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## Increasing evidence that the risks of rhAPC may outweigh its benefits

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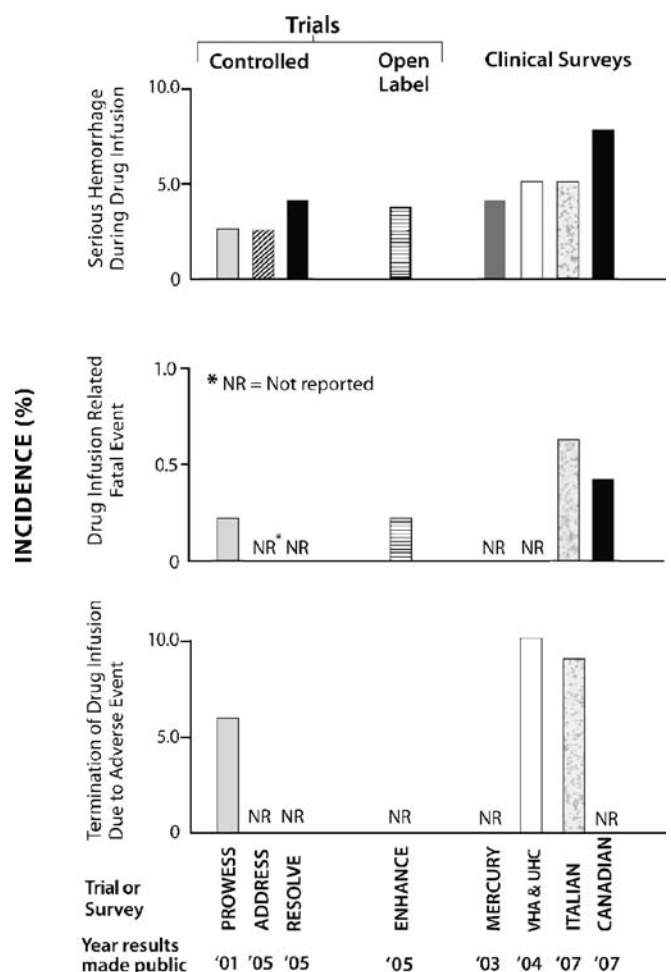
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Sir: The surveys by Kanji et al. and Bertolini et al. in this issue of "Intensive Care Medicine" are important in providing further insights into the increased bleeding risks associated with recombinant human activated protein C (rhAPC) in clinical practice [1, 2]. Following approval of rhAPC in 2001, early surveys and post-marketing studies suggested that the risk of bleeding during clinical use might be greater than was noted in the original phase-3 trial [Recombinant Human Activated protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial; 3, 4, 5, 6]. Even more concerning, two additional randomized controlled sepsis trials conducted post-approval have failed to show any significant benefit with rhAPC [7, 8]. In light of increasing experience with rhAPC, the critical care community should reconsider whether the bleeding risks associated with this agent outweigh its purported benefit.

Increased bleeding with rhAPC has been a consistent finding in all sepsis trials conducted to date. In both PROWESS ( $n=1,690$ ) and a second randomized controlled trial in adults [Administration of Drotrecogin Alfa (Activated) During Early Severe Sepsis (ADDRESS;  $n=2,640$ )], serious bleeding was greater during rhAPC



**Fig. 1** Incidence (percentage of patients) during rhAPC infusion of serious hemorrhage (*top panel*), a drug related fatal event (*middle panel*), or termination of treatment due to a drug-related adverse event (*lower panel*). Data are from three randomized controlled trials and one open-label trial and four clinical use surveys [1, 2, 3, 4, 5, 6, 7, 8, 11]. The full titles are provided in the text of the editorial for each trial or survey

