



# LUND UNIVERSITY

## Treatment of the critically ill patient with protein C: Is it worth the cost?

Nilsson, Gunnar; Höjgård, Sören; Berntorp, Erik

*Published in:*  
Thrombosis Research

*DOI:*  
[10.1016/j.thromres.2009.09.008](https://doi.org/10.1016/j.thromres.2009.09.008)

2010

[Link to publication](#)

*Citation for published version (APA):*

Nilsson, G., Höjgård, S., & Berntorp, E. (2010). Treatment of the critically ill patient with protein C: Is it worth the cost? *Thrombosis Research*, 125(6), 494-500. <https://doi.org/10.1016/j.thromres.2009.09.008>

*Total number of authors:*  
3

### General rights

Unless other specific re-use rights are stated the following general rights apply:

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: <https://creativecommons.org/licenses/>

### Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117  
221 00 Lund  
+46 46-222 00 00





LUND UNIVERSITY  
Faculty of Medicine

---

# LUP

*Lund University Publications*

Institutional Repository of Lund University

---

This is an author produced version of a paper published in Thrombosis Research. This paper has been peer-reviewed but does not include the final publisher proof-corrections or journal pagination.

Citation for the published paper:  
Gunnar Nilsson, Sören Höjgård, Erik Berntorp

"Treatment of the critically ill patient with protein C:  
Is it worth the cost?"

Thrombosis Research 2009 125(6), 494 - 500

<http://dx.doi.org/10.1016/j.thromres.2009.09.008>

Access to the published version may require journal  
subscription.

Published with permission from: Elsevier

# Treatment of the critically ill patient with protein C: is it worth the cost?

**Gunnar Nilsson<sup>a,\*</sup>, Sören Höjgård<sup>b</sup>, Erik Berntorp<sup>c</sup>**

<sup>a</sup> Department of Anaesthesiology and Intensive Care, Lund University, Malmö University Hospital, Malmö, Sweden

<sup>b</sup> Swedish Agricultural University, Uppsala, Sweden

<sup>c</sup> Department of Coagulation Disorders, Lund University, Malmö University Hospital, Malmö, Sweden

Running head: Protein C: is it worth the cost?

\*Corresponding author:

Gunnar Nilsson, MD PhD  
Department of Anaesthesiology and Intensive Care  
Lund University  
Malmö University Hospital  
SE-205 02 Malmö  
Sweden  
E-mail: [gunnar.a.nilsson@skane.se](mailto:gunnar.a.nilsson@skane.se)  
Phone: +46-40-33 35 32  
Fax: +46-40-33 73 80

## **Abstract**

*Introduction:* We have shown that low protein C levels predict poor survival up to five years in a general intensive care unit patient material and hypothesize that treatment with protein C is beneficial. The objectives were to calculate costs of protein C treatment, at best-case scenario, per statistical life saved.

*Materials and methods:* Ninety-two patients with deranged global haemostatic tests admitted to the mixed surgical medical intensive care unit, Malmö University Hospital. We hypothesized that increasing protein C levels in patients with low levels would enhance survival to the same rate as a cohort with higher protein C. Number of statistical lives saved were estimated using survival analysis. Costs per life saved at 30 days were calculated.

*Results:* Total costs per life saved in 2007 prices (upper limit of 95% CI) were calculated at €50,200 (recombinant activated protein C, drotrecogin alfa (activated), Xigris<sup>®</sup>) and €46,000 (zymogen protein C, Ceprotin), which may be compared to the value of a statistical life (€937,000).

*Conclusions:* Our theoretical model of converting a low protein C group to a higher protein C group by treating with activated protein C or the protein zymogen showed no major difference between the treatments in terms of costs, and that costs are lower than the value of a statistical life. Although our study has several caveats the results support the PROWESS study, in that patients with a very severe disease, having low protein C levels, may benefit from protein C treatment in a cost effective way.

## **Keywords**

Critical care; health care costs; intensive care units; medical economics; protein C; survival analysis.

## **Abbreviations**

APACHE II, Acute Physiology and Chronic Health Evaluation II; APC, activated protein C; APTT, Activated Partial Thromboplastin Time; ICU, intensive care unit; INR, International Normalized Ratio; SIRS, Systemic Inflammatory Response Syndrome; VOSL, value of a statistical life.

Recombinant activated protein C (APC) (drotrecogin alfa (activated), Xigris<sup>®</sup>, Lilly, Indianapolis, IN, USA) [1] exerts, in addition to its inhibitory and regulating effect on the coagulation system, anti-inflammatory and profibrinolytic functions, which counteract the Systemic Inflammatory Response Syndrome (SIRS) [2]. This is a product costly to use and the therapeutic value in critically ill patients is not fully delineated. APC has been shown beneficial in high-risk patients with sepsis [3], whereas patients at lower risk do not seem to benefit. The protein zymogen (Ceprotin, Baxter, Glendale, CA, USA) is a plasma derived non-activated form of protein C used for replacement in congenital protein C deficiency, but also reported to be useful in treating meningococcal sepsis [4].

Low levels of protein C in an early phase of severe sepsis are associated with unfavourable clinical outcome [5,6]. We have shown that low protein C levels at admission to a main intensive care unit (ICU) predict poor long-term survival up to 5 years [7]. In the present study, the objective was to calculate the costs of treatment with protein C per statistical life saved. The underlying principle was prediction of the best-case scenario, i.e., that treatment of patients with low protein C levels on admission would increase survival to the same level as patients with higher protein C levels.

