Commentary
Drotrecogin alfa (activated): does current evidence support treatment for any patients with severe sepsis?
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Abstract
Two international multicentre randomised controlled trials of drotrecogin alfa (activated) (DrotAA), the Recombinant Human Activated Protein C Worldwide Evaluation of Severe Sepsis (PROWESS) and Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) trials, have produced inconsistent results. When 28-day mortality data from these trials for patients with severe sepsis and at high risk of death are pooled using a standard random-effects meta-analysis technique, there is no statistically significant survival benefit (for patients with Acute Physiology and Chronic Health Evaluation (APACHE II) scores of 25 or more), or a borderline significant benefit (for patients with multi-organ failure). We argue that two important methodological issues might explain the disparate results between the two trials. These issues centre on early trial stopping, which exaggerates treatment effects, and reliance on subgroup analyses, which for DrotAA yields inconsistent results across different definitions of high risk. These concerns call into question the effectiveness of DrotAA in any patients with severe sepsis. Consequently, further randomised trials of this agent in prospectively defined high-risk patients are required to clarify its role in the management of severe sepsis.

Introduction
Severe sepsis is a condition with important public health ramifications because it is common and has a high case-fatality rate [1]. Drotrecogin alfa (activated) (DrotAA), more commonly known as recombinant human activated protein C, is the first specific therapy for sepsis to show an important survival benefit. On the basis of the favourable results of the Recombinant Human Activated Protein C Worldwide Evaluation of Severe Sepsis (PROWESS) trial [2], DrotAA was approved for patients with severe sepsis and at high risk of death. However, regulatory approval for DrotAA was controversial [3,4], and the recently published Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) trial [5] has heightened this
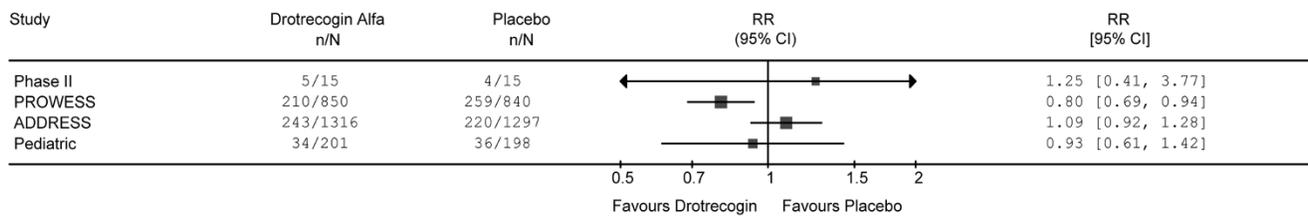
controversy. The results of this study demonstrated no evidence of benefit for DrotAA in patients with severe sepsis and at low risk of death, and unexpectedly raised concerns regarding its efficacy among patients at high risk of death [6]. In this commentary we argue that the cumulative evidence for a survival benefit in DrotAA-treated patients with severe sepsis and at high risk of death is weaker than originally believed. We also suggest methodological explanations for discrepant results of these two rigorous multicentre trials. These findings have important implications not only for clinicians treating patients with severe sepsis but also for the interpretation of other single, seemingly pivotal, randomised controlled trials.

Effect of DrotAA on 28-day survival
Figure 1 shows the effect of DrotAA therapy on 28-day survival, as observed in all three published trials (a phase II trial [7], PROWESS [2], and ADDRESS [5]) and in an additional unpublished trial in children with severe sepsis [8]. (A recent systematic review and health technology assessment of DrotAA [9] found no additional trials.) PROWESS suggested a survival benefit for all severely septic patients who received DrotAA. This survival benefit seemed to be concentrated in patients at high risk of death, defined either by an Acute Physiology and Chronic Health Evaluation (APACHE II) [10] threshold of 25 or by multiple organ failure. Consequently, regulatory authorities restricted DrotAA approval to severely septic patients with an APACHE II score of 25 or more (USA) or multiple organ failure (many European countries). The ADDRESS study provided new data and an excellent opportunity to retest the hypothesis that DrotAA is effective only in these high-risk subgroups. Although designed to study patients at low risk of death, ADDRESS enrolled patients with an APACHE II score of 25 or more, or

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ADDRESS = Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis; APACHE = Acute Physiology and Chronic Health Evaluation; DrotAA = drotrecogin alfa (activated); PROWESS = Recombinant Human Activated Protein C Worldwide Evaluation of Severe Sepsis.

