

Drotrecogin alfa (activated) administration across clinically important subgroups of patients with severe sepsis

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Objective: To assess the effects of drotrecogin alfa (activated) therapy, a recombinant human activated protein C, across clinically relevant subpopulations in a randomized, phase 3, placebo-controlled study of patients with severe sepsis (recombinant human activated protein C worldwide evaluation in severe sepsis [PROWESS]).

Design: Univariate and multivariable analysis of prospectively defined subgroups from the PROWESS study.

Setting: A total of 164 medical centers in 11 countries.

Patients: A total of 1,690 patients with severe sepsis.

Measurements and Main Results: We report observed 28-day mortality rates for drotrecogin alfa (activated) and placebo patients for subgroups prospectively defined by demographic data, surgical status, type and site of infection, and clinical and biochemical measures of disease severity. We performed subgroup analyses to explore the consistency of the mortality benefit observed in the overall population and performed tests for both quantitative and qualitative interactions. To examine the magnitude of the treatment benefit with drotrecogin alfa (activated) across the underlying predicted risk of mortality spectrum, we used stepwise logistic regression on PROWESS placebo patients to generate a predicted risk of mortality model that simultaneously included many clinical and biochemical markers of mortality risk. Because drotrecogin alfa (activated) has anticoagulant

properties, we also present analyses of bleeding and thrombotic events. Actual mortality rates were lower with drotrecogin alfa (activated) compared with placebo for nearly all prospectively defined subgroups. Both univariate and multivariable regression analyses showed a consistent relative risk reduction in 28-day mortality rates for drotrecogin alfa (activated). Larger absolute risk reductions were found with drotrecogin alfa (activated) in patients with a higher baseline predicted risk of mortality, and actual mortality rates were lower with drotrecogin alfa (activated) in all subgroups defined by disease severity measures where a $\geq 20\%$ placebo mortality was observed. Although discriminatory power was limited by few observed events, the increased absolute risk of experiencing a serious bleeding event with treatment did not seem to vary according to the baseline predicted risk of mortality.

Conclusions: The administration of drotrecogin alfa (activated) to patients with severe sepsis was associated with a significant survival benefit that tended to increase with higher baseline likelihood of death. Current data suggest that the increased risk of bleeding does not vary according to likelihood of death. (Crit Care Med 2003; 31:12–19)

KEY WORDS: drotrecogin alfa (activated); activated protein C; Xigris, severe sepsis; subgroups; Acute Physiology and Chronic Health Evaluation

Drotrecogin alfa (activated), a recombinant human activated protein C, has become the first drug approved by the U.S. Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products for treatment of patients with severe sepsis (patients with sepsis compli-

cated by the development of acute organ dysfunction). The drug is approved for use in severe sepsis patients at high risk of death as determined, for example, by Acute Physiology and Chronic Health Evaluation (APACHE) II (1) score as suggested in the U.S. label or by the presence of multiple organ dysfunction as indicated in the Eu-

ropean Union label. These decisions were based on the results of a large multicenter, multinational trial (recombinant human activated protein C worldwide evaluation in severe sepsis [PROWESS]) that demonstrated a reduction in 28-day mortality from 31% in patients receiving placebo to 25% in patients receiving a 96-hr infusion

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of drotrecogin alfa (activated) ($p = 0.005$) (2). Approval has also been obtained or is currently being sought with regulatory authorities in other countries.

When a new therapy is demonstrated to improve outcomes, an important question is whether the effect is consistent across different patient subgroups. Unfortunately, clinical trials are typically powered to detect an overall effect, and are thus underpowered to make strong inferences about particular subgroups. Whereas quantitative differences (differences in the *magnitude* of treatment effect across subgroups) are common, as more evidence accrues, qualitative differences (differences in the *direction* of treatment effect) are rarely found (3–5). Thus, there is controversy over the value of subgroup analyses from a clinical trial (4, 6). Such analyses may be misleading because of a combination of reduced statistical power, increased variance, multiplicity, and the play of chance (4). Over-interpretation of subgroup analyses has theoretically been linked to harm through either inappropriate treatment or withholding potentially life-saving therapy (7). Many experts recommend considering the “average” result of a randomized clinical trial as the most reliable estimate of treatment effect in a given subgroup rather than the observed results within the subgroup itself (3, 4). Although seemingly counterintuitive, this is more reliable statistically (3, 8, 9).

Although inflammation and coagulopathy occurred nearly universally in the PROWESS cohort (2), it is well recognized that severe sepsis is clinically a very heterogeneous condition, arising in a broad mix of patients secondary to several different infections. Therefore, it was determined *a priori* that in addition to reporting the overall trial results, subgroup analyses would be performed to address the following two hypotheses: 1) the efficacy of drotrecogin alfa (activated) is not attributed predominantly to one or a small subgroup of patients, and 2) there is no convincing evidence that any one particular subgroup enrolled into PROWESS has a high likelihood of harm. Such a subgroup analysis would also serve to generate hypotheses that may help guide future trial design. Therefore, as part of our prospectively defined analysis plan, we present mortality subgroup data from the PROWESS trial and discuss the implications for appropriate clinical application of drotrecogin alfa (activated). Because drotrecogin alfa (activated) has anticoagulant properties, we also

present analyses of bleeding and thrombotic events.