## Materials and methods

Our study population includes 92 of the 1114 patients admitted to the main ICU, Department of Anaesthesiology, Malmö University Hospital, during March 1997 to April 1998. Inclusion criteria were, irrespective of causative background diagnosis, one or more of the following global haemostatic test results: platelet count  $<100 \times 10^9 \text{ L}^{-1}$ , INR  $>1.36$ , APTT  $>45 \text{ s}$  [7]. The study which the current calculations are based on was approved by the Ethics Committee, Lund University. The study cohort characteristics are given in Table 1.

For each patient, we recorded the length of stay in the ICU and the hospital, and survival up to five years.

Thirty-two patients were still alive five years after admittance to the ICU. Hence, survival analysis (non-parametric Kaplan-Meier and semi-parametric Cox proportional hazards models) [8,9] was used to investigate whether life expectancy differed according to protein C level. All estimations were done using the statistical package SPSS for Windows version 12.0.2 (SPSS, Chicago, IL, USA). The hazard function for individual  $i$  is the probability of an event occurring in the short interval from  $t=T$  to  $t=T+\Delta T$ , conditional upon that it has not already occurred. In the Cox proportional hazards model, it is specified as:

$$h_i(t) = \exp\left[\sum_{j=1}^n \beta_j x_{ji}\right] h_0(t) \quad (1)$$

where  $\exp(\sum \beta_j x_{ji})$  captures the effects of characteristics  $j$  for individual  $i$ , and the base-line hazard  $h_0(t)$  captures the effect of time, on the conditional probability of dying in the interval  $\Delta T$ . It is called a “proportional” hazard since the effects of individual characteristics are simply to increase (or decrease) the hazard proportionally. Hence, the expression  $\exp(\beta_j)$  is the hazard for someone with the characteristic  $j$ , relative to that of

someone without it. It is, therefore, an estimate of the relative risk. The survival function is:

$$S_i(t) = \exp \left[ - \int_0^T h_i(t) dt \right] = S_0(t)^{\exp(\sum_{j=1}^n \beta_j x_{ji})} \quad (2)$$

where  $S_0(t)$  is the base-line survival function  $= \exp \left[ - \int_0^T h_0(t) dt \right]$ .

Since the survival function in (2) is also proportional, it is easily estimated by most software programs.

Our data include readings of platelet count, International Normalized Ratio (INR), Activated Partial Thromboplastin Time (APTT), protein C, and antithrombin within twelve hours after admission to the ICU [7]. These variables are all expected to return to normal levels when the patient recovers from the coagulation disturbance after the “acute” period. As our time-horizon stretches up to five years after admission, we should allow for such unobserved changes in some of our explanatory variables. Hence, in addition to age, protein C, platelet count, INR, APTT, antithrombin, APACHE II score (Acute Physiology and Chronic Health Evaluation II – a system for classification of severity of disease for the first 24 hours) [10], gender, and diagnosis category, we also included interaction terms between these variables (except gender) and time in the Cox proportional hazards model. The “acute” period was defined as 30 days (0.0821 years), after which it was assumed that time only affected the effect of age. The  $\beta$ -coefficient for the basic variable is interpreted as the effect of differences *at admittance*, while that of its time-interaction term measures how the effect of the initial differences develops over our period of observation [9]. *Opposite* signs for the  $\beta$ -coefficient of the basic variable and its time-interaction term indicate that the effect of initial differences decreases over time, and vice versa. If the time-interaction terms are statistically significant, the values of the individual characteristics are functions of time. Then the hazard function for individual  $i$  becomes:

$$h_i(t) = \exp \left[ \sum_{j=1}^n \beta_j x_{ji}(t) \right] h_0(t). \quad (3)$$

Hence, the hazard function is no longer proportional and the survival function becomes:

$$S_i(t) = \exp \left\{ - \int_0^T \exp \left[ \sum_{j=1}^n \beta_j x_{ji}(t) \right] h_0(t) dt \right\}. \quad (4)$$

This survival function depends on the values of the time-dependent individual characteristics over the interval from  $t=0$  to  $t=T$ , as well as on the values of the base-line hazard  $h_0(t)$  over the same interval. To our knowledge, there is no software capable of estimating  $S_i(t)$  under these circumstances [9,11-15]. However, we may approximate it, using the survival probabilities at different points of time given by the Kaplan-Meier estimates and some parametric specifications of  $h_0(t)$  (for which some guidance is offered by the Kaplan-Meier estimates).

We experimented with two different ways of including the protein C variable: (1) as a continuous variable, and (2) as a dichotomous variable according to cutpoint 0.39 IU/mL as described [7]. We also separated the patients into two groups according to the cutpoint, and estimated the Cox model separately for each group including protein C as a continuous variable.

To calculate the costs of treatment, we considered two strategies for patients with protein C levels <0.39 IU/mL; (1) *activated* protein C, Xigris<sup>®</sup>, or (2) *non-activated* protein C, Ceprotin.

*Activated* protein C is administered as an intravenous infusion. Dosage, independent of actual protein C level (indication severe sepsis and multiple organ failure), is 24 µg per kilogram of body weight per hour for 96 hours. In this study we calculate with the same dosage.

*Non-activated* protein C is given as iterated intravenous bolus injections. Our estimate is based on initial raising of protein C levels from median of the lower protein C subgroup (0.34 IU/mL) to median of the higher subgroup (0.50 IU/mL) and then not letting received protein C level go down below splitting level between subgroups (0.39 IU/mL) until next bolus injection and then again raise protein C level to 0.50 IU/mL and so on for totally 96 hours (same time as treatment with APC). Half time ( $T_{1/2}$ ) is not well known, but a reasonable time according to available data (given by the manufacturer on the Internet; <http://www.fass.se>) is ten hours. Recovery is also fairly uncertain and estimation is 50%.

All costs are converted into euros and in 2007 prices.