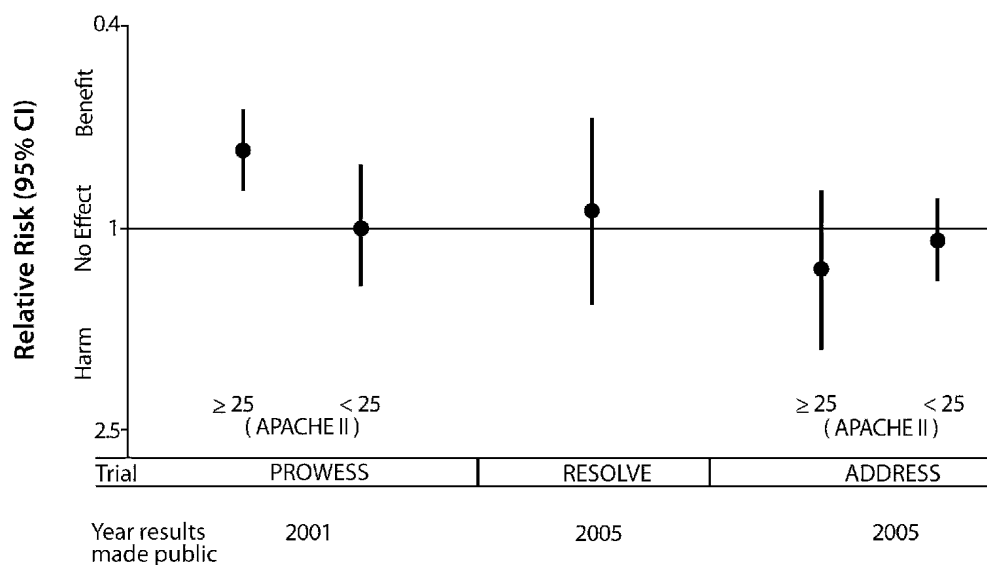
infusion than placebo (2.4 vs. 1.0 and 2.4 vs. 1.2%, respectively,  $p=0.02$  for both comparisons) [6, 7, 8, 9]. Furthermore, in surgical patients with one organ injury – a subgroup particularly susceptible to the risk of bleeding – mortality rates were increased with treatment in both trials prompting a “black box” restriction on the rhAPC label [10]. In an open-label trial of rhAPC [Extended Evaluation of rhAPC trial (ENHANCE;  $n=2,378$ )], despite employing inclusion and exclusion criteria similar to PROWESS, serious bleeding during drug administration was greater (3.6%) than in the two controlled trials [11]. Finally, in a controlled trial in children [Resolution of Organ Failure in Pediatric Patients with Severe Sepsis (RESOLVE;  $n=399$ )], although the incidence of overall serious hemorrhage did not differ in study groups, a troubling increase in the number of intracerebral hemorrhages was associated with infusion of rhAPC (4 with treatment vs. 1 with placebo) [8]. Due in part to this finding and in part to lack of efficacy, the trial was stopped early.

The risk of hemorrhage with rhAPC during clinical use has been consistently greater than reported in controlled trials of the agent (Fig. 1). In two early surveys in septic adults, one a retrospective observational study performed in 2002 (MERCURY;  $n=274$ ) and the other encompassing medical utilization evaluations done in 2002 and 2003 ( $n=599$ ) by the Voluntary Health Association and University Health System Consortium (VHA and UHC), the incidences of serious bleeding with rhAPC treatment were 4.0 and 4.7%, respectively [3, 4, 5]. In the more recent survey by G. Bertolini the incidence of serious bleeding was 4.6% [2]. S. Kanji’s survey [1] reports the risk of bleeding during rhAPC use as 7.3%, three times greater than in the original PROWESS trial [6]. In addition to increasing the risk of bleeding, rhAPC infusion in these clinical use studies was associated with a relatively high fatal event rate

and an increased need to discontinue rhAPC due to bleeding (Fig. 1).

