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Cost-effectiveness of activated protein C in real-life clinical practice

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ABSTRACT

Background: Recombinant human activated protein C (rhAPC) has been reported as cost-effective in severely ill septic patients in studies using data from the pivotal randomized trial. We assessed cost-effectiveness of rhAPC in patients with severe sepsis and multiple organ failure in real-life intensive care practice.

Methods: A prospective observational study involved adult patients recruited before and after rhAPC was licensed in France. Inclusion criteria were defined according to the label approved in Europe. The expected recruitment bias was controlled by building a sample of patients matched on their propensity score. Complete hospitalization costs were quantified using a regression equation involving intensive care units variables. rhAPC acquisition costs were added, assuming that all costs associated with rhAPC were already included in the equation. Costs comparisons were conducted using the non-parametric bootstrap method. Cost-effectiveness quadrants and acceptability curves were used to assess uncertainty of the cost-effectiveness ratio.

Results: In the initial cohort (n=1096), post-license patients were younger, had less comorbid conditions, and failure of more organs than pre-license patients (all: $p<0.0001$). In the matched sample (n=840), mean age was 62.4 ± 14.9 years, Simplified Acute Physiology Score II was 56.7 ± 18.5, and number of organ failures was 3.20 ± 0.83. When rhAPC was used, 28-day mortality tended to be reduced (34.1 vs. 37.4% pre-license, $p=0.34$), bleeding events were more frequent (21.7 vs. 13.6%, $p=0.002$), and hospital costs higher (€47,870 vs. €36,717, $p<0.05$). The incremental cost-effectiveness ratio gained was €20,278 per life-year gained and €33,797 and per QALY gained. There was a 74.5% probability that rhAPC would be cost-effective, if there is willingness to pay €50,000 per life-year gained. The probability was 64.3% if there is willingness to pay €50,000 per QALY gained.

Conclusion: This study on matched samples shows that, in real-life clinical practice, the probability for rhAPC to be cost-effective at the €50,000 per life-year gained willingness to pay threshold is equal to 74.5%.

INTRODUCTION

Severe sepsis with multiple organ failure is a life-threatening systemic response to infection, leading to death in 34 to 65% of patients [1-5]. It is common in intensive care in France, where more than 10% of admitted patients are affected [4]. Several studies have shown that high incidence and mortality rates in severe sepsis are associated with substantial healthcare costs [1, 5].

The recombinant human activated protein C (rhAPC), drotrecogin alfa (activated), is a new treatment for severe sepsis. Evidence for the efficacy of rhAPC comes primarily from a large pivotal, randomized, placebo-controlled trial called PROWESS [6]. This study demonstrated a statistically significant, absolute reduction of 6.5% in 28-day mortality. *A priori* subgroup analyses showed that the relative risk of death progressively decreases with increasing number of organ failures [7]. Absolute reduction in mortality was higher in patients who had two or more organ failures (7.7%) than in the whole PROWESS population. Drotrecogin alfa (activated) is licensed in the European Union since 2002 for the treatment of adult patients with severe sepsis and multiple organ failure when added to best standard care.

However, the expenses linked to this new treatment have raised concerns about its cost-effectiveness. Indeed, the costs associated with rhAPC in patients with severe sepsis and multiple organ failure comprise not only the acquisition cost of the drug (€7,500 per 70-kg patient for the full recommended 96-hour course), but also potential costs associated with bleeding episodes, hospitalization costs related to additional survivors of severe sepsis and, where deemed appropriate, long-term healthcare costs associated with additional survivors of severe sepsis. Such additional costs vary markedly in the published literature [8-14], due to country-specific settings as well as the choice of different modeling approaches for estimating these costs; for instance resources utilization perimeter used for calculating the cost

per patient treated or untreated with rhAPC. However, in most of these models, the intervention always remains at a level that would be regarded as cost-effective to most decision makers, especially for patients with an Acute Physiology And Chronic Health Evaluation II (APACHE II) score exceeding 24 [8, 9, 11] or those with multiple organ failure [13, 14].

Moreover, all cost-effectiveness studies of rhAPC used efficacy data extracted from the PROWESS trial, which most likely do not reflect the daily practice at bedside [15]. Our study PREMISS aimed to assess whether cost-effectiveness demonstrated from the PROWESS data could be replicated in clinical practice. We prospectively observed the patients' outcome and actual hospital costs before and after rhAPC was available in France and established the real-life cost-effectiveness of rhAPC in patients with severe sepsis and multiple organ failure.

PATIENTS AND METHODS

Study design and patients

The primary objective of this national, prospective, observational study was to estimate the costs of patients treated with rhAPC compared with untreated patients. The secondary objective was to determine rhAPC cost-effectiveness in clinical practice. Its effectiveness was estimated for carrying out the economical analyses only [16]. rhAPC efficacy has already been demonstrated in the PROWESS study [6]. No randomization was conducted in order that none of the patients included after the molecule was made available on the French market suffered loss of opportunity. In addition, as the costs were to be estimated in patients for whom rhAPC was prescribed in real practice, it was essential that the study interfered as little as possible with intensive care physicians' practices [17]. External validity, that is the

ability of the study to provide reproducible results in other studies, was given preference over internal validity, that is the ability of the study to provide results which truly reflect the variables measured. Therefore, rather than reproducing the results of PROWESS, the present study ensured that its results could be generalized in the setting of everyday intensive care practice in France.

A pre-post design was considered as the most appropriate. Patients were included before (pre-license study phase) and after (post-license study phase) rhAPC was available in France (January 2003). Inclusion/exclusion criteria were defined in accordance with the rhAPC (Xigris®) label approved in the European Union.

Collected data included demographics, clinical information and use of resources on admission, at enrolment and during hospital course, and patients' outcome at 28 days.