According to assumptions above and 70 kg body weight, need of APC and protein C would be 161.3 mg and 4002 IU, respectively, and cost for Xigris<sup>®</sup> and Ceprotin €8,134 and €7,061, respectively [16]. Regarding Ceprotin, in critically ill patients, both  $T_{1/2}$  and recovery might be shorter and lower, respectively, and thus cost might be higher.

APC increased incidence of serious bleeding from 2.0% (placebo) to 3.5% ( $p=0.06$ ; PROWESS study [1]). The costs of clinically important gastrointestinal bleeding in the ICU have been examined [17]. This means an average additional cost of €248 because of APC.

Average cost being at ICU was €4,059 per 24-hour period (personal communication). The corresponding cost staying at nursing wards was €558 (obtained from the hospital administration).

## Results

Including protein C as a continuous, as well as a categorical variable, in the Cox proportional hazards model, resulted in a statistically significant effect on the hazard for each time-horizon (30 and 180 days, and one and five years), confirming the results in [7]. However, when separating patients into subgroups defined by the cutpoint, and running separate regressions for each subgroup with protein C as a continuous variable, no statistically significant effect was found (results available from authors on request). Thus, it seems as if the cutpoint 0.39 IU/mL of protein C is more critical for survival



than the actual protein C level. Accordingly, in the continued analysis, protein C was included as a dichotomous variable.

Table 2 presents the results of the Kaplan-Meier estimates. The test statistics for equality of survival distributions all indicate that the survival functions differ between the two subgroups. The median survival time is 1246 days longer in the higher subgroup (difference statistically significant).

In the Cox-regressions, the estimation procedure was that of backwards elimination. The results of the final model for the five-year time-horizon are shown in Table 3 (starting model see Table A1 in the Appendix).

The difference in  $-2$  log-likelihood between the final and the starting models (9.977) was not statistically significant ( $p > 0.10$  at 6 df). In the final model age, INR, APACHE II, APTT and their time-interaction terms were statistically significant. This was also the case for protein C (though its time-interaction may be questionable) and gender. All variables having time-interaction terms, had the expected opposite signs for the covariate and its time-interaction term. Surprisingly, a higher INR at admittance decreased the hazard, but this effect diminished quickly because of the opposite sign of the  $\beta$ -coefficient of the time-interaction term.

The final model refutes the assumption of a proportional hazards model. To approximate the survival function, we use the empirical hazards from the Kaplan-Meier estimates (Table 2). They suggest that the hazard is decreasing during the first 30 days after admittance, after which it is nearly constant. Hence, we should opt for a parametric specification of  $h_0(t)$  that allows for this pattern. This can be achieved by assuming that  $h_0(t)$  is simply a constant  $=k$ . In that case, the decrease in the hazard

$h_i(t) = \exp[\sum_{j=1}^n \beta_j x_{ji}(t)] h_0(t)$ , comes from the time-dependent effect of individual

characteristics. Accordingly, we try the parametric specification:

$$h_i(t) = \exp[\sum_{j=1}^n \beta_j x_{ji}(t)] k. \quad (5)$$

The Kaplan-Meier estimate of the survival function for the lower protein C subgroup at  $t=30$  days is 0.4074 (Table 2). Inserting the values of the statistically significant individual characteristics for this subgroup (Table 4), multiplying by their coefficients from Table 3, and solving for  $k$ , we find that  $k=0.00033$  (Appendix, equations A1 to A4). Hence, the base-line hazard is constant over time and equal to  $3.3E-4$ . The base-line hazard is the conditional risk of dying for a person with "zeros" in the vector of individual characteristics. In our case, this is a newborn girl-child with protein C  $\geq 0.39$  IU/mL, and no critical levels of INR, APTT, or APACHE II. To further check whether this is reasonable, we use our value of the base-line hazard in combination with the values of the individual characteristics for the group with protein C  $\geq 0.39$  IU/mL and calculate the value of their survival function at  $t=30$  days. We find that it is 0.7963. This is not very different from the Kaplan-Meier point estimate of their survival function at  $t=30$  days, and well within the 95% CI (0.6491–0.8585, Table 2).

Given our approximation of the base-line hazard, the survival function would increase from 0.4074 to 0.7878 for the patients with low protein C concentration if it was raised to  $\geq 0.39$  IU/mL directly after admittance.

The number of lives saved at  $t=30$  days equals the difference between the survival functions times the number of patients at risk. Since there were 27 patients in this subgroup, about ten lives (95% CI 7–13, using the Kaplan-Meier estimate of the standard error of the survival function) would be saved.

The costs per life saved (Table 5) consist of; (1) the costs of *administering protein C*, (2) the expected *costs of containing serious bleedings* due to treatment with APC (though not quite statistically significant ( $p=0.06$ ; [1], we include them not to underestimate costs, for similar reasons we assume the same costs under the Ceprotin strategy), and, (3) the *costs for the hospital stay*. The median stay at nursing wards after ICU was 1.6 and 9.9 days for patients in the lower and higher protein C subgroups, respectively ( $p=0.009$ ; exact Mann-Whitney U-test). Since there was no statistically significant difference in the length of ICU-stay between the protein C subgroups (1.0 and 1.7 days, respectively;  $p=0.31$ ; exact Mann-Whitney U-test), these costs were excluded.