MATERIALS AND METHODS

Study Protocol and Patient Population. PROWESS was a randomized, double-blind, placebo-controlled, phase 3 trial evaluating the efficacy of drotrecogin alfa (activated) (Xigris, Eli Lilly and Company, Indianapolis, IN) in adults with severe sepsis (2). The ethical review board at each center approved the study protocol. After obtaining informed consent, patients were randomly assigned to receive either drotrecogin alfa (activated) at a dose of 24 $\mu\text{g}/\text{kg}/\text{hr}$ or placebo for a total of 96 hrs (10) and were followed for 28 days from the start of study-drug administration or until death. Both groups also received standard supportive care. The intention-to-treat population, defined as those patients who received study drug for any length of time, totaled 1,690 patients. Patients at high risk of bleeding and those likely to die of other serious comorbid conditions other than sepsis within the 28-day follow-up period were excluded from the trial.

Baseline Data Collection and Organ Dysfunction Definitions. We assessed patient-specific covariates at baseline, before the administration of study drug, rather than later in the clinical course to avoid variables that may have been affected by treatment. Baseline characteristics assessed in the 24-hr period immediately preceding start of study-drug infusion included demographics, preexisting conditions, site and type of infection, laboratory values, need for mechanical ventilation and vasopressor support, and APACHE II scores.

Organ function was assessed within the 48-hr period immediately preceding start of study-drug infusion as the presence or absence of prospectively defined cardiovascular, respiratory, renal, and hematologic dysfunction, as well as the presence of metabolic acidosis (2). Baseline cardiovascular, respiratory, renal, hematologic (platelet count), hepatic, Glasgow Coma Scale, and Sequential Organ Failure Assessment (11) scores were determined based on local laboratory data, vasopressor dosages, and the need for mechanical ventilation. Functional dependency status was assessed as the presepsis activity of daily living scores (12).

Laboratory Assays. A central laboratory performed all assays. Citrated plasma samples obtained at baseline were assayed for protein C levels (Stacot Protein C clotting assay), D-dimer (STA-Liatest D-DI), prothrombin time (STA-Neoplastine CI Plus, rabbit brain thromboplastin), and activated partial thromboplastin time (STA-PTTA) using reagents from Diagnostica Stago (Asnieres, France). Interleukin (IL)-6 levels were determined from baseline serum samples as previously described (2). Platelet count was determined using flow-cytometric methodology.

Definition of Bleeding and Thrombotic Events. We determined the subset of bleeding events within all study adverse events by applying a prospective *bleeding event* (“any

bleeding”) definition. For each bleeding event, the patient’s clinical investigator assessed event severity (mild, moderate, severe). Serious bleeding events were defined as any intracranial hemorrhage, any life-threatening bleed, a requirement of ≥ 3 units of packed red blood cells per day for two consecutive days, or any bleeding event meeting any of the other criteria defining a serious adverse event (2). A blinded physician review of all serious bleeding events determined whether the event was causally related to an invasive procedure. A serious *thrombotic event* was defined as any of the following serious adverse events: cerebral arterial thrombosis, cerebral infarct, cerebrovascular accident, myocardial infarction, peripheral arterial thrombosis, deep venous thrombosis, or pulmonary thromboembolism.

Analyses Across Subgroups. We report observed 28-day mortality rates for drotrecogin alfa (activated) and placebo patients for many clinically relevant subgroups. We defined a “within” subgroup result to be consistent with the benefit observed in the overall trial if the “within” subgroup 95% confidence interval for the relative risk contained the overall relative risk point estimate of 0.806 observed for the entire population. Of note, “consistent” is defined here in terms of *relative* risk, and not *absolute* risk. Thus, results across subgroups may be “consistent” even if their absolute reductions vary in magnitude. For example, if one subgroup has absolute mortality rates of 50% and 40% in the placebo and treatment arms, the absolute reduction is 10% and the relative reduction is 20% (10%/50%). Another subgroup may demonstrate a decrease from 25% in the placebo arm to 20% in the treatment arm. For this subgroup, the absolute risk reduction is 5% but the relative risk remains unchanged (5%/25% = 20% relative risk reduction).

As recommended by the Consolidated Standards of Reporting Trials guidelines and others for subgroup analyses (13, 14), we assessed potential treatment-by-subgroup interactions by using the Breslow-Day test for homogeneity of odds ratios across strata because the odds ratio scale is the most generally accepted scale to perform interaction analyses across subgroups (15, 16). We assessed potential qualitative treatment-by-subgroup interactions using the qualitative interaction range test (17). No statistical adjustments were made for the multiplicity of subgroup analyses presented.