Based on estimated average costs of €31,800 and €39,500 in the pre- and post-license phases, respectively, according to a French pharmacoeconomic model [18], and assuming a normal distribution of the costs, 340 patients were to be included in each study phase to detect a difference of €7,700 in the average costs with a first degree risk α of 0.05 and a power β of 0.80. If the study objective had been to detect a difference of effectiveness (mortality), we estimate from the PROWESS results that 600 patients per phase would have been needed.

The two French Intensive Care Societies launched the study in 2002, at the request of the Health Ministry. Approval of an Ethics Committee was not required.

Measurement and reduction of recruitment bias

Given the absence of randomization, there is no guarantee that patients in the two study phases are comparable.

We described the presence of recruitment bias by calculating the standardized differences of each baseline variable between the two groups [19].

In order to achieve an unbiased comparison of costs, we controlled for recruitment bias using the propensity score method [20, 21]. The propensity score summarizes all observed baseline variables in a single figure. We then used it to construct a sample of comparable patients in the two phases by a matching process, using the SAS© "match" macro [22] to obtain an optimal match. More details of the propensity score approach are given in appendix II.

Estimation and comparison of costs

Cost analysis was performed from the point of view of the health-care provider since treatment of patients with severe sepsis is almost exclusively dispensed by hospital services. Complete hospitalization costs were estimated from the CUB-Rea (College of Intensive Care Database Users) database [23] and from a multiple regression equation derived from a micro costing study, based on 211 stays in intensive care unit (ICU) in 1996 in France [24]. The French information system for the medico-economic description and measurement of the hospital activity [Programme de médicalisation des systèmes d'information], which is based on medical unit summaries ([Résumés d'unité médicale], RUM), provided the following: age, sex, length of stay, diagnoses on admission and at discharge, and diagnostic / therapeutic procedures performed. The CUB-Rea database provided the following specific intensive care indicators: SAPS II score, Omega score, McCabe score, and admission type. Hospitalization costs used in the micro-costing study included the following: (i) ICU costs (variable direct costs such as tests [laboratory, imaging], small materials, drugs and blood products, time spent by care staff [state registered nurse, health care assistant]; fixed direct costs such as time spent by medical nursing staff

calculated on a *pro rata* basis for length of stay; and variable indirect costs such as restaurant services, laundry, pharmacy and administration); and (ii) post intensive care costs (number of days, valued by the departmental tariff category).

The equation obtained [14] had a good determination coefficient (R^2=93%) and was expressed as follows:

$$CC = \beta_0 + \beta_1 * LOS + \beta_2 * LOS * 1_{DCR=1} + \beta_3 * \Omega_{TOT} + \beta_4 * (SAPS2)^2 + \beta_5 * 1_{DCR=1}$$

where CC was the total complete cost of the hospital stay (in French Francs1996); LOS was the length of stay in ICU; Ω_{TOT} was the total Omega score; SAPS2 was the SAPS II score; $1_{DCR=1}$ was the variable indicating death in intensive care; β_0 = -8,881.50; β_1 = 5,465.60; β_2 = 3,715.10; β_3 = 183.75; β_4 = 5.27; and β_5 = -18,078.50.

The way the equation was formulated implied that, for a short length of stay (less than 5 days), the cost incurred by survivors was greater than that generated by patients who die in intensive care. Beyond that given threshold, patients who eventually died in intensive care sustained increasing costs as their length of stay increased.

This general equation applied both to patients suffering from severe sepsis and to those suffering from other diseases, but did not take into account the medical costs associated with administration of rhAPC. The acquisition costs of rhAPC were therefore added to the complete hospitalization costs, assuming that all the connate costs associated with rhAPC administration (adverse events, longer-term follow up, etc.) were incorporated in the equation through the Omega score, the SAPS II and the length of stay in intensive care. This was an essential assumption, as it ensured that the total cost of patients receiving care with rhAPC was not underestimated. It was also a realistic assumption, as these three indicators have been designed to best represent activity in intensive care.

The year 2004 was chosen to harmonize all the costs that have been calculated in this study because it contained the latest patient inclusions. The CUB-Rea equation was initially expressed in French $Francs_{1996}$ and inflation rates from the national institute INSEE [25] were used to obtain nominal values for 2002, 2003 and 2004. All costs were then discounted for the year 2004, using a discount rate of 3.5%.
Cost comparisons were performed using the non-parametric bootstrap method [26], since cost variables are often asymmetric. 10 000 samples of size n (starting sample size) obtained from the empirical distribution function of costs were generated by drawing with replacement n individuals randomly from the initial sample. The mean costs in each bootstrap sample was calculated for both groups, together with the difference between the two mean costs. We then tested whether this difference was significantly different from 0.

Estimation of effectiveness

The effectiveness metric was life expectancy at 28 days after onset of sepsis. This data point was however not directly available since only mortality at 28 days was recorded in the case report forms. The life expectancy of survivors was therefore estimated using the McCabe score. A set of assumptions was made [14]. (i) Patients suffering from a short-term fatal disease (1 year) were allocated a life expectancy of 0.5 years. (ii) The life expectancy of patients suffering from a long-term fatal disease (5 years) was estimated to be 3 years. (iii) The life expectancy of patients without fatal comorbidities was calculated from the life expectancy of the French general population published in the INSEE tables [27], grouped by age and sex for the year 2003. One study [28] estimated that the life expectancy of patients who had suffered severe sepsis was reduced by half compared to people of the same age and sex in

the general population. The life expectancy extracted from the INSEE tables was therefore divided by two for this patient category.

Life expectancy was then adjusted on quality of life to obtain a quality-adjusted life-year (QALY) gained outcome. Studies evaluating quality of life after intensive care stay reported a range of coefficients from 0.6 to >0.8 [8, 9, 29, 30]. The lowest coefficient (0.6) was used in the present study.