The costs of €35,100 (Xigris<sup>®</sup> strategy) and €32,200 (Ceprotin strategy) may be compared to the value of a statistical life (VOSL). This is elicited by asking respondents how much they would be willing to pay for reducing fatal risks, and then dividing by the absolute risk reduction. Being preference based, the VOSL may be regarded as a measure of the value society attaches to saving the life of an unknown person [18,19]. Estimates have been obtained for several countries at different points in time [20,21]. They tend to differ depending on the income of the respondents. Hence, VOSL-estimates are not readily transferred between countries, or from one point of time to another. A fairly recent Swedish VOSL-estimate is €2,730,000 [19]. This applies to an unknown person with the age of 45 years (personal communication). Since age influenced VOSL significantly, we have (simplified):

$$\text{Ln VOSL} = \beta_1 \text{Ln age} + \beta_2 \text{Ln (age - mean age)}^2 + C. \quad (6)$$

In our study, the median age in the lower protein C subgroup was 67 years. We accordingly adjust the VOSL using coefficients estimated in [19]:

$$\text{Ln VOSL}_{67} = \text{Ln VOSL}_{45} - 0.791(\text{Ln } 67 - \text{Ln } 45) - 0.122 \{ \text{Ln}[(67 - 45)^2 + 1] - \text{Ln}[(45 - 45)^2 + 1] \}$$

where we added 1 to each squared term since the logarithm of zero is undefined. Hence, the VOSL for our subgroup is €937,000.

### *Sensitivity analysis*

Above, the number of lives saved were estimated assuming that raising protein C levels above the threshold level for the lower subgroup would result in acquiring the approximated survival function of 0.7878 at 30 days. Assuming instead that treatment entails a 75%, a 50%, and a 25% probability, respectively, of the lower subgroup acquiring the approximated survival function implies that eight, five, and three lives, respectively, will be saved. This, in turn, results in the Xigris<sup>®</sup> strategy in a cost per life saved of €43,900, €70,300, and €117,000, respectively, and in a cost-benefit ratio

(costs divided by VOSL) of 0.047, 0.075, and 0.125, respectively, using the VOSL of € 937,000. The corresponding costs in the Ceprotin strategy are €40,300, €64,500, and € 107,000, respectively, and the cost-benefit ratios are 0.043, 0.069, and 0.115, respectively.

Using VOSLs applied in other countries result in other cost-benefit ratios. Table 6 presents results for the VOSLs applied in the United States, Canada, the United Kingdom, the Netherlands, and Germany [22-24]. In all cases the cost-benefit ratio is well below 1, indicating that benefits exceed costs.

## Discussion

Costs per statistical life saved by administering protein C to patients with clinically significant coagulation disturbances were assessed using the survival rate in 92 patients admitted to a main ICU analysed by Kaplan-Meier estimates and Cox proportional hazards models. We confirmed our results [7] that lower protein C levels are associated with higher risk of death up to five years. This was true when other factors contributing to risk of death, as well as time-dependence, were accounted for. When the cohort was separated into two subgroups by protein C level 0.39 IU/mL, separate regression models, using protein C as a continuous variable, identified no statistically significant effect in either subgroup. Thus, belonging to the subgroup category is a better predictor of prognosis than the exact level. The base-line hazard was constant, implying that the increased mortality risk depended on individual characteristics. This suggests that events during a life, rather than time, increase the risk. Using our assumptions, treatment with protein C preparations in the low level subgroup resulted in ten lives saved at 30 days, a large number in such a small cohort.

We hypothesized that raising protein C levels from the lower subgroup to the higher subgroup would improve short- and long-term prognosis and save lives. Dosing of APC (Xigris<sup>®</sup>, Lilly) is standardized and is not conditional on plasma levels. In contrast, the zymogen (Ceprotin, Baxter) replaces the deficiency of protein C. According to data from manufacturer of Ceprotin regarding  $T_{1/2}$  (4.4–15.8 hours) and recovery (20.4–83.2%), cost of one Ceprotin treatment may vary by a factor of 0.45 to 4.2 compared to our previous calculations. In the critically ill patient pharmacodynamics probably differ from those seen in a stable patient with congenital protein C deficiency and the calculated dosing schedule for Ceprotin includes some uncertainty.

Our study has a number of caveats. The two products have been studied primarily in sepsis. Only Xigris<sup>®</sup> has been investigated in trials with strong scientific designs (PROWESS [1] and ENHANCE [25]). Indications and inclusion criteria have been generally restricted to sepsis for both drugs (congenital protein C deficiency for the zymogen, also), and the use of APC cannot definitively be recommended in patients with polytrauma or surgery [26]. The increased risk of bleeding with APC treatment [1,25] cannot directly be assumed for the present study. Treatment with the zymogen protein C in children with purpura fulminans and meningococcal septic shock resulted in increased levels of activated protein C [27]. The effect of the zymogen can still be questioned, as conversion of protein C to APC may be jeopardized by dysfunction of the protein C activation pathway [28,29]. Thus, the cost figures obtained in our study per life saved, i.e. €46,000 to 50,200 (upper limit of 95% CI), may probably

underestimate the cost, as the effectiveness of the products have not been documented in a general ICU population and the number of lives saved by protein C treatment may be overestimated. However, according to our presumptions, the cost of a saved life is lower than the value of a statistical life at similar age (€937,000).

It is known from previously published studies that treatment with APC may reduce mortality in patients with severe sepsis [1,25]. Economic evaluations in several countries including the United Kingdom, France, Germany, Sweden, the United States, and Canada [30-37] show that APC is cost effective, on a short-term basis, in severe sepsis. Further, when APC is administered, according to the PROWESS criteria, to individuals with more severe disease (APACHE II score  $\geq 25$ ), it has a lifetime cost-effectiveness profile that compares well to that of many widely accepted therapies [33,35]. Lately, the use of APC has been increasingly questioned; the risks may outweigh the benefits [38,39].