Figure 1

Study	Drotrecogin Alfa n/N	Placebo n/N	RR (95% CI)	RR [95% CI]
Phase II	5/15	4/15		1.25 [0.41, 3.77]
PROWESS	210/850	259/840		0.80 [0.69, 0.94]
ADDRESS	243/1316	220/1297		1.09 [0.92, 1.28]
Pediatric	34/201	36/198		0.93 [0.61, 1.42]

0.5   0.7   1   1.5   2

Favours Drotrecogin   Favours Placebo

Relative risk (RR) and 95% confidence intervals (95% CI) for 28-day mortality in each study. RR is plotted on the natural logarithm scale. $n/N =$ number of deaths at 28 days divided by the total number of patients randomly assigned to drotrecogin alfa (activated) or placebo. For the phase II trial, only patients who were randomized to the same dose and duration of drotrecogin alfa (activated) used in the Recombinant Human Activated Protein C Worldwide Evaluation of Severe Sepsis (PROWESS) and Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) trials are included [37].

multiple organ failure, when investigators perceived the risk of death to be low on other clinical grounds.

Figure 2 shows, for PROWESS [2,11] and ADDRESS [5,12], the effect of therapy on patients grouped by risk of death. These subgroup data are not published for the phase II adult trial or for the paediatric trial. We pooled results by using standard meta-analysis software (Review Manager, Version 4.2; The Cochrane Collaboration, Oxford, UK) and a conservative random-effects model. Pooled estimates confirm no evidence of benefit for DrotAA in low-risk patients. For high-APACHE II patients, the results vary substantially between studies ($p = 0.01$ for heterogeneity, $I^2 = 84\%$; I^2 describes the percentage of total variation in results across studies that is due to heterogeneity rather than chance [13]), and pooled data show a trend towards survival benefit that is not statistically significant. For high-risk patients defined by multiple organ failure, the two trials are more consistent ($p = 0.23$ for heterogeneity, $I^2 = 32\%$), with the pooled results suggesting a clinically important survival benefit that just reaches the conventional threshold for statistical significance.

To summarize, these analyses show that the effect of DrotAA varies substantially between the two adult trials overall, and in the high-risk subgroups. This suggests that the PROWESS trial's estimate of survival benefit in severely septic patients might not be robust and that the true effect is probably more modest.

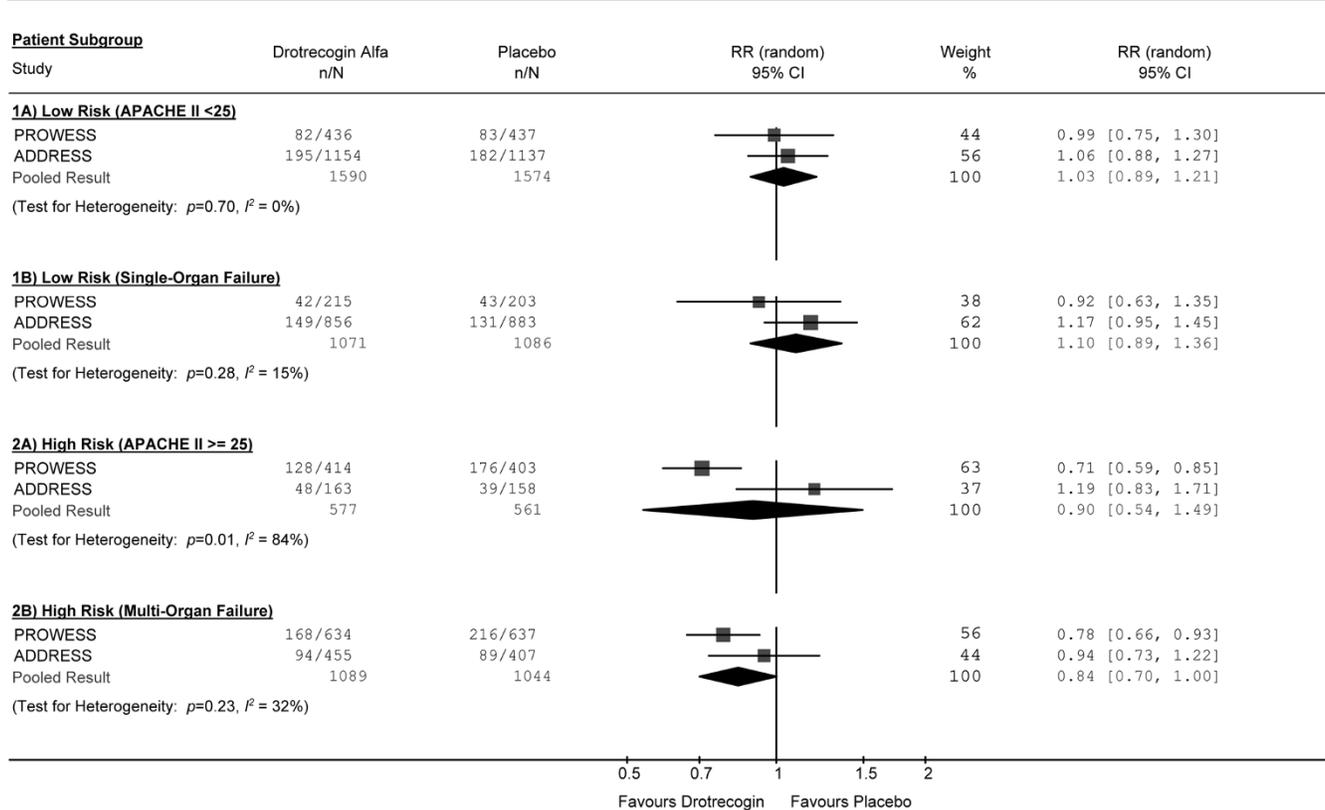## Explanations for disparate results in high-risk patients