Although most analysts agree that costs should be discounted in any study having a time horizon longer than one year, there is no consensus on whether or not the consequences or benefits of intervention should be discounted, and at which rate. It was therefore decided not to discount the measure of effectiveness.

Cost-effectiveness ratio

Unlike the previous rhAPC cost-effectiveness estimations, our cost-effectiveness ratio derives from a trial collecting both effectiveness and cost data and not from a model combining different data sources. The approach taken to deal with uncertainty in the estimates is consequently statistical and not based on sensitivity analyses. The difficulty of obtaining the distribution of a ratio has been discussed elsewhere in the literature [31]. We used once again the non-parametric bootstrap method, by generating 10 000bootstrap samples of the mean effectiveness, the mean cost and the cost-effectiveness ratio. The results were represented in a cost-effectiveness plane, linking effectiveness to costs.

From the same bootstrap samples, an acceptability curve of rhAPC was also constructed. This curve shows the probability that the treatment is efficient according to the decision-makers' willingness to pay. For a willingness to pay of λ, this probability is equal to the proportion of bootstrap samples in which the ratio

calculated is less than λ. This curve provides another measurement of uncertainty linked with the overview estimate of the cost-effectiveness ratio [32].

RESULTS

Patients' characteristics in the initial cohort (1096 patients)

Overall, 85 participating ICUs recruited 1096 patients with severe sepsis and multiple organ failure. The inclusion rate during the post-license phase using rhAPC was much lower than during the pre-license phase: 509 patients were enrolled between July 2002 and December 2002 (before the French license was obtained), and 587 patients between January 2003 and December 2004 (after the French license was obtained). Patients' baseline characteristics are provided in Table 1, overall and by study phase. The overall cohort characteristics corresponded to those of the population targeted in the European recommendations for using rhAPC. Patients were severely ill with high risk of death, and had failure of two or more organs. Mean Simplified Acute Physiology Score II (SAPS II) [33] was 56.6 ± 18.6, which corresponds to a predicted hospital mortality of 61%, and mean Logistic Organ Dysfunction (LOD) score [34] was 7.67 ± 2.82. Neurological failure was excluded from the calculation of organ failure because most of the patients were sedated at enrolment in both phases. Despite this, the observed mean number of organ failures in the initial cohort was higher than three (3.21 ± 0.86).

Presence and correction of recruitment bias

Of the 81 standardized differences calculated, 43 exceeded the 10% threshold, reflecting an imbalance between the two phases. Even though the patients recruited in the two phases had similar severity indices (SAPS II and LOD score), they did not

have the same type of severity. More patients in the post-license group had respiratory failure whereas patients in the pre-license group had more severe neurological disorders. In addition, patients recruited for rhAPC treatment were younger and less liable to die within the year. More patients in the pre-license phase were admitted through internal transfer into the ICU. Also, more of them were suffering from endo-cardiovascular and urinary tract infections.

Matching using the propensity scores produced a sample of 840 patients, 420 in each phase. The new sample corresponded to 76.6% of the initial cohort. Patients' characteristics are presented in Table 2. Overall, mean age was 62.4 ± 14.9 years, mean SAPS II score was 56.7 ± 18.5, and mean number of organ failures was 3.20 ± 0.83.

Recruitment biases were markedly reduced or nearly absent, as only five variables (among 81) still showed a standardized difference exceeding 10% (Figure 1). These variables reflected that patients aged 80 years or more (difference: 14.9%) and non-ventilated patients (difference: 10.5%) were more numerous in the pre-license phase. Subsequent analyses have been conducted in this matched population.

Hospital course, burden of care, and costs

Table 3 summarizes hospital course, burden of care, and costs in the matched population. Patients in the post-license phase stayed longer in the ICU (24.4 vs. 21.3 days, $p=0.002$) and tended to stay longer in hospital (40.4 vs. 37.9 days, $p=0.09$) than those in the pre-license phase. The burden of care was higher in the post-license phase, as assessed by the relative cost index (2,862 vs. 2,430, $p<0.05$) and the Omega score (427 vs. 373, $p<0.05$). A multivariate model showed that the increase in burden of care (measured by relative cost indices) was essentially due to the increase in length of stay in the ICU ($p<0.0001$). However, after adjustment on

the length of stay in the ICU, the difference between both study phases for the burden of care remained statistically significant (p=0.048). Similar results were found when the burden of care was measured through the Omega score. The burden of care during the post-license phase when using rhAPC was therefore higher, due to both length of stay in the ICU and daily resource utilization.

The increase in drug costs observed in the post-license phase was related not only to the acquisition of rhAPC itself (€6,717 in average), but also to that of other therapies, including antimicrobial agents (€1,900 vs. 1,321, p<0.05). Blood and plasma transfusion costs were also higher in the post-license phase (€1,043 vs. 751, p <0.05), the occurrence of transfusions being essentially due to the bleeding events observed (At least one event for 21.67% vs 13.57% of the patients, p<0.05,). Overall, complete hospitalization costs were higher in the post-license phase (€47,870 vs. 36,717; p<0.05). Sixty percent of this difference was attributable to the rhAPC acquisition costs.

When survivors and non-survivors in the post-license phase were compared (Table 3), the length of stay in ICU and hospital was lower in non-survivors (p<0.05). Total hospitalization costs in the post-license phase, however, whether or not including rhAPC acquisition costs, were similar in survivors and non-survivors.

Survival

Both study phases did not differ significantly for the 28-day mortality (34.1 post-license vs. 37.4% pre-license, respectively, p=0.34). The mean life expectancy was 6.68 ± 7.33 years for patients in the post-license phase and 6.13 ± 7.20 years for patients in the pre-license phase. This difference (0.55 years gained when rhAPC was used) was also not significant (p = 0.22). By applying a quality of life coefficient of 0.6, patients in the pre-license phase gained 3.68 ± 4.32 QALYs and those in the

post-license phase gained 4.01 ± 4.40 QALYs, resulting in a difference of 0.33 QALY gained when rhAPC was used.

