

## ORIGINAL ARTICLE



# Drotrecogin Alfa (Activated) in Adults with Septic Shock

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## 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](#).)

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,<sup>1</sup> 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<sup>1</sup> to patients with more than one sepsis-related dysfunctional organ or with an APACHE II score<sup>2</sup> of more than 24 [on a scale of 0 to 71, with scores ranging from 0 to 71, with scores of 0 to 24 indicating less severe illness]. 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

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APACHE II score<sup>2</sup> of more

NEW 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.<sup>3,4</sup> 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 trials<sup>5</sup> called into question the results of the PROWESS study and thus the efficacy of the drug.<sup>6</sup>

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.<sup>7</sup> In 2007, the agency concluded that sufficient doubt existed to warrant a new placebo-controlled trial.<sup>8</sup> We conducted the PROWESS-SHOCK study to test the hypothesis that DrotAA, as compared with placebo, would reduce mortality in patients with septic shock.<sup>2</sup>

## Methods

### STUDY PATIENTS

The study protocol has been published previously ([www.springerlink.com/content/t3353213r20835ul/fulltext.pdf](http://www.springerlink.com/content/t3353213r20835ul/fulltext.pdf)).<sup>2</sup> 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,  $\geq 5.0$  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  $\mu$ g 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  $\mu$ g 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  $\geq 25$ ), 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 d  
function, the ratio of the partial pressure of oxygen to arterial pressure to measure cardiovascular  
respiratory function, and the serum creatinine level to measure renal function.

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The steering committee designed the study in collaboration with the sponsor, Eli Lilly, as reported previously.<sup>9</sup> 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.<sup>10</sup>

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.<sup>9</sup> The protocol specified an increase in sample size if the 28-day mortality for 750 patients was less than 30%.

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.

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%) ([Figure 1](#)).

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. Have questions about this content? [Try AI Companion.](#)