In conclusion, our study shows that general ICU patients belonging to a cohort with higher protein C levels have better short- and long-term outcome, expressed as survival, compared to patients with lower levels. Our theoretical model of converting the low protein C subgroup to the higher subgroup by treatment with APC or the protein zymogen suggests no major difference between the treatments in terms of costs, which are lower than the value of a statistical life. Our study has several caveats but supports findings from the PROWESS study in that patients with a very severe disease, having low protein C levels, may benefit from protein C treatment in a cost effective way.

### **Conflict of interest statement**

There are no conflicts of interest.

### **Acknowledgements**

The study was supported by grants from the Malmö University Hospital and from Region Skåne.

## Appendix

To solve for the constant  $k$ , we note that 30 days is 0.0821 years and, since the survival function is  $\exp\left[-\int_0^T h_i(t)dt\right]$  (see for instance [9]), we have:

$$S_i(t=30) = \exp\left[-\int_0^{0.0821} \left\{\sum_{j=1}^n \exp[\beta_j x_{ji}(t)]\right\} k dt\right] = 0.4074. \quad (A1)$$

Taking logarithms:

$$\text{Ln } S_i(t=30) = -\int_0^{0.0821} \{\exp[\beta_j x_{ji}(t)]\} k dt = \text{Ln}(0.4074). \quad (A2)$$

Integrating (A2) by parts:

$$-\int_0^{0.0821} \{\exp[\beta_j x_{ji}(t)]\} k dt = -k \left\{ \left( \sum_{j=1}^n \beta_j x_{ji} \right)^{-1} \exp\left[\sum_{j=1}^n \beta_j x_{ji}(t)\right] \right\}_0^{0.0821} = \text{Ln}(0.4074).$$

Note that  $\exp\left[\sum_{j=1}^n \beta_j x_{ji}(t)\right]$  may be re-written as  $\exp\left[\sum_{j=1}^n (\beta_{bj} x_{ji} + \beta_{tj} x_{ji} t)\right]$ , where  $\beta_{bj}$  is

the basic effect (i.e. the effect of differences in  $x_{ji}$  at admittance), and  $\beta_{tj}$  indicates how the effect of initial differences changes over time. As the basic effect is constant, we may re-write the above expression as:

$$-k \exp\left(\sum_{j=1}^n \beta_{bj} x_{ji}\right) \left\{ \left( \sum_{j=1}^n \beta_{tj} x_{ji} \right)^{-1} \exp\left[\sum_{j=1}^n \beta_{tj} x_{ji} t\right] \right\}_0^{0.0821} = -0.898, \quad (A3)$$

$$\text{hence, } k = \frac{-0.898}{-\exp\left(\sum_{j=1}^n \beta_{bj} x_{ji}\right) \left\{ \left( \sum_{j=1}^n \beta_{tj} x_{ji} \right)^{-1} \exp\left[\sum_{j=1}^n \beta_{tj} x_{ji} t\right] \right\}_0^{0.0821}} = 0.00033. \quad (A4)$$

## References

- [1] Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ Jr. Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;**344**:699-709.
- [2] Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G. SCCM/ESICM/ACCP/ATS/SIS. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003;**31**:1250-6.
- [3] Abraham E, Laterre PF, Garg R, Levy H, Talwar D, Trzaskoma BL, Francois B, Guy JS, Bruckmann M, Rea-Neto A, Rossaint R, Perrotin D, Sablotzki A, Arkins N, Utterback BG, Macias WL. Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) Study Group. Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. *N Engl J Med* 2005;**353**:1332-41.
- [4] White B, Livingstone W, Murphy C, Hodgson A, Rafferty M, Smith OP. An open-label study of the role of adjuvant hemostatic support with protein C replacement therapy in purpura fulminans-associated meningococcemia. *Blood* 2000;**96**:3719-24.
- [5] Mesters RM, Helterbrand J, Utterback BG, Yan SB, Chao YB, Fernandez JA, Griffin JH, Hartman DL. Prognostic value of protein C concentrations in neutropenic patients at high risk of severe septic complications. *Crit Care Med* 2000;**28**:2209-16.
- [6] Yan SB, Helterbrand JD, Hartman DL, Wright TJ, Bernard GR. Low levels of protein C are associated with poor outcome in severe sepsis. *Chest* 2001;**120**:915-22.
- [7] Nilsson G, Astermark J, Lethagen S, Verneris E, Berntorp E. Protein C levels can be forecasted by global haemostatic tests in critically ill patients and predict long-term survival. *Thromb Res* 2005;**116**:15-24.
- [8] Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York: John Wiley and Sons; 1980. p. 12-20, 70-119.
- [9] Collett D. Modelling survival data in medical research. London: Chapman and Hall; 1997. p. 15-31, 53-106, 223-237.
- [10] Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;**13**:818-29.
- [11] Blossfeld HM, Hamerle A, Mayer KU. Event history analysis. New Jersey: Lawrence Erlbaum Associates; 1989. p. 89-91.
- [12] SPSS Statistics 17.0. Homepage on the Internet; cited 2009 February 16. SPSS Inc, Headquarters. Wacker Drive, Chicago, IL, USA. Available from: <http://www.spss.com/statistics>.