Cost-effectiveness estimates

Without adjusting for quality of life, incremental cost-effectiveness of rhAPC was €20,278 per life-year gained. After adjusting for quality of life, it was €33,797 per QALY. Figure 2 shows the distribution of incremental cost-effectiveness ratios in terms of life expectancy and of QALY after 10,000 bootstrap replicates. Quadrants to the right of the y-axis represent the region where treatment with rhAPC is associated with a net gain in effect (85.92%). Quadrants above the x-axis represent the region where treatment is associated with a net increase in cost (100%). Both distributions were thus predominantly in the “more costly, more effective” upper right quadrant. The acceptability curves (Figure 3) show, for each willingness to pay, the probability that rhAPC is acceptable, i.e. the probability that the ratio is below the willingness to pay. The asymptote of the acceptability curves was not equal to 1, simply due to the fact that the bootstrap samples included data in which rhAPC added to best standard care was less effective than best standard care alone. The asymptote was equal to the proportion of bootstrap samples, for which the number of (quality-adjusted) life years gained was greater in the post-license phase than in the pre-license phase (85.92%). There was a 74.5% probability that the use of rhAPC in septic patients with multiple organ failure would be cost-effective if there is willingness to pay €50,000 per life-year gained. The probability was 64.3% if there is willingness to pay €50,000 per QALY gained.

DISCUSSION

This study shows, for the first time in real-life clinical practice, that rhAPC is cost-effective in patients with severe sepsis and multiple organ failure. There was a 74.5% probability that rhAPC would be cost-effective, if there is willingness to pay €50,000 per life-year gained. The results also suggest that ICU physicians targeted preferably the most severely ill patients with reasonable life expectancy for rhAPC treatment.

Target for rhAPC treatment in clinical practice and selection bias

ICU physicians enrolled patients on the basis of the same inclusion/exclusion criteria (defined according to the approved rhAPC label) throughout the whole study duration. However, patients in the post-license phase, that is patients who actually received rhAPC, were younger and had less underlying diseases, but more organ failures at study entry than those in the pre-license phase (initial cohort). We speculate that physicians, in the real-life clinical practice, when giving such an expensive drug with an increased risk of bleeding, excluded the very elderly (> 80 years), patients with advanced underlying disease (McCabe 3), and patients with less than three organ failures in order to target the most severely ill patients with reasonable life expectancy if they survive the episode of severe sepsis. It is interesting to note that rhAPC was not overused, even though two thirds of the drug acquisition costs have been paid by the Ministry of Health throughout the present study.

The markedly longer period of recruitment after the French license was obtained (24 vs. 6 months for the pre-license phase) also advocates for an additional selection of patients who actually received rhAPC. Furthermore, although the occurrence of all bleeding events was significantly different between the two phases (13.6 vs. 21.7%), it was still lower than that observed in the patients with multiple organ failure of the

PROWESS trial in both the placebo and rhAPC groups (17.9 vs. 25.4%) [7]. This could be due either to the fact that, in our observational study, adverse events were not reported as rigorously as in a trial setting or, more likely, to a drastic selection of patients without any serious risk of bleeding in real-life clinical practice.

It is also worth noting that the reduction of 28-day mortality in the post-license phase when using rhAPC was modest despite the fact that a markedly larger proportion of patients were treated with low-dose steroids in the post-license phase than in the pre-license phase (80.5 vs. 55.0%, $p<0.0001$), probably linked to the higher severity of illness. Indeed, low doses of hydrocortisone and fludrocortisone have been shown to significantly reduce the risk of death in patients with septic shock and relative adrenal insufficiency without increasing adverse events [35]. No interaction between steroids and rhAPC has been published to our knowledge and, in the PROWESS trial, mortality was lower with rhAPC than with placebo whether steroids were given at baseline or during the infusion period or not given at all [36, 37].

Dealing with selection bias

Recruitment biases inherent to non randomized study designs are well known. Being aware, at the time the study was designed, that imbalance in patient characteristics was likely to occur and of the resulting incomparability of the groups in terms of resource used, hence of costs in the initial cohort, we took preventive measures. Using the propensity score was planned to control for these biases. The main limit of the propensity score is to take into account the observed biases only [20, 21]. The case record forms were thus designed in order to collect all initial clinical characteristics deemed likely to affect effectiveness, resource utilization and costs. 46 such variables were collected. The probability that a confounding factor was left out is therefore quite low. As a result, in the sample of patients matched on their

propensity score, recruitment biases were markedly reduced or almost entirely removed. No statistically significant differences between the two phases were found. Consequently, we are confident that the observed differences with regards to rhAPC cost-effectiveness were not related to the characteristics of the patients.
We believe selection bias is smaller in a pre-post design than in a post-license only study matching untreated patients to rhAPC treated patients since rhAPC is not an option in the pre-license phase.