Univariate Analysis. We evaluated the consistency of the drotrecogin alfa (activated) treatment effect on mortality across the following prospectively defined subgroups: demographics, recent surgery within 30 days of study entry, site of infection (lung, intra-abdominal, urinary tract, or other), type of infecting organism as determined by the investigator (pure Gram-positive, pure Gram-negative, mixed Gram bacterial, or no microorganism identified), protein C deficiency, baseline coagulation parameters of prothrombin time class, activated partial thromboplastin time class, and platelet class, IL-6 levels,

ventilator or vasopressor use, types and numbers of organ dysfunctions, and APACHE II quartile. In addition, we present the results for two nonprospective, but clinically relevant, subgroups: baseline overt disseminated intravascular coagulation (DIC) status and baseline total Sequential Organ Failure Assessment score quartile (18). Overt DIC was defined based on an adaptation of the definition proposed by the International Society of Thrombosis and Hemostasis (19).

Multivariable Logistic Regression Analysis. We employed stepwise logistic regression using data collected on PROWESS placebo patients to generate a predicted risk of mortality model that could simultaneously include many clinical and biochemical markers of mortality risk (see Appendix for variables considered for inclusion). We chose the Schwartz criterion as the method of adjusting the $-2 \times \log$ likelihood statistic for the number of terms in the resultant model and assessed the goodness-of-fit of the multivariable risk model to the observed placebo data using the Hosmer-Lemeshow chi-square statistic (20). We assessed the superiority of the multivariable risk model to individual predictors of mortality risk (for example, APACHE II score, IL-6) using Mallows's Cp statistic (21). All computations were performed using S-Plus 2000 Professional Release 3 for PC (Insightful Corporation, Seattle, WA) and SAS Release 6.12 for Windows (SAS Institute, Cary, NC).

From the resultant risk model based on placebo patients, we calculated the baseline predicted risk of mortality for each drotrecogin alfa (activated) and placebo patient in the PROWESS trial. We assessed the consistency of the drotrecogin alfa (activated) treatment effect across the predicted risk of mortality spectrum using the same methods applied to the prospectively defined subgroups above.

RESULTS

Overall Trial. The administration of drotrecogin alfa (activated) to patients with severe sepsis was associated with a 6.1% absolute reduction in 28-day all-cause mortality (adjusted relative risk reduction = 19.4%; $p = .005$) (2). During the 28-day study, 17.7% ($n = 149$) of placebo and 24.9% ($n = 212$) of drotrecogin alfa (activated) patients had at least one bleeding event ($p = .001$, relative risk = 1.41 [1.17–1.69]). Of the patients with bleeding events, 57% had their bleeding event(s) classified as mild or moderate in severity by the investigator. In the drotrecogin alfa (activated) group, 3.5% ($n = 30$) of patients experienced a serious bleeding event within 28 days compared with 2.0% ($n = 17$) of patients in the placebo group

($p = .06$) (2). The increased proportion of patients with at least one serious bleeding event in the drotrecogin alfa (activated) treatment group (2) was primarily related to recent traumatic injury or instrumentation of a major blood vessel or highly vascular organ, with serious bleeding upon restarting the drug in these patients, whereas the number of non-procedure-related serious bleeding events was similar in the treatment and placebo groups ($n = 15$ and $n = 14$). In the drotrecogin alfa (activated) group, 2.0% ($n = 17$) of patients experienced a serious thrombotic event compared with 3.0%

($n = 25$) of patients in the placebo group ($p = .20$) (2).

Mortality Rates by Subgroups. Actual 28-day mortality rates were lower for drotrecogin alfa (activated) patients compared with placebo patients across all subgroups defined by age, sex, racial origin, geographic region, prior or preexisting conditions of congestive heart failure, chronic obstructive pulmonary disease, or cancer, and both “recent surgery” and “no recent surgery” subgroups (Fig. 1). The actual mortality was slightly higher with drotrecogin alfa (activated) compared with placebo in the small subgroup