DrotAA investigators have postulated several explanations for this between-trial difference in treatment effect among high-risk patients. These include a lower average APACHE II score and baseline risk of death in the high-APACHE II subgroup of ADDRESS than in PROWESS [5] and potential misclassification of patients with respect to the APACHE II threshold of 25 in ADDRESS [14]. The first observation suggests that the treatment effect of DrotAA may be quite variable even in patients with an APACHE II score of 25 or more, and the

second highlights the practical difficulty of applying any APACHE II threshold to patient selection for DrotAA. Investigators also discovered a higher prevalence of poor prognostic factors in patients receiving DrotAA, compared with placebo, in the high-APACHE II subgroup of ADDRESS [12]. An adjusted analysis incorporating relevant baseline covariates would address this possibility. Similar adjusted analyses should be performed for the PROWESS trial, because at least some poor prognostic factors seem to be more prevalent in the high-risk placebo subgroups [15]. However, even if the adjusted and unadjusted analyses were to differ, more data would still be required to clarify the discrepant findings.

Two other more general methodological considerations may be more important in explaining the differences between the PROWESS and ADDRESS results.

First, in stopping early after a predefined interim analysis, the PROWESS trial probably overestimated the treatment effect [16,17]. Current research suggests that such overestimation is less prominent in trials accumulating a large number of outcome events [16], such as PROWESS (469 outcome events and $p = 0.005$ for overall survival benefit). However, another recent sepsis trial illustrates the potential hazard of stopping early even after accumulating many outcome events. In the randomised placebo-controlled Optimized Phase 3 Tifacogin in Multicenter International Sepsis Trial (OPTIMIST) [18], investigators studied the effect of tifacogin (recombinant tissue factor pathway inhibitor) in patients with severe sepsis and an elevated international normalized ratio. A planned interim analysis of the first 722 patients (about 245 events) demonstrated a significant mortality improvement in patients receiving tifacogin (29.1% versus 38.9%, $p = 0.006$). However, after reaching the target enrolment of 1,754 patients (597 events), the apparent mortality difference disappeared (34.2% versus 33.9%, $p = 0.88$). Similar issues have arisen in oncology trials [19,20]. These examples illustrate the potentially misleading estimates of treatment effect when trials are stopped early for efficacy, even if supported by many events and extreme p values.

Figure 2

Patient Subgroup	Drotrecogin Alfa	Placebo	RR (random)	Weight	RR (random)
Study	n/N	n/N	95% CI	%	95% CI
1A) Low Risk (APACHE II <25)					
PROWESS	82/436	83/437		44	0.99 [0.75, 1.30]
ADDRESS	195/1154	182/1137		56	1.06 [0.88, 1.27]
Pooled Result	1590	1574		100	1.03 [0.89, 1.21]
(Test for Heterogeneity: p=0.70, I^2 = 0%)					
1B) Low Risk (Single-Organ Failure)					
PROWESS	42/215	43/203		38	0.92 [0.63, 1.35]
ADDRESS	149/856	131/883		62	1.17 [0.95, 1.45]
Pooled Result	1071	1086		100	1.10 [0.89, 1.36]
(Test for Heterogeneity: p=0.28, I^2 = 15%)					
2A) High Risk (APACHE II >= 25)					
PROWESS	128/414	176/403		63	0.71 [0.59, 0.85]
ADDRESS	48/163	39/158		37	1.19 [0.83, 1.71]
Pooled Result	577	561		100	0.90 [0.54, 1.49]
(Test for Heterogeneity: p=0.01, I^2 = 84%)					
2B) High Risk (Multi-Organ Failure)					
PROWESS	168/634	216/637		56	0.78 [0.66, 0.93]
ADDRESS	94/455	89/407		44	0.94 [0.73, 1.22]
Pooled Result	1089	1044		100	0.84 [0.70, 1.00]
(Test for Heterogeneity: p=0.23, I^2 = 32%)					