- [13] LIMDEP version 9.0. Homepage on the Internet; cited 2009 February 16. Econometric Software, Inc. Gloria Place, Plainview, NY, USA. Available from: <http://www.limdep.com>.
- [14] SAS/STAT 9.2. Homepage on the Internet; cited 2009 February 16. SAS Institute Inc. SAS Campus Drive, Cary, NC, USA. Available from: <http://support.sas.com/rnd/app/da/new/dastat92.html>.
- [15] STATA 10. Homepage on the Internet; cited 2009 February 16. StataCorp LP. Lakeway Drive, College Station, TX, USA. Available from: <http://www.stata.com>.
- [16] FASS (Pharmaceutical specialities in Sweden). Homepage on the Internet; cited 2007 July 11. Sweden. Available from: <http://www.fass.se>.
- [17] Heyland DK, Gafni A, Griffith L, Cook D, Marshall J, Fuller H, Todd T, Guslits B, Heule M, Hewson J, Lacroix J, Noseworthy T, Powles P. The clinical and economic consequences of clinically important gastrointestinal bleeding in critically ill patients. *Clin Intensive Care* 1996;**7**:121-5.
- [18] Viscusi WK. Fatal tradeoffs: public and private responsibilities for risk. New York: Oxford University Press; 1992. p. 19-21.
- [19] Persson U, Norinder A, Hjalte K, Gralén K. The value of a statistical life in transport: findings from a new contingent valuation study in Sweden. *J Risk Uncertain* 2001;**23**:121-34.
- [20] Viscusi WK. The value of risks to life and health. *J Econ Lit* 1993;**31**:1912-46.
- [21] Vicusi WK, Aldy JE. The value of a statistical life: A critical review of market estimates throughout the world. *J Risk Uncertain* 2003;**27**:5-76.
- [22] Baker R, Chilton S, Jones-Lee M, Metcalf H. Valuing lives equally: Defensible premise or unwarranted compromise? *J Risk Uncertain* 2008;**36**:125-38.
- [23] Alberini A, Cropper M, Krupnick A, Simon NB. Does the value of a statistical life vary with age and health status? Evidence from the United States and Canada. *Resources for the Future*. Discussion paper No. 02-19, 2002.
- [24] de Blaeij A, Koetse M, Tseng Y, Rietveld P, Verhoef E. Valuation of safety, time, air pollution, climate change, and noise: methods and estimates for various countries. Report for the EU project ROSEBUD. Vrije Universiteit, Amsterdam, 2004.
- [25] Vincent JL, Bernard GR, Beale R, Doig C, Putensen C, Dhainaut JF, Artigas A, Fumagalli R, Macias W, Wright T, Wong K, Sundin DP, Turlo MA, Janes J. Drotrecogin alfa (activated) treatment in severe sepsis from the global open-label trial ENHANCE: further evidence for survival and safety and implications for early treatment. *Crit Care Med* 2005;**33**:2266-77.

[26] Dahabreh Z, Dimitriou R, Chalidis B, Giannoudis PV. Coagulopathy and the role of recombinant human activated protein C in sepsis and following polytrauma. *Expert Opin Drug Saf* 2006;**5**:67-82.

[27] de Kleijn ED, de Groot R, Hack CE, Mulder PG, Engl W, Moritz B, Joosten KF, Hazelzet JA. Activation of protein C following infusion of protein C concentrate in children with severe meningococcal sepsis and purpura fulminans: A randomized, double-blinded, placebo-controlled, dose-finding study. *Crit Care Med* 2003;**31**:1839-47.

[28] Faust SN, Levin M, Harrison OB, Goldin RD, Lockhart MS, Kondaveeti S, Laszik Z, Esmon CT, Heyderman RS. Dysfunction of endothelial protein C activation in severe meningococcal sepsis. *N Engl J Med* 2001;**345**:408-16.

[29] Liaw PC. Endogenous protein C activation in patients with severe sepsis. *Crit Care Med* 2004;**32**[Suppl.]:S214-8.

[30] Davies A, Ridley S, Hutton J, Chinn C, Barber B, Angus DC. Cost effectiveness of drotrecogin alfa (activated) for the treatment of severe sepsis in the United Kingdom. *Anaesthesia* 2005;**60**:155-62.

[31] Green C, Dinnes J, Takeda AL, Cuthbertson BH. Evaluation of the cost-effectiveness of drotrecogin alfa (activated) for the treatment of severe sepsis in the United Kingdom. *Int J Technol Assess Health Care* 2006;**22**:90-100.

[32] Riou Frana L, Launois R, Le Lay K, Aegerter P, Bouhassira M, Meshaka P, Guidet B. Cost-effectiveness of drotrecogin alfa (activated) in the treatment of severe sepsis with multiple organ failure. *Int J Technol Assess Health Care* 2006;**22**:101-8.

[33] Frampton JE, Foster RH. Drotrecogin alfa (activated): a pharmacoeconomic review of its use in severe sepsis. *Pharmacoeconomics* 2004;**22**:445-76.

[34] Neilson AR, Burchardi H, Chinn C, Clouth J, Schneider H, Angus D. Cost-effectiveness of drotrecogin alfa (activated) for the treatment of severe sepsis in Germany. *J Crit Care* 2003;**18**:217-27.

[35] Angus DC, Linde-Zwirble WT, Clermont G, Ball DE, Basson BR, Ely EW, Laterre PF, Vincent JL, Bernard G, van Hout B. PROWESS Investigators. Cost-effectiveness of drotrecogin alfa (activated) in the treatment of severe sepsis. *Crit Care Med* 2003;**31**:1-11.

[36] Manns BJ, Lee H, Doig CJ, Johnson D, Donaldson C. An economic evaluation of activated protein C treatment for severe sepsis. *N Engl J Med* 2002;**347**:993-1000.

[37] Hjelmgren J, Persson U, Tennvall GR. Local treatment pattern versus trial-based data: a cost-effectiveness analysis of drotrecogin alfa (activated) in the treatment of severe sepsis in Sweden. *Am J Ther* 2005;**12**:425-30.

[38] Eichacker PQ, Natanson C. Increasing evidence that risks of rhAPC may outweigh its benefits. *Intensive Care Med* 2007;**33**:396-9.