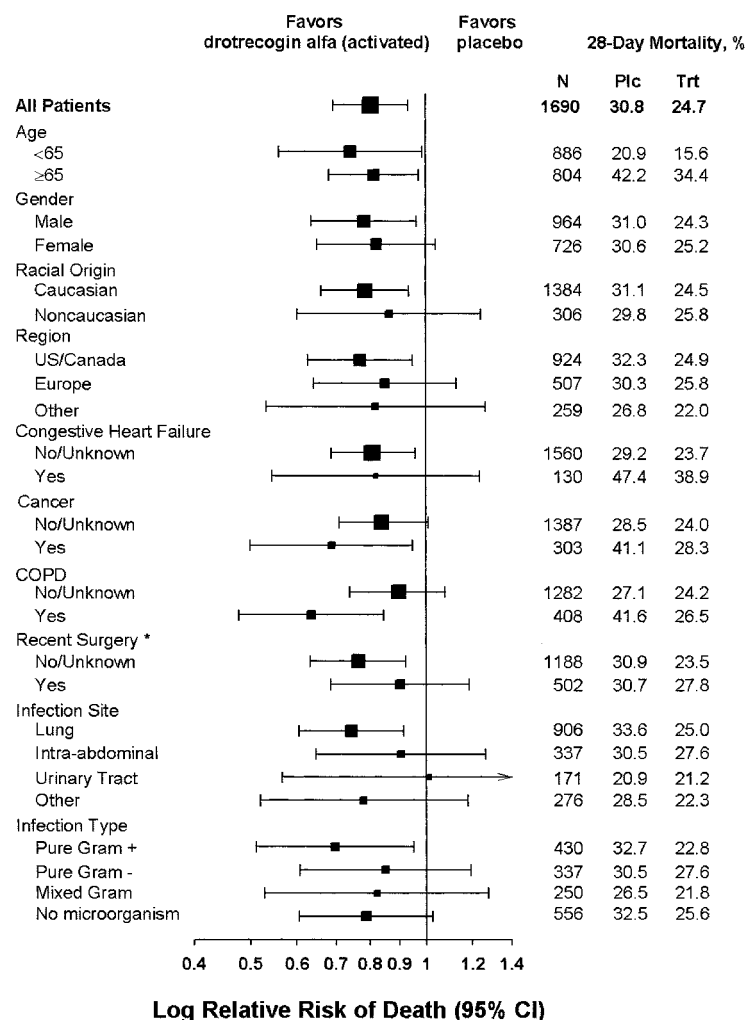


Figure 1. Illustration of 28-day all-cause mortality across subgroups defined by demographic data, surgical status, and infection characteristics. The point estimate of relative risk of death in each subgroup is indicated by a solid square and the 95% confidence interval (CI) by the horizontal lines. The size of the point estimate symbol is proportional to the number of patients in the subgroup compared with the overall trial population. The All Patients group shows the relative risk and 95% CI, with accompanying mortality rates, for the overall trial population. N, total number of patients in the subgroup; Plc, placebo group; Trt, drotrecogin alfa (activated) group; COPD, chronic obstructive pulmonary disease. *Recent surgery within the past 30 days. The Breslow-Day interaction p value for COPD was .03, and all other interaction p values ranged from .21 to .89.

of urosepsis patients. Regardless of the type of infecting pathogen, actual mortality rates were lower for drotrecogin alfa (activated) patients compared with placebo patients. Only the major groups of pathogens are displayed. Other groups of types of infection (e.g., fungal) had very small numbers of patients.

Actual mortality rates were lower with drotrecogin alfa (activated) compared with placebo for all subgroups defined by measures of baseline overt DIC status, protein C deficiency, prothrombin time class, activated partial thromboplastin time class, platelet class, and IL-6 levels (Fig. 2). With the exception of the overt DIC status subgroup, the total size of the subgroups based on laboratory markers of coagulation is <1,690 patients because of collection of samples not suitable for measurement of these markers or sample mishandling before receipt of the sample at the central laboratory.

Figure 3 shows mortality results for subgroups based on multiple clinical measures of baseline disease severity. Actual mortality rates were lower for drotrecogin alfa (activated) patients in subgroups defined by the use of mechanical ventilation or vasopressor support and in subgroups defined by the presence or absence of each of the prospectively defined cardiovascular, respiratory, hematologic (platelet count), renal, and metabolic organ dysfunction criteria used as entry criteria into the trial (data not shown). Observed reductions in the relative risk of dying in these subgroups ranged from 13% to 28%, with all absolute risk reductions >3.5%. The total size of the number of organ dysfunction subgroup is 1,689 patients because of the enrollment of one patient in the trial that had no organ dysfunction.

Actual mortality rates were lower with drotrecogin alfa (activated) regardless of the number of organ dysfunctions present at baseline. Within the subgroup of 418 patients with a single organ dysfunction at baseline, 85% of the patients had either respiratory or cardiovascular dysfunction. Of those patients, actual mortality rates were lower with drotrecogin alfa (activated) versus placebo for patients with solitary respiratory dysfunction (n = 231, 18.6% vs. 24.6%; relative risk = 0.76 [0.46–1.25]) and solitary cardiovascular dysfunction (n = 124, 13.6% vs. 15.5%; relative risk = 0.88 [0.37–2.06]). A higher actual mortality rate with drotrecogin alfa (activated) compared with placebo was observed in the small

subgroup of patients with solitary renal, metabolic acidosis, or hematologic organ dysfunction (n = 63, 33.3% vs. 18.5%; relative risk = 1.80 [0.72–4.50]).

Actual mortality rates were lower with drotrecogin alfa (activated) compared with placebo in the second, third, and fourth APACHE II quartiles, with a higher mortality rate observed for treatment patients in the first (lowest severity) APACHE II quartile. The treatment-by-APACHE II score quartile interaction *p* value was .09. The formal statistical test for a true qualitative (change in direction of effect) interaction was not significant (*p* = .45). No treatment-by-total Sequential Organ Failure Assessment quartile in-

teraction was observed (*p* = .68) in an exploratory analysis for a treatment-by-acute physiology interaction.

