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

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## 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®) 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 Heath 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®, 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 menigococcal 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 $<100 \times 10^9$ $L^{-1}$, INR >1.36, APTT >45 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+ΔT, conditional upon that it has not already occurred. In the Cox proportional hazards model, it is specified as:

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

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 ΔT. 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:

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

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®, 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 ($T_{½}$) 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® and Ceprotin € 8,134 and € 7,061, respectively [16]. Regarding Ceprotin, in critically ill patients, both $T_{½}$ 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:

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

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® 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):

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

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]:

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

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® 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®, 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 $T_{½}$ (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® 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 meningococceal 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 overweigh 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

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## 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:

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

Taking logarithms:

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

Integrating (A2) by parts:

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

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

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

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

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# 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, $<67 \times 10^9 L^{-1}$, >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**

| **Characteristic** | **Result** | **Reference interval (95% interval)** |
|---|---|---|
| Gender, females / males | 35 / 57 | —— |
| Age, years* | 69.0 (58.2, 76.8) | —— |
| Diagnosis category, medicine /surgery | 24 / 68 | —— |
| Platelet count, $10^9$ /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**

| Variable | β | SE | df | Signif | Exp(β) | 95% CI for Exp(β) |
|---|---|---|---|---|---|---|
| Age | 0.1165 | 0.0178 | 1 | <0.001 | 1.124 | 1.085 – 1.164 |
| Age × 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 × 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 × 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 × 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 × 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**

| **Characteristic** | **Patients with protein C ≥0.39 IU/mL (n=65)** | **Patients with protein C <0.39 IU/mL (n=27)** | ***p*-value** |
|---|---|---|---|
| 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**

| **Specification** | **Xigris® strategy** | **Ceprotin strategy** |
|---|---|---|
| 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**

| **Country** | **The United States** | | **Canada** | | **The United Kingdom** | | **The Netherlands** | | **Germany** | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Strategy** | **Xigris®** | **Ceprotin** | **Xigris®** | **Ceprotin** | **Xigris®** | **Ceprotin** | **Xigris®** | **Ceprotin** | **Xigris®** | **Ceprotin** |
| 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 |
| VOSL | 5,117,000 | | 4,474,000 | | 2,194,000 | | 1,836,000 | | 1,326,000 | |

**Table A1**

| Variable | β | SE | Df | Signif | Exp(β) | 95% CI for Exp(β) |
|---|---|---|---|---|---|---|
| Age | 0.1276 | 0.0193 | 1 | <0.001 | 1.136 | 1.094 – 1.180 |
| Age × 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 × 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 × 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 × 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 × 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 × 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 × 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 × 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 | —— | —— | —— |