0.5 0.7 1 1.5 2

Favours Drotrecogin   Favours Placebo

Effect of drotrecogin alfa (activated) on 28-day mortality. Results are classified by low-risk and high-risk subgroups from the Recombinant Human Activated Protein C Worldwide Evaluation of Severe Sepsis (PROWESS) and Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) trials, defined by either Acute Physiology and Chronic Health Evaluation (APACHE II) score (less than 25, and 25 or more) or organ failure (single and multiple). Weight refers to the contribution of each study to the overall pooled estimate of treatment effect for each low-risk and high-risk subgroup. The weight of each study is calculated as the inverse of the variance of the natural logarithm of its relative risk. Each summary relative risk (RR) is plotted on the natural logarithm scale. The size of the symbol denoting each point estimate approximates the weighting of each study to each pooled effect measure. Each pooled effect measure is calculated with the use of a random-effects model. n/N = number of deaths at 28 days divided by the total number of patients in each particular subgroup randomly assigned to drotrecogin alfa (activated) or placebo. The numbers of patients and deaths at 28 days in each subgroup were estimated from data provided in references [2], [4] and [11] for the PROWESS trial, and in references [5] and [12] for the ADDRESS trial.

Second, the PROWESS and ADDRESS trials differed in the results of an analysis of the effect of DrotAA in high-APACHE II versus low-APACHE II patients: PROWESS found a differential effect, whereas ADDRESS did not. This raises the possibility that this subgroup effect in PROWESS was due to chance. Current teaching [21–23] suggests that results of subgroup analyses are most likely to be true when they are pre-specified, and when large in magnitude and statistically significant – all of which were true of the PROWESS APACHE II subgroup analysis. However, it was one of about 25 pre-specified subgroup analyses (rather than one of few), it was not consistent across different definitions of high risk (such as presence versus absence of multiple organ failure, mechanical ventilation, or vasopressor support) [11], there is no other independent evidence to support this subgroup effect, and the biological rationale for it is unclear. If the high-

APACHE II versus low-APACHE II subgroup effect in PROWESS is due to chance, then the best estimate of DrotAA's effect for any patient is the overall pooled result of the two trials, which demonstrates no statistically significant benefit (relative risk 0.93, 95% confidence interval 0.69 to 1.26). [The pooled estimate is very similar whether the phase II patients are also included (relative risk 0.95, 95% confidence interval 0.72 to 1.25) or all four trials shown in Figure 1 are included (relative risk 0.94, 95% confidence interval 0.76 to 1.17)]. Alternatively, if this subgroup effect is real, the pooled analyses in Figure 2 show that the degree of survival benefit depends on the operational definition of 'high risk of death' and at best just reaches the conventional threshold for statistical significance. In either case, more data are required to clarify the degree of benefit, if any, in this or any other subgroup of patients with severe sepsis.

Comparisons with other sepsis therapies

Single randomised controlled trials of two other therapies have recently suggested mortality benefits in critically ill patients. A trial of intensive insulin therapy was stopped early for benefit [24], and another trial showed that low-dose steroid treatment improved survival in a pre-specified subgroup of patients with vasopressor-dependent septic shock [25]. Both treatments have been incorporated into current consensus recommendations for the treatment of severe sepsis [26], similarly to the situation for DrotAA. To confirm the encouraging results of both studies, further trials are being conducted [27-31]. This situation contrasts with DrotAA, for which, to our knowledge, no additional trials in patients with sepsis and at high risk of death are either under way or planned to confirm initial findings and to resolve the subgroup discrepancies.

Conclusion

Patients with severe sepsis and at high risk of death are among the most vulnerable patients in the intensive care unit. In the light of new findings from the ADDRESS trial, the role for DrotAA in these patients is less clear than before. Others have raised important safety concerns by observing a higher risk of serious bleeding, including intracranial haemorrhage, in open-label use [32,33]. We share the concerns of others [3,15,33-36] and believe that further trials of DrotAA in prospectively defined high-risk patients are required to clarify its role in the management of severe sepsis.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JF was involved with the conception and design of the study, acquisition, analysis and interpretation of data, and wrote the first draft of the manuscript. NA was involved with the conception and design of the study, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. MM was involved with the interpretation of data and critical revision of the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

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