Treatment Effect by Predicted Risk of Death. In the construction of the stepwise logistic regression model built on placebo patients, the following variables were retained: APACHE II score, age (yrs), log IL-6, dependency status, comorbidity status, and whether or not the presumed site of infection indicated urosepsis (Appendix). The Hosmer-Lemeshow goodness-of-fit statistic was 9.8 with 18 degrees of freedom, signaling the model's excellent fit to the PROWESS placebo patient data (*p* = .94). The model was superior at predicting placebo mortality

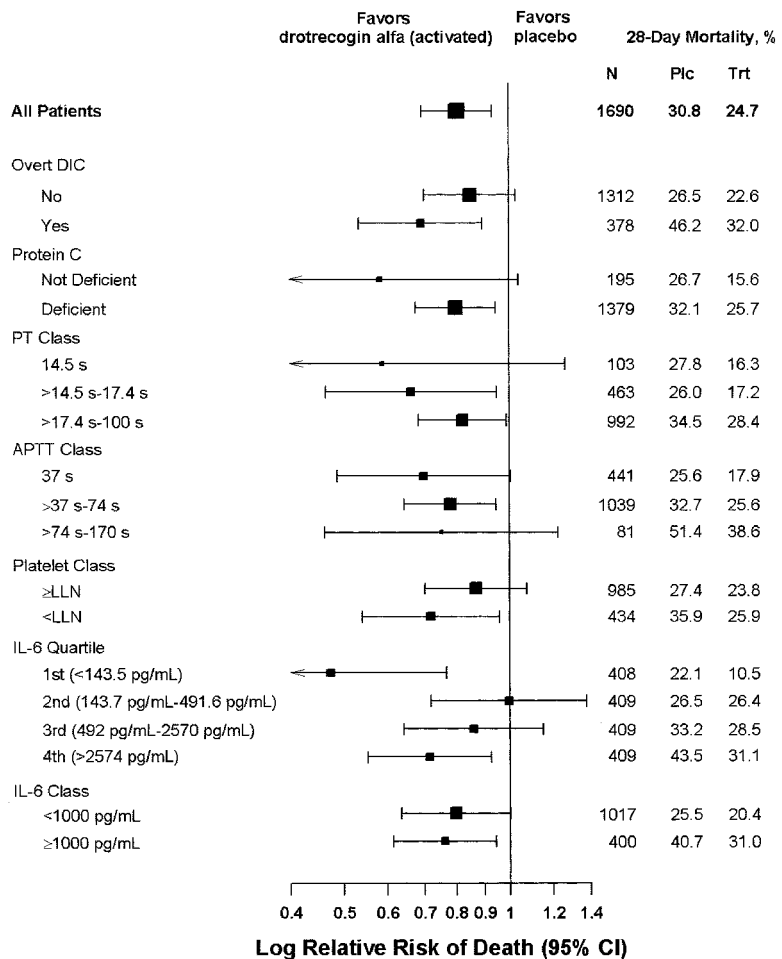


Figure 2. Illustration of 28-day all-cause mortality across subgroups defined by hematologic and inflammation measures of baseline disease severity. The point estimate of relative risk of death in each subgroup is indicated by a solid square and the 95% confidence interval (CI) by the horizontal lines. The size of the point estimate symbol is proportional to the number of patients in the subgroup compared with the overall trial population. The All Patients group shows the relative risk and 95% CI, with accompanying mortality rates, for the overall trial population. *N*, total number of patients in the subgroup; *DIC*, disseminated intravascular coagulation; *Plc*, placebo group; *Trt*, drotrecogin alfa (activated) group. Protein C deficiency was defined as a level <81%. *PT*, prothrombin time; *APTT*, activated partial thromboplastin time; *LLN*, lower limit of normal (140×10^9 platelets/L); *IL-6*, interleukin-6. The Breslow-Day interaction *p* value for IL-6 quartile was .07, and all other interaction *p* values ranged from .12 to .89.