Relation to other studies

The present study confirms the discrepancy that is often seen between rigorously planned clinical trials and real-life clinical practice. Cost-effectiveness of rhAPC in our study was less favorable than that described previously in the literature. However, and by contrast with ours, all other studies used the effectiveness data of the randomized, double-blind, placebo-controlled clinical trial PROWESS [6]. For comparison, the incremental cost-effectiveness ratio per life-year gained and per QALY gained were €20,278 and €33,797, respectively, in the present study. In the other studies, the ratio in the most severely ill patients (APACHE II score > 24 for North America, and multiple organ failure for Europe) was around US$15,000 in the North American studies [8-11] and €13,000 in the European studies [12-14] per life-year gained. It was around US$30,000 and €22,000 per QALY gained, respectively. The higher cost-effectiveness ratio obtained in this present study was due to a lower absolute reduction in the 28-day mortality between matched groups when compared to PROWESS (-3.3 vs. -6.1 overall and -7.7% in the subgroup with multiple organ failure) [6, 7], rather than to hospital costs. This was unexpected. Indeed, the very

severely ill patients theoretically represented a more favorable population than the PROWESS global population to benefit from rhAPC, since reduction in mortality was demonstrated to be the highest in patients with an APACHE II score higher than 24 [45] and those with multiple organ failure enrolled in PROWESS [7]. When compared to the global population [6] and subgroup with multiple organ failure [7] of PROWESS, the 840 patients in the matched population of PREMISS had different baseline characteristics: higher predicted mortality (61.3 vs. 52.6 and 55.9%, respectively, calculated from the mean SAPS II or APACHE II score); higher number of organ failures (3.20 vs. 2.40 and 2.92, respectively) although neurological failure was not taken into account in the present study; higher proportion of mechanically ventilated patients (94.6 vs. 75.5 and 81.1%, respectively); higher proportion of shock patients (94.3 vs. 71.0 and 82.4%, respectively); and higher proportion of patients requiring vasopressor agents (88.6 vs. 70.9 and 72.7%, respectively).

This discrepancy may be explained as follows. First, the effect of rhAPC on mortality might be limited in the most severely ill patients. This hypothesis would however not be consistent with the PROWESS subgroup analyses [38], which showed that absolute reduction in the 28-day mortality was lower in patients with failure of one or two organs (1.7 and 5.3%, respectively) than in patients with failure of three or four organs (8.2 and 7.9%, respectively). Second, the small recruitment bias that persisted after the matching process may be responsible for the apparent lower efficacy of the drug when compared to PROWESS. This phenomenon is unlikely, as the only variables concerned showed small standardized differences (below 15%) and should counter-balance each other: the very elderly (more numerous by 14.9% pre-license) are more vulnerable than the youngest, whilst non-ventilated patients (more numerous by 10.1% pre-license) are less vulnerable than mechanically-ventilated patients. Third, physicians might have delayed administration of rhAPC

after sepsis onset in face of a transient stabilization of the patient after conventional treatment. Indeed, administration of the drug after the first 24 hours of sepsis onset has been shown to lead to an apparent lower efficacy [39, 40]. However, 70% of the patients enrolled in the post-license phase received rhAPC within the first day of admission in ICU. Fourth, the decrease in mortality observed in PROWESS might have overestimated the real effect of the drug, because the proportions of patients who had septic shock, who were being treated with vasopressor agents, who were receiving mechanical ventilation, or who suffered from underlying diseases were higher in the placebo group than in the rhAPC group [6]. Larger differences in baseline underlying diseases were observed in the placebo subgroup with multiple organ failure [7], in particular in liver and cardiovascular diseases which are known to strongly influence mortality of patients with severe sepsis after the first three days [3, 4]. Although no difference was statistically significant, these imbalances slightly favor the rhAPC group, especially in patients with multiple organ failure [36, 41]. Our study could then represent the real-life reduction of mortality related to rhAPC.

The higher cost-effectiveness ratio observed compared to other studies might also be due to increased hospital costs, but to a limited extent only. In the matched population, rhAPC added to best standard care significantly increased resource use and total hospital costs in both survivors and non-survivors to severe sepsis with multiple organ failure. This was related to both higher length of ICU stay and more intense daily intensive care. Among the seven economic studies devoted to rhAPC, only that of Angus et al. [9] reported hospital course and burden of care assessed by the TISS-28 points. No differences between the placebo and treatment groups were observed for the length of ICU stay and the burden of care in the cost cohort (US patients of the PROWESS trial). The explanation of these apparently conflicting results is unknown. We presume that the rhAPC-related improvement of the status of

our very severely ill patients required a longer length of ICU stay and higher intensity of daily intensive care than those of the PROWESS trial. However, the incremental cost per patient treated was similar in both studies (US$9,800 vs. €11,153), and was significantly different only when the acquisition cost of the drug was taken into account in the hospitalization costs.

LIMITATIONS OF THE STUDY

To sum up, the main limitations of the study are:

- The absence of randomization, in order to avoid a loss of opportunity to patients denied a treatment deemed effective in a previous trial [6]. Our study shows some evidence of selection bias, that we controlled using propensity score matching.
- The choice of the control group. In a pre-post design, historical controls are used. As the control patients were recruited only a few months before the first treated patients, and exploratory analyses did not show signs of temporal trends, we have no reason to think the results were biased by temporal evolutions.
- The sample size was tailored for cost comparisons. As a result, this study is underpowered to deal with effectiveness issues. The absence of a significant difference in effectiveness in our study is not a reason not to perform a cost-effectiveness analysis, although it adds to the variability of the cost-effectiveness estimate.
- The absence of follow-up of patients once they left the hospital. Some assumptions had to be made regarding their expected life expectancy and quality of life. These assumptions are based on those made in previous cost-effectiveness models [14]. However, since the assumptions are the same for both treatment strategies compared, the final estimates are much less sensitive to a change in these parameters than to a change in 28-day mortality.

CONCLUSIONS

This prospective, observational study shows that, in real-life clinical practice, rhAPC is cost-effective in the management of severe sepsis with multiple organ failure. It is the first cost-effectiveness study of rhAPC that does not derive its primary data from one large pivotal study.

