alfa (activated) in children with severe sepsis: a multicentre phase III randomised controlled trial. *Lancet* 2007;369:836-43.
- Marti-Carvajal AJ, Solà I, Lathyris D, Cardona AF. Human recombinant activated protein C for severe sepsis. *Cochrane Database Syst Rev* 2011;4:CD004388.
- Gårdlund B. Activated protein C (Xigris) treatment in sepsis: a drug in trouble. *Acta Anaesthesiol Scand* 2006;50:907-10.
- European Medicines Agency. Marketing authorization. Drotrecogin alfa (activated). 2002 (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000396/human_med_001160.jsp#authorisation).
- 4th Annual reassessment of Xigris. 2007 (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion_-_Variation/human/000396/WC500058072.pdf).
- Finfer S, Ranieri VM, Thompson BT,

- et al. Design, conduct, analysis and reporting of a multi-national placebo-controlled trial of activated protein C for persistent septic shock. *Intensive Care Med* 2008;34:1935-47. [Erratum, *Intensive Care Med* 2011;37:372.]
10. Thompson BT, Ranieri VM, Finfer S, et al. Statistical analysis plan of PROWESS SHOCK study. *Intensive Care Med* 2010; 36:1972-3.
 11. Ranieri VM, Thompson BT, Finfer S, et al. Unblinding plan of PROWESS-SHOCK trial. *Intensive Care Med* 2011;37:1384-5.
 12. Ely EW, Laterre PF, Angus DC, et al. Drotrecogin alfa (activated) administration across clinically important subgroups of patients with severe sepsis. *Crit Care Med* 2003;31:12-9.
 13. Bernard GR, Macias WL, Joyce DE, Williams MD, Bailey J, Vincent JL. Safety assessment of drotrecogin alfa (activated) in the treatment of adult patients with severe sepsis. *Crit Care* 2003;7:155-63.
 14. Dhainaut JF, Laterre PF, Janes JM, et al. Drotrecogin alfa (activated) in the treatment of severe sepsis patients with multiple-organ dysfunction: data from the PROWESS trial. *Intensive Care Med* 2003; 29:894-903.
 15. Vincent JL, Angus DC, Artigas A, et al. Effects of drotrecogin alfa (activated) on organ dysfunction in the PROWESS trial. *Crit Care Med* 2003;31:834-40.
 16. Fry DE, Beilman G, Johnson S, et al. Safety of drotrecogin alfa (activated) in surgical patients with severe sepsis. *Surg Infect (Larchmt)* 2004;5:253-9.
 17. Levi M, Levy M, Williams MD, et al. Prophylactic heparin in patients with severe sepsis treated with drotrecogin alfa (activated). *Am J Respir Crit Care Med* 2007;176:483-90.
 18. Barie PS, Hydo LJ, Shou J, Eachempati SR. Efficacy of therapy with recombinant human activated protein C of critically ill surgical patients with infection complicated by septic shock and multiple organ dysfunction syndrome. *Surg Infect (Larchmt)* 2011;12:443-9.
 19. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008;358:877-87.
 20. Escarce JJ, Kelley MA. Admission source to the medical intensive care unit predicts hospital death independent of APACHE II score. *JAMA* 1990;264:2389-94.
 21. Koperna T, Semmler D, Marian F. Risk stratification in emergency surgical patients: is the APACHE II score a reliable marker of physiological impairment? *Arch Surg* 2001;136:55-9.
 22. Maharaj R. Vasopressors and the search for the optimal trial design. *Contemp Clin Trials* 2011;32:924-30.
 23. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 2010;362:779-89.
 24. Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008;358:111-24.
 25. Rao SR, Schoenfeld DA. Survival methods. *Circulation* 2007;115:109-13.
 26. Dhainaut JF, Yan SB, Joyce DE, et al. Treatment effects of drotrecogin alfa (activated) in patients with severe sepsis with or without overt disseminated intravascular coagulation. *J Thromb Haemost* 2004;2:1924-33.
 27. Macias WL, Nelson DR. Severe protein C deficiency predicts early death in severe sepsis. *Crit Care Med* 2004;32: Suppl:S223-S228.
 28. Shorr AF, Bernard GR, Dhainaut JF, et al. Protein C concentrations in severe sepsis: an early directional change in plasma levels predicts outcome. *Crit Care* 2006;10:R92.
 29. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001;29:1303-10.
 30. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003;348:1546-54.
 31. Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* 2006;34:344-53.
 32. Australasian Resuscitation in Sepsis Evaluation (ARISE) Investigators. The outcome of patients with sepsis and septic shock presenting to emergency departments in Australia and New Zealand. *Crit Care Resusc* 2007;9:8-18.
 33. Levy MM, Dellinger RP, Townsend SR, et al. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Crit Care Med* 2010; 38:367-74.
 34. Rice TW, Wheeler AP, Bernard GR, et al. A randomized, double-blind, placebo-controlled trial of TAK-242 for the treatment of severe sepsis. *Crit Care Med* 2010; 38:1685-94.
 35. Tidswell M, Tillis W, Larosa SP, et al. Phase 2 trial of eritoran tetrasodium (E5564), a toll-like receptor 4 antagonist, in patients with severe sepsis. *Crit Care Med* 2010;38:72-83. [Erratum, *Crit Care Med* 2010;38:1925-6.]
 36. Angus DC, Laterre PF, Helterbrand J, et al. The effect of drotrecogin alfa (activated) on long-term survival after severe sepsis. *Crit Care Med* 2004;32:2199-206.
 37. Food and Drug Administration. Voluntary market withdrawal of Xigris [drotrecogin alfa (activated)] due to failure to show a survival benefit. 2011 (<http://www.fda.gov/Drugs/DrugSafety/ucm277114.htm>).

Copyright © 2012 Massachusetts Medical Society.

SEND A 200TH ANNIVERSARY MESSAGE TO NEJM

Join your peers in posting an anniversary message and read the collected messages at the NEJM 200th Anniversary website, <http://NEJM200.NEJM.org>. We look forward to hearing from you!