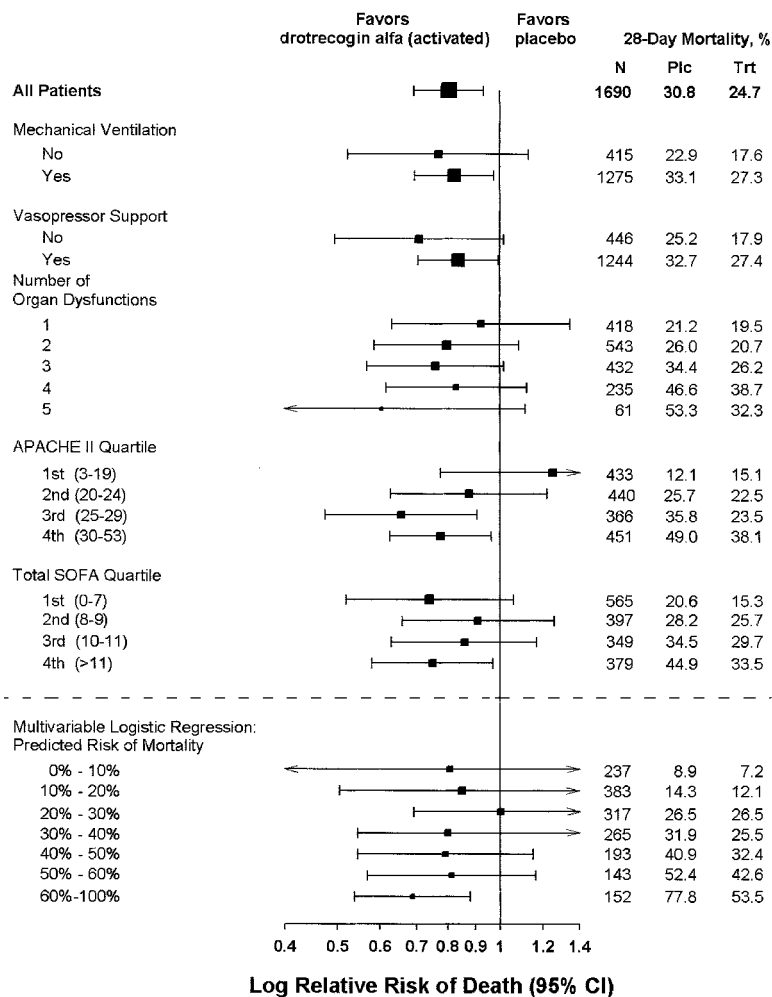


Figure 3. Illustration of 28-day all-cause mortality across subgroups defined by clinical measures of baseline disease severity and predicted risk of mortality. The point estimate of relative risk of death in each subgroup is indicated by a solid square and the 95% confidence interval (CI) by the horizontal lines. The size of the point estimate symbol is proportional to the number of patients in the subgroup compared with the overall trial population. The All Patients group shows the relative risk and 95% CI, with accompanying mortality rates, for the overall trial population. N, total number of patients in the subgroup; Plc, placebo group; Trt, drotrecogin alfa (activated) group. The range of Acute Physiology and Chronic Health Evaluation (APACHE) II scores or total Sequential Organ Failure Assessment (SOFA) scores for the respective quartiles are indicated. The area below the gray dashed line represents the multivariable logistic regression. The Breslow-Day interaction *p* value for APACHE II quartile was .09, and all other interaction *p* values ranged from .33 to .86.

compared with solely using the APACHE II score, IL-6 level, or the other risk model variables individually (all decreases in Mallows's $C_p > .77$). The same or lower mortality rates were observed with treatment compared with placebo in all predicted risk of mortality classes, and all predicted risk of mortality subgroup results were consistent with the overall PROWESS results (Fig. 3). The interaction test across the predicted risk of mortality classes was not statistically significant ($p = .33$). In addition, the formal test for a qualitative interaction was not statistically significant ($p > .98$). Visual

inspection of the multivariable regression data presented in Figure 3 shows that the relative risk remained fairly constant, whereas Figure 4 illustrates that the absolute benefit with drotrecogin alfa (activated) increased in patients at higher risk of death.

Bleeding Rates by Subgroups. Across the same subgroups shown in Figures 1–3, the relative risk of “any bleeding” with treatment compared with placebo ranged from 0.65 to 1.86 (data not shown). No statistically significant treatment-by-subgroup interactions were noted (all $p = .15$ to .96). Using the same

consistency criteria employed for mortality, “any bleeding” and “serious bleeding” results for all subgroups were consistent with the overall trial results. For bleeding event end points (any or serious bleeding), there was no statistically significant interaction with predicted risk of mortality ($p = .55$ and $p = .21$).

Of particular interest are the lowest APACHE II quartile, recent surgery, and overt DIC subgroups. No significant interaction *p* values for “any bleeding” were observed across subgroups defined by APACHE II quartile, recent surgery status, and overt DIC status ($p = .53$, .94, and .97, respectively). There were eight more serious bleeding events in drotrecogin alfa (activated) patients compared with placebo patients in the lowest APACHE II quartile (10 vs. 2). Two of the 10 treatment bleeding events were fatal; however, this result alone would not explain the first APACHE II quartile mortality observation (seven more deaths in the drotrecogin alfa (activated) group than the placebo group). The differences between drotrecogin alfa (activated) and placebo patients in observed serious bleeding event rates were comparable for those with recent surgery (3.7% vs. 1.9%) and without recent surgery (3.5% vs. 2.1%). In addition, the differences between drotrecogin alfa (activated) and placebo groups in serious bleeding event rates were also similar for patients with overt DIC (4.6% vs. 2.7%) and patients without overt DIC (3.2% vs. 1.8%).

Also of interest was the $<30,000/\text{mm}^3$ platelet count subgroup. There were six hemorrhagic deaths of 210 total deaths in the drotrecogin alfa (activated) group compared with two of 259 deaths in the placebo group. Four of the hemorrhagic deaths occurred during infusion of drotrecogin alfa (activated) and were considered by the investigator to be related to the administration of study drug. Three of the four hemorrhagic deaths that occurred during infusion of drotrecogin alfa (activated) were associated with severe thrombocytopenia (platelet counts $<30,000/\text{mm}^3$).