While surveys [1, 2, 3, 4, 5] indicate that the bleeding risk with rhAPC during clinical use is greater than originally estimated in PROWESS [6], the efficacy of rhAPC noted in this early trial has not been reproduced in subsequent trials [7, 8]. Neither of the controlled trials that followed PROWESS (i.e., ADDRESS and RESOLVE) noted any significant benefit with rhAPC, regardless of underlying severity of disease (Fig. 2) [6, 7, 8]. Across all trials that compared rhAPC to placebo (enrolling approximately 5,000 patients), only two subgroups from one study demonstrated benefit (i.e., the two highest APACHE-II quartiles from the PROWESS trial) [12]. These two subgroups included only 414 patients receiving rhAPC (i.e., 17% of all patients receiving the agent in controlled trials). Notably, the later ADDRESS trial ( $n=2,639$  patients) also enrolled high-risk patients [i.e., APACHE-II score  $\geq 25$  ( $n=324$ ) receiving either rhAPC or placebo] but failed to reproduce the finding of efficacy. In fact, for high-risk patients the treatment effect in ADDRESS was on the side of harm, opposite to and significantly different from the effect of rhAPC in PROWESS (Fig. 2) [12]. In PROWESS the decision to treat patients with rhAPC was not based on the APACHE score. Since these scores were determined retrospectively using the most extreme values obtained over a 24-h period before the drug was administered, it is unknown if this even represents a clinically definable population. Conversely, in ADDRESS, APACHE-II scores (or other measure of risk) were calculated prospectively and used to determine whom to treat. This is similar to what would occur in clinical practice, perhaps making the results more relevant. Casting further doubt on efficacy in clinical practice, mortality rates from surveys describing patients

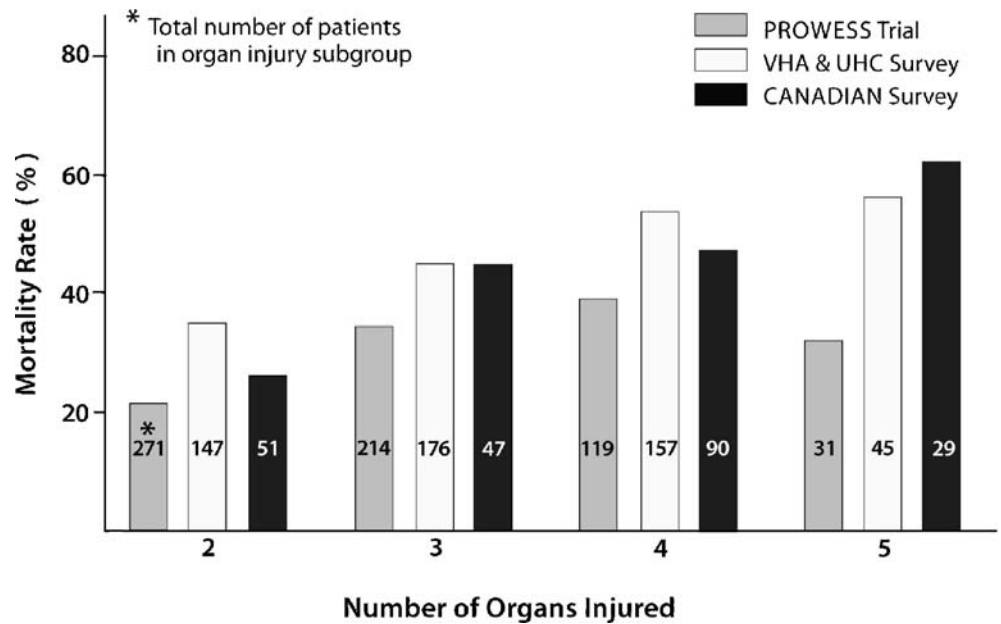
**Fig. 2** Effect of rhAPC on the relative risk of death in three controlled trials. Adult patients in the PROWESS [6] and ADDRESS [7] were stratified based on whether their admission APACHE-II scores were greater or less than 25