KEY MESSAGES

- Complete hospitalization costs were higher in the post-license phase (€47,870 vs €36,717). Sixty percent of this difference was attributable to the rhAPC acquisition cost.
- There was a 74.5% probability that rhAPC would be cost-effective for a willingness to pay of €50,000.
- Without adjusting for quality of life, the incremental cost-effectiveness of rhAPC was of €20,300 per life-year gained. After adjusting for quality of life it was of €33,797 per QALY.
- The cost-effectiveness ratio is higher than the previously published, PROWESS-based, estimates. This is due to a lower absolute reduction in 28-day mortality (-3.3 in our study vs -6.1 overall and -7.7% in the subgroup with multiple organ failure in the PROWESS study) rather than to hospital costs.
- These less favorable estimates confirm the discrepancy between rigorously planned protocol trials and real-life clinical practice.

List of abbreviations: APACHE = Acute Physiology And Chronic Health Evaluation; CI = confidence interval; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus; ICU = intensive care unit; INSEE = [Institut National de la Statistique et des Etudes Economiques]; LOD = Logistic Organ Dysfunction; PREMISS = [Protocole en Réanimation d'Evaluation Médico-économique d'une Innovation dans le Sepsis Sévère], Intensive Care Study devoted to the Medico-Economic Evaluation of a New Innovative Therapy in Severe Sepsis; PROWESS = Protein C Worldwide Evaluation in Severe Sepsis; QALY = quality-adjusted life-year; rhAPC = recombinant human activated protein C; SAPS = Simplified Acute Physiology Score; SD = standard deviation.

Competing interests: J-FD has served as paid consultant for serving in an advisory board for GlaxoSmithKline, Lilly, and AstraZeneca, and for participating as a speaker in scientific meetings organized by GlaxoSmithKline and Lilly. BV has served as paid technical support for Edwards Life Sciences. All other authors declare that they have no competing interest.

Authors' contributions: J-FD and BV obtained the funding. J-FD, BV, and RL conceived the study and participated in its design and coordination. BG participated in its design. KL developed a study-specific online data acquisition system and participated in the data management. SP and LRF carried out the statistical analysis. RL carried out the economical analysis. J-FD, RL, LRF and SP drafted the manuscript. All authors read and approved the final manuscript.

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Appendix II: The Propensity Score Approach.

Treatment comparisons can be achieved only if the populations being compared share common characteristics before receiving treatment. In randomized clinical trials, comparability is ensured through randomization of patients in different treatment groups. This process guarantees that observed as well as non-observed characteristics are similar in the groups under study. In the present non-randomized study, inclusion of a patient in one of the two groups was the result of a decision process guided by the drug availability and the choices of both the physician and the patient. There was no *a priori* to guarantee patient comparability in the two study phases. Recruitment bias was therefore expected from this type of two-phase design. Steps have been taken to remove this bias. One of the most widely used criteria to identify recruitment biases is the balance of initial features between groups. This was done by standardizing their differences [19]. In effect, the difference between the means of a particular variable was weighted by its common standard deviation. If the observed difference between the two groups was significantly large compared to the variance of a particular variable, the groups were deemed incomparable for that variable. The threshold of balance for any given variable was set at 10%. If a standardized difference for a variable was above 10%, it meant, therefore, that there was a recruitment bias on this variable.

Any recruitment bias must be controlled in order to allow correct comparison of costs. The propensity score is a well-recognized method used to do so [20]. It indicates the probability that a subject with given characteristics is exposed to treatment. It can reduce a large number of covariates into a single composite variable, which correctly summarizes all of the features observed. Its distribution provides a criterion to assess comparability between populations which are exposed or not exposed to treatment [21]. If two patients have similar scores, it also means that they have similar initial characteristics.

The propensity score was estimated using a logistic regression model. The score was then used to construct a sample of comparable patients in the two phases by a matching process, that is, pairing a patient from the pre-license phase with a patient from the post-license phase who had a similar propensity score. The matching algorithm used was the SAS© “match” macro [22]. This process is regarded as optimal because it matches patients from the two different phases depending on their propensity score in order to minimize the total distance between the propensity score of matched patients (each distance representing the absolute value of the difference between the two propensity scores of the matched patient pair). The sample thus obtained is generally considered more balanced in terms of the observed features than the initial sample.

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FIGURE LEGENDS

Figure 1. Changes in standardized differences before and after matching

Figure 2. Cost-effectiveness of rhAPC

The figure shows the distribution of the incremental cost-effectiveness ratios in terms of life expectancy (left panel) and of QALY (right panel) after 10,000 bootstrap replicates. Quadrants to the right of the y-axis represent the region where treatment with rhAPC is associated with a net gain in effect (85.92%). Quadrants above the x-axis represent the region where treatment is associated with a net increase in cost (100%). Both distributions were thus predominantly in the “more costly, more effective” upper right quadrant.

Figure 3. Cost-effectiveness acceptability curves of rhAPC

The curves represent the probability that treatment with rhAPC is associated with a cost per life-year gained and a cost per QALY gained that are lower than the corresponding incremental cost-effectiveness ratios displayed on the x axis. There was a 74.5% probability that the use of rhAPC would be cost-effective if there is willingness to pay €50,000 per life-year gained and a 64.3% probability if there is willingness to pay €50,000 per QALY gained.