DISCUSSION

More than 2,000 people each day develop severe sepsis in the United States alone, and a third of these patients die (22). Severe sepsis, defined as sepsis associated with at least one acute organ dysfunction, results from derangements in procoagulant and inflammatory host

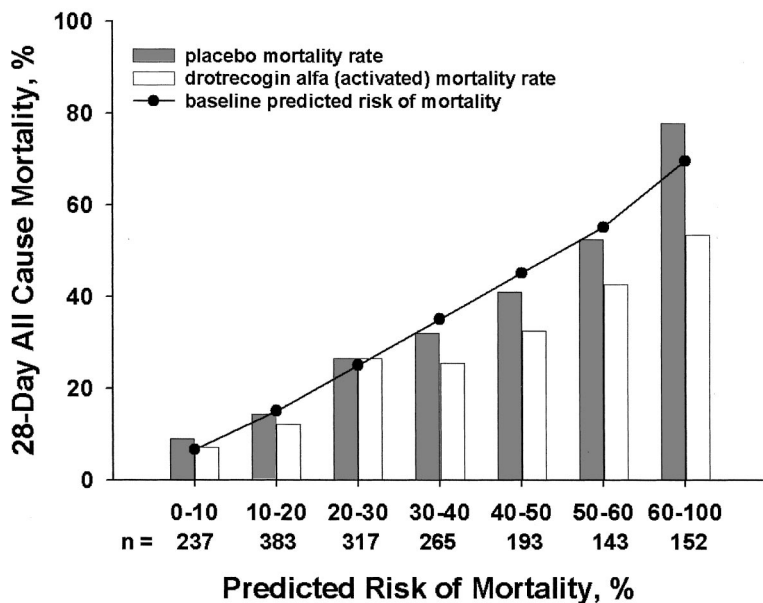


Figure 4. Multivariable logistic regression analysis—mortality rate compared with predicted risk of mortality. *Solid circles* (connected by *line*) represent predicted underlying risk of death based on logistic regression model performed on the placebo patient population. Each bin on the x-axis is based on deciles of predicted risk of death. *Solid bars* are actual mortality rates for the placebo group. *Open bars* are actual mortality rates for the drotrecogin alfa (activated) group. The number of patients in each subgroup of predicted risk is indicated below the x-axis.

responses to infection (23, 24). Activated protein C is an endogenous plasma protein with antithrombotic, profibrinolytic, and anti-inflammatory properties, which modulates these host responses (25–33). Drotrecogin alfa (activated) was the first drug to demonstrate a clear survival benefit for patients with severe sepsis, and the purpose of this investigation was to assess the consistency of the effects of drotrecogin alfa (activated) across clinically important subpopulations.

Actual mortality rates were lower with drotrecogin alfa (activated) compared with placebo in all prospectively defined subgroups in which a $\geq 20\%$ placebo mortality was observed, including those defined by demographics, comorbidities, surgical status, biochemical derangements, infection site and type of organism, and clinical measures of disease severity. Multivariable regression analysis complemented these univariate results, and supported two important conclusions: 1) drotrecogin alfa (activated) resulted in larger *absolute* risk reductions in death rates as patients' baseline predicted risk of mortality increased, and 2) drotrecogin alfa (activated) provided a consistent *relative* risk reduction for mortality.

Higher mortality with drotrecogin alfa (activated) compared with placebo was observed in the subgroup of patients with

the lowest APACHE II scores. However, true differences in the direction of the effect of any drug are rarely seen clinically (3, 4), and the trial data suggest that a true qualitative interaction with treatment within the PROWESS population is unlikely. Using the predicted risk of death regression model derived from PROWESS placebo patients (Fig. 4), which predicted mortality better than either APACHE II or IL-6 alone, there was no indication of increased mortality in patients at relatively low risk of death. Whereas the *relative risk reduction* remained approximately 20% across predicted risk of mortality classes (with the exception of the 20% to 30% predicted risk of death group), patients seemed to receive little *absolute* mortality benefit when their predicted risk of death was $< 30\%$. As mentioned above, regulatory agencies in the United States and Europe have approved drotrecogin alfa (activated) for use in severe sepsis patients at higher risk of death as determined, for example, by APACHE II score or the presence of multiple organ dysfunction. Of note, neither the PROWESS placebo multivariable risk of mortality model presented in this report nor the APACHE II (1) scoring system have been validated as tools or are intended for use for individual patient risk assessments.

Drotrecogin alfa (activated) seems to be a major advance in our therapeutic armamentarium for patients with severe sepsis.