[39] Williams MD, Macias W, Rustige J. Safety of drotrecogin alfa (activated): a fair comparison requires consistent definitions. *Intensive Care Med* 2007;**33**:1487-8.

## Legends to Tables

### Table 1

#### **Descriptive data and blood test results of the 92 patients included in the study**

\* Numbers are given as median (first and third quartiles within parentheses).

### Table 2

#### **Kaplan-Meier estimates of the median survival times, test statistics, and survival functions in each protein C subgroup; observation time five years**

An approximation of the point estimate of the hazard function may be obtained by dividing the number of persons who die at each day ("No. of events") by the number of persons who could have died during that day (i.e. all who have not died before that day).

### Table 3

#### **Results of the Cox proportional hazards model (final model)**

The cutpoints for protein C, INR, APTT, and APACHE II score ( $<0.39$  IU/mL,  $>1.60$ ,  $>39$  s,  $>19$ , respectively) are calculated according to 80% survival. Gender: 0 indicating female, 1 indicating male.

### Table 4

#### **Test statistics of differences in age, INR, APTT, APACHE II score, and gender at admittance to ICU between the two different protein C level subgroups**

\* Median (first and third quartiles within parentheses).

† Distribution of dummy variables 0 and 1, explanation see Table 3 (legend).

‡ Test statistics by exact Mann-Whitney U-test.

§ Test statistics by exact Pearson chi-squared test.

**Table 5**

**Costs per life saved in €**

Costs per patient treated are multiplied by 2.7 (27 patients in the lower protein C subgroup, at best-case scenario ten lives saved) to receive costs per life saved.

**Table 6**

**Cost-benefit ratios of administering APC and protein C to the lower protein C subgroup under different assumptions of efficiency of treatment and values of statistical lives (in €)**

**Table A1**

**Results of the Cox proportional hazards model (starting model)**

The cutpoints for protein C, platelets, INR, APTT, antithrombin, and APACHE II score ( $<0.39$  IU/mL,  $<67 \times 10^9 \text{ L}^{-1}$ ,  $>1.60$ ,  $>39$  s,  $<0.41$  IU/mL,  $>19$ , respectively) are calculated according to 80% survival. Diagnosis category: 0 indicating medical subgroup, 1 indicating surgical subgroup. Gender: 0 indicating female, 1 indicating male.

**Table 1**

<b>Characteristic</b>	<b>Result</b>	<b>Reference interval (95% interval)</b>
Gender, females / males	35 / 57	——
Age, years*	69.0 (58.2, 76.8)	——
Diagnosis category, medicine /surgery	24 / 68	——
Platelet count, 10 <sup>9</sup> /L*	92 (65, 160)	125 – 340
International Normalized Ratio (INR)*	1.48 (1.36, 1.64)	<1.20
Activated Partial Thromboplastin Time (APTT), s*	37 (33, 44)	24 – 37
Protein C, IU/mL*	0.46 (0.37, 0.55)	0.70 – 1.30
Antithrombin, IU/mL*	0.51 (0.41, 0.64)	0.82 – 1.11
APACHE II score*	18 (13, 24)	——

**Table 2**

Group		N	Events	Censored	Median no. of days		SE	95% CI
Protein C ≥0.39 IU/mL		65	37	28	1252		481	309 – 2195
Protein C <0.39 IU/mL		27	24	3	6.0		1.7	2.6 – 9.4
Statistics for equality of survival distributions					df	Significance		
Log rank			13.94	1	<0.001			
Breslow			14.41	1	<0.001			
Tarrone-Ware			14.34	1	<0.001			
Protein C ≥0.39 IU/mL				Protein C <0.39 IU/mL				
Time (days)	No. of events	Cum. surv.	SE	Time (days)	No. of events	Cum. surv.	SE	
0	1	0.9846	0.0153	0	3	0.8889	0.0605	
1	5	0.9077	0.0359	1	4	0.7407	0.0843	
5	2	0.8769	0.0407	3	3	0.6296	0.0929	
6	2	0.8462	0.0448	4	1	0.5926	0.0946	
7	1	0.8308	0.0465	5	1	0.5556	0.0956	
10	1	0.8154	0.0481	6	2	0.4815	0.0962	
11	1	0.8000	0.0496	7	1	0.4444	0.0956	
25	1	0.7846	0.0510	12	1	0.4074	0.0946	
28	1	0.7692	0.0523	224	1	0.3704	0.0929	
30	1	0.7538	0.0534	374	1	0.3333	0.0907	
44	1	0.7385	0.0545	477	1	0.2963	0.0879	
47	1	0.7231	0.0555	481	1	0.2593	0.0843	
74	1	0.7077	0.0564	577	1	0.2222	0.0800	
83	1	0.6923	0.0572	1008	1	0.1852	0.0748	
113	1	0.6769	0.0580	1282	1	0.1481	0.0684	
124	1	0.6615	0.0587	1766	1	0.1111	0.0605	
142	1	0.6462	0.0593	—	—	—	—	
151	1	0.6308	0.0599	—	—	—	—	
172	1	0.6154	0.0603	—	—	—	—	
307	1	0.6000	0.0608	—	—	—	—	
382	1	0.5846	0.0611	—	—	—	—	
505	1	0.5692	0.0614	—	—	—	—	
514	1	0.5538	0.0617	—	—	—	—	
515	1	0.5385	0.0618	—	—	—	—	
654	1	0.5231	0.0620	—	—	—	—	
994	1	0.5077	0.0620	—	—	—	—	
1252	1	0.4923	0.0620	—	—	—	—	
1253	1	0.4769	0.0620	—	—	—	—	
1333	1	0.4615	0.0618	—	—	—	—	
1350	1	0.4462	0.0617	—	—	—	—	
1418	1	0.4308	0.0614	—	—	—	—	