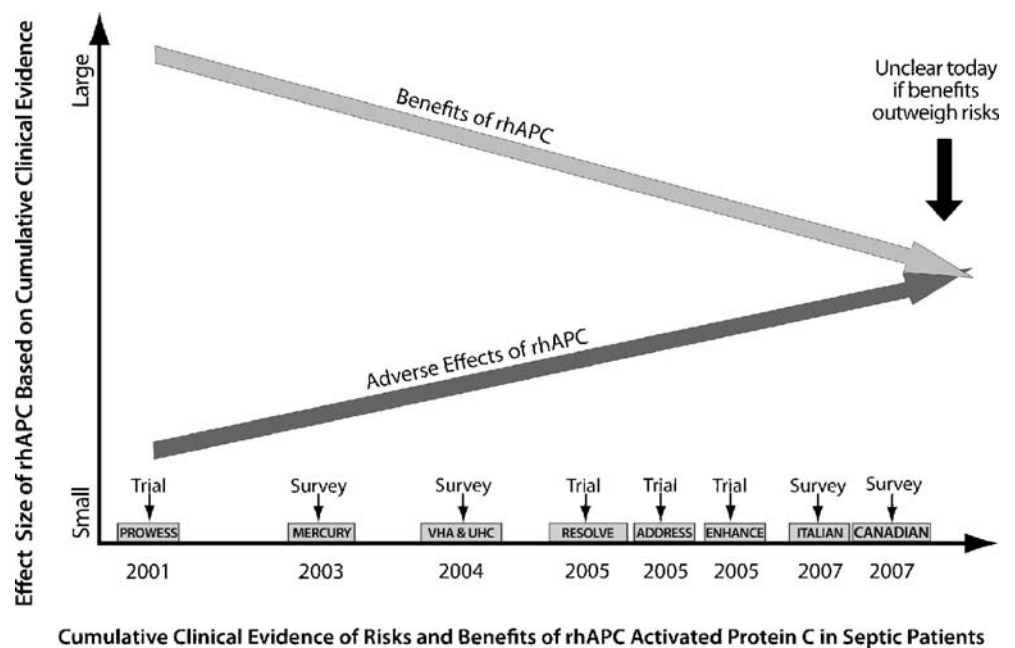
treated with rhAPC [1, 4, 5] have been consistently higher than was seen in PROWESS [6], even after stratifying for severity of illness (Fig. 3). While this does not constitute proof of harm, it is worrisome. Additionally, while rhAPC was approved for high-risk patients based on PROWESS, in the survey by Kanji et al. patients with four to five injured organs and a high risk of death had a marked increase in the risk of serious bleeding with rhAPC [1]. At this time therefore, it appears that it would be difficult for clinicians to confidently identify a population of patients that is likely to benefit from rhAPC.

While the apparent efficacy of rhAPC in PROWESS [6] has not been reproduced in subsequent trials [7, 8], an increased risk of bleeding has been confirmed in controlled trials and documented at even higher rates in clinical use (Figs. 1, 2) [1, 2, 3, 4, 5]. Why this risk appears more pronounced than during the original PROWESS trial is likely multi-factorial [13, 14]. For example, investigating rhAPC in larger numbers of patients in the ADDRESS trial was necessary to clearly document the agent's risk in surgical patients. Also, during controlled trials that are designed primarily to show the efficacy of an agent, exclusion cri-

**Fig. 3** The mortality rate in patients treated with rhAPC, stratified by number of organs injured in the PROWESS trial [6], VHA/UHC survey [4, 5], and Canadian [1] survey. Despite similar numbers of injured organs, mortality rates were greater in patients treated with rhAPC in both clinical surveys compared with the PROWESS trial. Similar data was not available for analysis from the other controlled trials and clinical surveys



**Fig. 4** Our understanding of the relative size of the beneficial and adverse effects of rhAPC. This is based on accumulating evidence from controlled trials and clinical surveys starting in 2001 following completion of the PROWESS trial and licensing of rhAPC for clinical use. Since the original beneficial effects of rhAPC have not been confirmed in subsequent trials, but the incidence of bleeding has persisted in trials and increased in clinical use, it is unclear presently whether the benefit of this agent outweighs its risks



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teria are frequently applied that minimize the occurrence of adverse effects. During clinical use of an agent, such exclusion criteria may not be applied as rigorously and the incidence of adverse events would be expected to increase. Overall, however, our growing experience with rhAPC represents a change in our understanding of the

risk-to-benefit ratio of rhAPC (Fig. 4). Further randomized controlled trials are necessary to demonstrate whether patients can be prospectively identified that benefit from rhAPC and if such benefit is large enough to warrant the use of rhAPC in clinical practice where the risk of bleeding appears substantial.

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