The only safety concern identified with drotrecogin alfa (activated) in PROWESS was bleeding (2), yet it must be remembered that the risk of fatal bleeding is already included in the mortality outcome of the trial. Severe sepsis patients have a notable baseline bleeding risk as evidenced by the fact that even after excluding those at highest risk for this complication, “any bleeding” (mild, moderate, or severe) occurred in 17.7% in the PROWESS placebo group, in agreement with a comparable rate of 12.8% in the placebo group of the multicenter phase 3 antithrombin trial in severe sepsis (34). Treating physicians classified the majority of the bleeding events in PROWESS as mild, and the increased risk of bleeding with drotrecogin alfa (activated) seemed consistent across the subgroups assessed. Although spontaneous bleeding may occur, the increased incidence of serious bleeding events was primarily related to resumption of the drug infusion after complications of invasive procedures. The small absolute increase in the number of patients experiencing a serious bleeding event precluded a robust assessment, yet the increased risk of serious bleeding with treatment did not seem to vary according to the baseline predicted risk of mortality, nor did it further increase in patients with recent surgical procedures or overt DIC (recognizing that DIC patients with platelets $< 30,000$ at baseline were excluded). In keeping with the properties of drotrecogin alfa (activated), there was a non-statistically significant reduction in serious thrombotic events in treatment patients compared with placebo patients.

The unavoidable limitations of subgroup analyses, including decreased statistical power, increased variance, multiplicity, and play of chance are imperative to consider (7, 13, 35). Both over- and underinterpretation of subgroup results could lead to harm either by inappropri-

ate treatment or withholding potentially life-saving therapy. Because trials are sized for treatment effects in the overall population only, rarely are there sufficient patient numbers in any individual subgroup to make definitive statistical conclusions regarding efficacy, lack of efficacy, or harm in the subgroup. The increased 28-day mortality among treated patients with urinary tract infection, APACHE II scores ranging from 3 to 19, and the smaller absolute risk reductions for patients with a <20% predicted risk of death could be suggestive of lack of efficacy or harm in these subgroups. In addition, it is not known the extent to which the results of this report apply to patient groups not enrolled in the PROWESS trial. Therefore, future studies will be required to understand the role of drotrecogin alfa (activated) in treating those with neutropenia or organ transplantation, those at both earlier and later stages of their septic process, and potentially noninfectious disease states with similar pathophysiology such as burn injury, pancreatitis, or the hemolytic uremic syndrome (36). A large study of drotrecogin alfa (activated) in severe sepsis patients deemed at low risk of death is currently ongoing, as well as other investigations to address cohorts such as those mentioned above.

CONCLUSIONS

In summary, the data from the 1,690-patient PROWESS trial demonstrated that drotrecogin alfa (activated) provided significant reductions in mortality. The main finding of this investigation was that larger absolute reductions in mortality were found with incrementally higher baseline degrees of illness. The drug poses a risk of bleeding that must be carefully weighed against the patient's risk of dying from their sepsis and organ dysfunction. The increased absolute risk of bleeding with treatment did not seem to vary according to baseline mortality risk.

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APPENDIX

Placebo Multivariable Risk of Mortality Model^a

The following available measures were considered for inclusion in the model: age, gender, racial origin, investigative site, geographic region of the investigative site, patient location before hospitalization, patient comorbidity (based on APACHE II chronic health points), functional dependency status (baseline ADL score, >0), patient's presumed infection site, Gram stain of organism cultured, patient surgical status (based on the APACHE II type of patient), APACHE II score, number of organ failures, renal SOFA score, respiratory SOFA score, cardiovascular SOFA score, ventilation status, shock status, protein C activity level, PT class (\leq ULN, >ULN to $1.2 \times$ ULN, $>1.2 \times$ ULN), APTT class (\leq ULN, >ULN to $2 \times$ ULN, $>2 \times$ ULN), and ln IL-6.

Details of model:

$$\text{Logit}(p) = 0.054 \times (\text{APACHE II}) + 0.030 \times (\text{age}) + 0.211 \times (\ln \text{IL-6}) + 0.494 \\ \times (\text{with dependency}) - 0.781 \times (\text{only urosepsis}) + 0.639 \times (\text{co-morbidity}) - 5.75$$

where with dependency (ADL, >0) = yes = 1, with urosepsis = yes = 1, co-morbidity (chronic health points > 0) = yes = 1.

Sample calculation:

Consider a patient with severe sepsis and the following baseline characteristics: APACHE II score = 27; age = 34; IL-6 = 500 mg/dL; ADL score >0; patient does not have urosepsis; chronic health points = 5

$$\text{Logit}(p) = .054 \times (27) + 0.030 \times (34) + 0.211 \times (\ln 500) + 0.494 \times (1) - 0.781(0) + 0.639 \times (1) - 5.75$$

$$\text{Logit}(p) = \text{probability of death} = \frac{e^{\text{logit}}}{1 + e^{\text{logit}}} = \frac{e^{-0}}{1 + e^{-}} = 0.304 \text{ or } 30.4\%$$

APACHE, Acute Physiology and Chronic Health Evaluation; ADL, activities of daily living; SOFA, Sequential Organ Failure Assessment; PT, prothrombin time; ULN, upper level of normal; APTT, activated partial thromboplastin time; IL, interleukin.

^aNeither the PROWESS placebo multivariable risk of mortality model nor the APACHE II (1) scoring system have been validated as tools to make individual patient risk assessments.