TABLES

Table 1. Patient characteristics in the initial cohort

	All patients n=1096	Pre-license n=509	Post-license n=587	p-value
Demographics				
Age (yrs)	60.8 ± 16.3	63.9 ± 15.1	58.1 ± 16.8	< 0.0001
> 60 yrs	57.9	64.1	52.5	0.0001
Male	62.0	61.5	62.5	0.7265
Weight (kg)	73.9 ± 17.4	73.5 ± 17.3	74.2 ± 17.4	0.5546
Prior location				0.0702
Medical or surgical department	40.4	44.0	37.3	
Emergency department	28.4	27.1	29.5	
Another acute care hospital	22.6	19.8	25.0	
Home	8.6	9.1	8.2	
Reason for ICU admission				0.9168
Medical	71.7	72.1	71.4	
Surgical	27.0	26.5	27.4	
Trauma	1.3	1.4	1.2	
Disease severity				
SAPS II on admission	56.6 ± 18.6	56.9 ± 19.1	56.2 ± 18.1	0.5427
LOD at enrolment*	7.67 ± 2.82	7.44 ± 2.93	7.87 ± 2.71	0.0112
Organ failure at enrolment*	3.21 ± 0.86	3.10 ± 0.86	3.31 ± 0.85	< 0.0001
- acute lung injury	2.1 ± 1.1	1.9 ± 1.2	2.2 ± 1.0	< 0.0001
- acute renal failure	3.4 ± 1.7	3.3 ± 1.8	3.4 ± 1.7	0.3777
- coagulopathy	0.3 ± 0.7	0.3 ± 0.6	0.3 ± 0.7	0.0629
- acute liver failure	0.3 ± 0.5	0.3 ± 0.5	0.3 ± 0.5	0.1831
- acute cardiovascular failure	1.6 ± 1.3	1.7 ± 1.3	1.6 ± 1.2	0.4399
Shock at enrolment	93.7	92.5	94.7	0.1375
Comorbid conditions				
McCabe				< 0.0001
0	36.4	30.8	41.5	
1	35.9	34.2	37.5	
2	21.5	26.0	17.5	
3	6.1	9.0	3.6	
Chronic renal failure	6.3	7.7	5.0	0.0649
Chronic liver disease	4.2	4.4	4.1	0.8593
Congestive cardiomyopathy	13.0	14.1	12.0	0.3018
COPD	14.3	14.7	14.1	0.7824
Diabetes mellitus	6.5	6.8	6.2	0.7123
Immunosuppressive treatment	6.1	5.7	6.4	0.6653
Chemotherapy	3.2	3.9	2.6	0.1982
Metastatic cancer	5.0	6.4	3.8	0.0553
Hematological malignancies	3.3	4.2	2.6	0.1450
HIV	1.8	1.4	2.1	0.4018
Infection site				
Lung	49.2	50.1	48.4	0.5867
Intra-abdominal	26.2	27.6	25.0	0.3454
Urinary tract	9.8	12.0	7.9	0.0273
CNS	4.9	2.7	6.7	0.0032

Values are means ± SD or proportions of patients. *Neurological failure excluded.
CNS, Central nervous system. COPD, Chronic obstructive pulmonary disease. HIV, Human immunodeficiency virus (infection). LOD, Logistic Organ Dysfunction score. SAPS, Simplified Acute Physiology Score.

Table 2. Patient characteristics in the matched sample

	All patients n=840	Pre-license n=420	Post-license n=420	p-value
Demographics				
Age (yrs)	62.4 ± 14.9	62.7 ± 15,3	62.0 ± 14.4	0.4584
> 60 yrs	61.5	61.4	61.7	0.9435
Male	62.4	60.7	64.1	0.3187
Weight (kg)	74.6 ± 17.4	74.1 ± 17.6	75.1 ± 17.1	0.4192
Prior location				0.8676
Medical or surgical department	40.9	41.9	40.0	
Emergency department	28.7	27.4	30.0	
Another acute care hospital	21.2	21.4	21.0	
Home	9.2	9.3	9.0	
Reason for ICU admission				0.8428
Medical	69.9	70.7	69.0	
Surgical	29.0	28.3	29.8	
Trauma	1.1	1.0	1.2	
Disease severity				
SAPS II on admission	56.7 ± 18.5	56.8 ± 19.1	56.6 ± 18.0	0.8833
LOD at enrolment*	7.60 ± 2.82	7.51 ± 2.91	7.70 ± 2.73	0.3384
Organ failure at enrolment*	3.20 ± 0.83	3.15 ± 0.84	3.25 ± 0.82	0.0676
- acute lung injury	2.1 ± 1.1	2.1 ± 1.1	2.2 ± 1.1	0.1922
- acute renal failure	3.3 ± 1.7	3.3 ± 1.8	3.4 ± 1.7	0.5274
- coagulopathy	0.3 ± 0.6	0.2 ± 0.6	0.3 ± 0.6	0.7368
- acute liver failure	0.3 ± 0.5	0.3 ± 0.5	0.3 ± 0.5	0.5669
- acute cardiovascular failure	1.6 ± 1.3	1.6 ± 1.3	1.6 ± 1.3	0.6664
Shock at enrolment	94.3	93.3	95.2	0.2344
Comorbid conditions				
McCabe				0.4541
0	35.1	34.8	35.4	
1	36.6	34.6	38.7	
2	22.7	24.2	21.2	
3	5.6	6.4	4.7	
Chronic renal failure	5.9	6.5	5.3	0.4775
Chronic liver disease	3.5	3.6	3.4	0.8552
Congestive cardiomyopathy	14.0	14.5	13.5	0.6684
COPD	15.4	14.7	16.1	0.5743
Diabetes mellitus	6.5	6.3	6.7	0.7854
Immunosuppressive treatment	4.8	4.8	4.8	0.9938
Chemotherapy	2.8	3.1	2.4	0.5259
Metastatic cancer	5.6	6.3	4.9	0.3761
Hematological malignancies	2.5	2.6	2.4	0.8208
HIV	5.9	6.5	5.3	0.3511
Infection site				
Lung	51.8	51.1	52.5	0.7078
Intra-abdominal	27.1	27.1	27.1	0.9987
Urinary tract	10.1	11.1	9.1	0.3417
CNS	3.3	3.0	3.5	0.7432

Values are means ± SD or proportions of patients. *Neurological failure excluded.
CNS, Central nervous system. COPD, Chronic obstructive pulmonary disease. HIV, Human immunodeficiency virus (infection). LOD, Logistic Organ Dysfunction score. SAPS, Simplified Acute Physiology Score.