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graph TD
    A[27,816 Patients were assessed for eligibility] --> B[3545 Patients were referred to the clinical coordinating center]
    A --> C[24,271 Did not meet inclusion criteria or more exclusion criteria  
43 Were treated with open-label DroAA and were excluded]
    B --> D[1495 Were excluded  
275 Were not expected to survive ≥ 28 days  
294 Did not meet toxicologic shock criteria  
168 Had no evidence of infection  
350 Had risk of bleeding  
678 Had other reasons]
    D --> E[2080 Were assessed for eligibility after review]
    E --> F[1697 Underwent randomization]
    E --> G[383 Did not undergo randomization  
232 Did not give consent  
43 Had condition improving  
17 Had condition worsen  
3 Received open-label DroAA  
68 Had other reasons]
    F --> H[852 Were assigned to receive DroAA  
833 (97.8%) Received DroAA  
18 Did not receive DroAA  
1 Had unknown reason or withheld consent]
    F --> I[845 Were assigned to receive placebo  
831 (98.4%) Received placebo  
12 Did not receive placebo]
    H --> J[6 Were excluded  
2 Were lost to follow-up  
4 Withdrew consent]
    I --> K[11 Were excluded  
4 Were lost to follow-up  
7 Withdrew consent]
    J --> L[846 Were included in the analysis at day 28]
    K --> M[834 Were included in the analysis at day 28]
    L --> N[7]
    M --> O[12 Were excluded  
6 Were lost to follow-up  
6 Withdrew consent]
    N --> P[NEW  
included in the analysis at day 90]
    O --> Q[822 Were included in the analysis at day 90]
  
```

Flowchart illustrating the patient flow through the trial, from initial assessment to final analysis.

- 27,816 Patients** were assessed for eligibility.
  - 24,271 Did not meet inclusion criteria or more exclusion criteria. 43 Were treated with open-label DroAA and were excluded.
  - 3545 Patients were referred to the clinical coordinating center.
- 3545 Patients** were referred to the clinical coordinating center.
  - 1495 Were excluded:
    - 275 Were not expected to survive ≥ 28 days
    - 294 Did not meet toxicologic shock criteria
    - 168 Had no evidence of infection
    - 350 Had risk of bleeding
    - 678 Had other reasons
  - 2080 Were assessed for eligibility after review.
- 2080 Patients** were assessed for eligibility after review.
  - 1697 Underwent randomization.
  - 383 Did not undergo randomization:
    - 232 Did not give consent
    - 43 Had condition improving
    - 17 Had condition worsen
    - 3 Received open-label DroAA
    - 68 Had other reasons
- 1697 Patients** underwent randomization.
  - 852 Were assigned to receive DroAA:
    - 833 (97.8%) Received DroAA
    - 18 Did not receive DroAA
    - 1 Had unknown reason or withheld consent
  - 845 Were assigned to receive placebo:
    - 831 (98.4%) Received placebo
    - 12 Did not receive placebo
- 852 Patients** assigned to receive DroAA:
  - 6 Were excluded
  - 2 Were lost to follow-up
  - 4 Withdrew consent
  - 846 Were included in the analysis at day 28
- 845 Patients** assigned to receive placebo:
  - 11 Were excluded
  - 4 Were lost to follow-up
  - 7 Withdrew consent
  - 834 Were included in the analysis at day 28
- 846 Patients** included in the analysis at day 28:
  - 7
  - NEW included in the analysis at day 90
- 834 Patients** included in the analysis at day 28:
  - 12 Were excluded
  - 6 Were lost to follow-up
  - 6 Withdrew consent
  - 822 Were included in the analysis at day 90

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±26.7 hours in the DrotAA group and 85.1±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 anticoagulants 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) ([Figure 2A](#)). There was no significant heterogeneity in the treatment effect on mortality at 28 days and 90 days in the prespecified subgroups ([Figure 2B](#), and Fig. S1 in the [Supplementary Appendix](#)). Changes in organ function during the 7-day study period 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, nonserious 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.

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

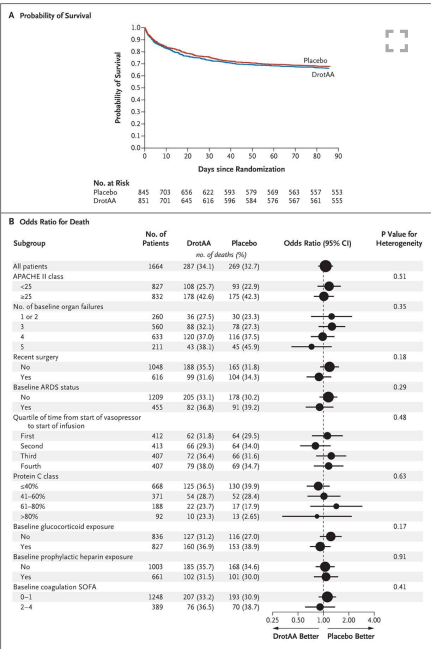
TABLE 1

| Table 1. Site and Cause of Infection.*                                              |                              |                |  |
|-------------------------------------------------------------------------------------|------------------------------|----------------|--|
| Variable                                                                            | Drotrecogin Alfa (Activated) |                |  |
| 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 initiation 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](#).

Site and Cause of Infection.

FIGURE 2



Probability of Survival and Odds Ratios for Death, According to Subgroup.

TABLE 2

| Outcome                                                                                                    | Drotrecogin Alfa (Activated) | Placebo        | Relative Risk (95% CI) | P Value |
|------------------------------------------------------------------------------------------------------------|------------------------------|----------------|------------------------|---------|
| Death—no./total no. (%)                                                                                    |                              |                |                        |         |
| At 28 days                                                                                                 | 223/864 (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    |

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

### Study Outcomes and Adverse Events.

## 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.<sup>1,3,12-18</sup> 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,<sup>19</sup> and such scores may reflect improved early resuscitation, since they are sensitive to lead-time bias.<sup>20,21</sup>

We used an adaptive design<sup>22</sup> 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.<sup>19,23,24</sup> 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.<sup>25</sup> We focused on mortality at 90 days,<sup>18</sup> 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.<sup>1,3,12,13,17,26</sup> The between-group difference in protein C activity in our trial was similar to that seen in the PROWESS study,<sup>27,28</sup> and this finding combined with the expected increase in nonserious bleeding events in the DrotAA group<sup>5,13</sup> 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,<sup>1,29–31</sup> but consistent with that observed in more recent observational studies<sup>32,33</sup> and trials.<sup>34,35</sup>

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.<sup>3,4</sup> Our results are consistent with the finding in the ADDRESS trial in that DrotAA was not effective in patients with an increased disease severity.<sup>4</sup> We cannot explain the inconsistency between our findings and the reduction in mortality at 28 days that was observed in the PROWESS study.<sup>1</sup> 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.<sup>3,6</sup>

Our study showed that DrotAA is an approved treatment. The fact that we have no longer have DrotAA available to treat patients with septic shock. [Have questions about this content? Try AI Companion.](#)

NEW patients for which it was an  
results should reassure clinicians

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## NOTES

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Drs. Ranieri and Thompson contributed equally to this article.

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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.

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## SUPPLEMENTARY MATERIAL

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**Supplementary Appendix** (nejmoa1202290\_appendix.pdf)

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## APPENDIX

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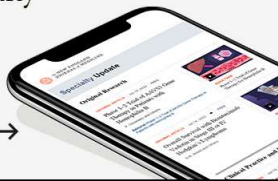
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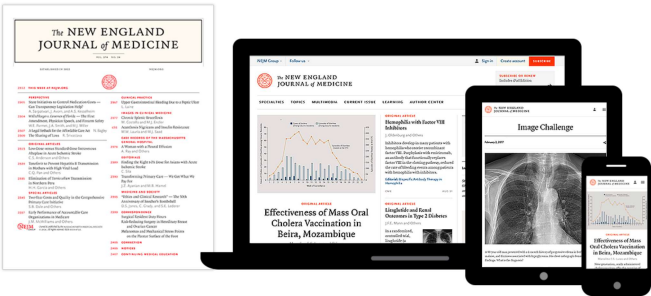
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