**Table 3**

<b>Variable</b>	<b><math>\beta</math></b>	<b>SE</b>	<b>df</b>	<b>Signif</b>	<b>Exp(<math>\beta</math>)</b>	<b>95% CI for Exp(<math>\beta</math>)</b>
Age	0.1165	0.0178	1	<0.001	1.124	1.085 – 1.164
Age $\times$ time	-0.0346	0.00532	1	<0.001	0.966	0.956 – 0.976
Protein C	1.82	0.639	1	0.004	6.20	1.77 – 21.7
Protein C $\times$ time	-19.3	10.3	1	0.060	4.00E-09	7.23E-18 – 2.21
INR	-2.66	0.757	1	<0.001	0.0696	0.0158 – 0.307
INR $\times$ time	35.5	11.5	1	0.002	2.70E+15	4.69E+05 – 1.55E+25
APTT	1.37	0.664	1	0.039	3.93	1.07 – 14.5
APTT $\times$ time	-23.1	10.8	1	0.033	9.72E-11	6.02E-20 – 0.157
APACHE II	3.08	0.814	1	<0.001	21.8	4.42 – 108
APACHE II $\times$ time	-32.3	11.1	1	0.004	9.78E-15	3.43E-24 – 2.79E-05
Gender	0.914	0.344	1	0.008	2.49	1.27 – 4.90
-2 log-likelihood	279.929	—	11	—	—	—

**Table 4**

<b>Characteristic</b>	<b>Patients with protein C ≥0.39 IU/mL (n=65)</b>	<b>Patients with protein C &lt;0.39 IU/mL (n=27)</b>	<b><i>p</i>-value</b>
Age*	70.0 (56.5, 78.5)	67.0 (59.0, 74.0)	0.50‡
INR†	52 / 13	13 / 14	0.003§
APTT†	49 / 16	13 / 14	0.015§
APACHE II score†	45 / 20	11 / 16	0.018§
Gender, females / males	29 / 36	6 / 21	0.059§

**Table 5**

<b>Specification</b>	<b>Xigris<sup>®</sup> strategy</b>	<b>Ceprotin strategy</b>
Protein C	21,961	19,065
Serious bleedings	670	670
Costs of hospital stay	12,495	12,495
Total costs per life saved	35,126	32,230
95% CI	27,020 – 50,180	24,792 – 46,043



**Table 6**

<b>Country</b>	<b>The United States</b>		<b>Canada</b>		<b>The United Kingdom</b>		<b>The Netherlands</b>		<b>Germany</b>	
<b>Strategy</b>	<b>Xigris®</b>	<b>Ceprotin</b>	<b>Xigris®</b>	<b>Ceprotin</b>	<b>Xigris®</b>	<b>Ceprotin</b>	<b>Xigris®</b>	<b>Ceprotin</b>	<b>Xigris®</b>	<b>Ceprotin</b>
Cost-benefit ratio if 10 lives saved	0.007	0.006	0.008	0.007	0.016	0.015	0.019	0.018	0.027	0.024
Cost-benefit ratio if 8 lives saved	0.009	0.008	0.010	0.009	0.020	0.018	0.024	0.022	0.033	0.030
Cost-benefit ratio if 5 lives saved	0.014	0.013	0.016	0.014	0.032	0.029	0.038	0.035	0.053	0.049
Cost-benefit ratio if 3 lives saved	0.023	0.021	0.026	0.024	0.053	0.049	0.064	0.059	0.088	0.081
<b>VOSL</b>	<b>5,117,000</b>		<b>4,474,000</b>		<b>2,194,000</b>		<b>1,836,000</b>		<b>1,326,000</b>	

**Table A1**

<b>Variable</b>	<b><math>\beta</math></b>	<b>SE</b>	<b>Df</b>	<b>Signif</b>	<b>Exp(<math>\beta</math>)</b>	<b>95% CI for Exp(<math>\beta</math>)</b>
Age	0.1276	0.0193	1	<0.001	1.136	1.094 – 1.180
Age $\times$ time	-0.0367	0.00579	1	<0.001	0.964	0.953 – 0.975
Protein C	1.85	0.728	1	0.011	6.37	1.53 – 26.6
Protein C $\times$ time	-21.6	11.5	1	0.059	4.04E-10	7.00E-20 – 2.33
Platelet count	0.932	0.666	1	0.16	2.54	0.688 – 9.36
Platelet count $\times$ time	-11.8	12.2	1	0.34	7.85E-06	3.29E-16 – 188000
INR	-3.01	0.825	1	<0.001	0.0493	0.00980 – 0.248
INR $\times$ time	46.1	12.8	1	<0.001	1.03E+20	1.36E+09 – 7.72E+30
APTT	1.28	0.780	1	0.10	3.61	0.782 – 16.6
APTT $\times$ time	-18.5	12.6	1	0.14	9.14E-09	1.77E-19 – 472
Antithrombin	-1.16	0.687	1	0.092	0.315	0.0819 – 1.21
Antithrombin $\times$ time	6.95	11.9	1	0.56	1040	8.36E-08 – 1.29E+13
APACHE II	3.18	0.809	1	<0.001	24.1	4.93 – 118
APACHE II $\times$ time	-32.9	10.9	1	0.002	5.23E-15	2.91E-24 – 9.42E-06
Diagnosis category	0.667	0.713	1	0.35	1.95	0.482 – 7.88
Diagnosis category $\times$ time	-19.7	10.8	1	0.067	2.72E-09	1.89E-18 – 3.93
Gender	0.893	0.368	1	0.015	2.44	1.19 – 5.02
-2 log-likelihood	269.952	—	17	—	—	—