Table 3. Burden of care and hospitalization costs in the matched patients

	All patients (n=840)			Survivors (n=471)			Non-survivors (n=369)		
	Pre-license	Post-license	95% CI	Pre-license	Post-license	95% CI	Pre-license	Post-license	95% CI
Omega score	373	427*	[9.12; 98.03]	380	433	[-10.12; 112.31]	364	418	[-13.36; 120.57]
Reference cost index	2,430	2,862*	[187; 662]	2,254	2,667*/**	[96.30; 722.05]	2,648	3,121*/**	[8.90; 936.01]
ICU stay (day)	21.3	24.4*	[0.32; 5.92]	23.8	26.7**	[-0.90; 6.57]	18.2	21.3**	[-0.89; 7.25]
Hospital stay (day)	37.9	40.4	[-1.79; 6.84]	49.2	51.1**	[-4.41; 8.37]	24.6	27.5**	[-2.02; 7.95]
Costs [-rhAPC] (€)	36,717	41,144	[-85; 8,991]	35,575	39,172	[-1,737; 8,680]	38,095	43,729	[-2,005; 13,380]
Total costs (€)	36,717	47,870*	[6,601; 15,709]	35,575	46,752*	[5,863; 16,313]	38,095	49,336*	[3,433; 19,084]

Values are means and 95% confidence intervals on the means.
*p<0.05 pre-license vs. post-license. **p<0.05 post-license survivors vs. non-survivors.
CI, Confidence interval. ICU, Intensive Care Unit. [-rhAPC], Without rhAPC acquisition costs.

Figure 1. Changes in standardized differences before and after matching

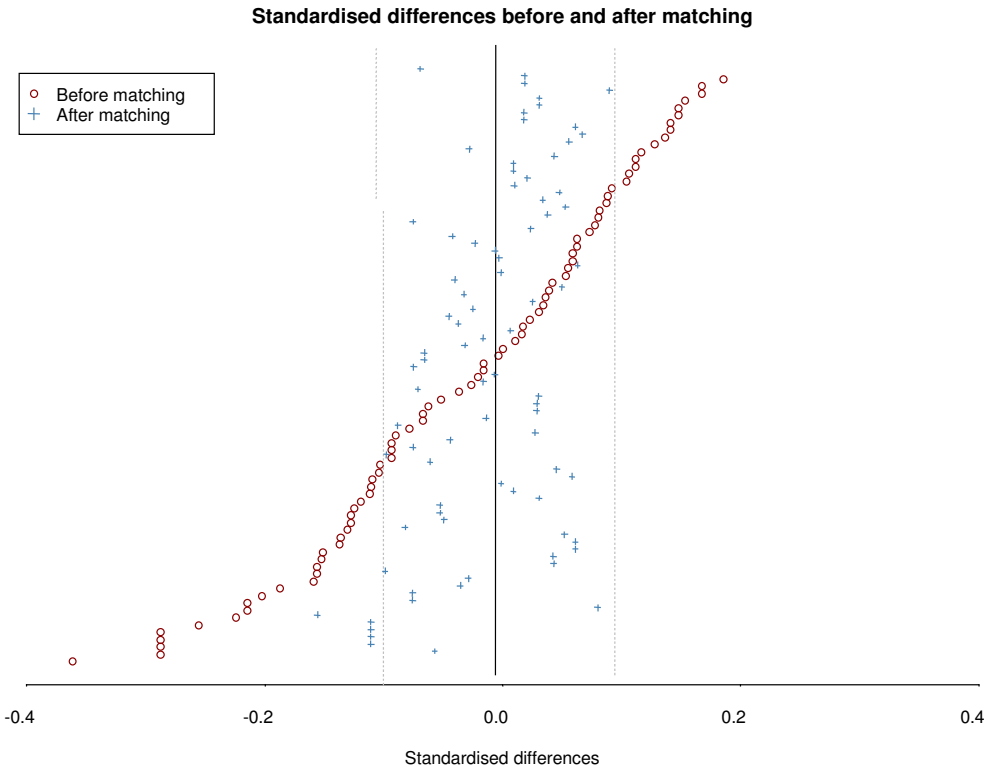
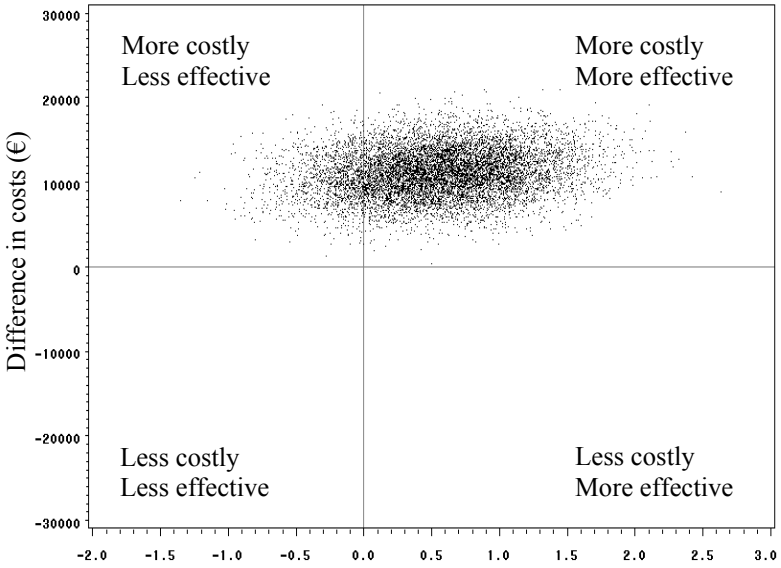


Figure 1

Figure 2. Cost-effectiveness of rhAPC



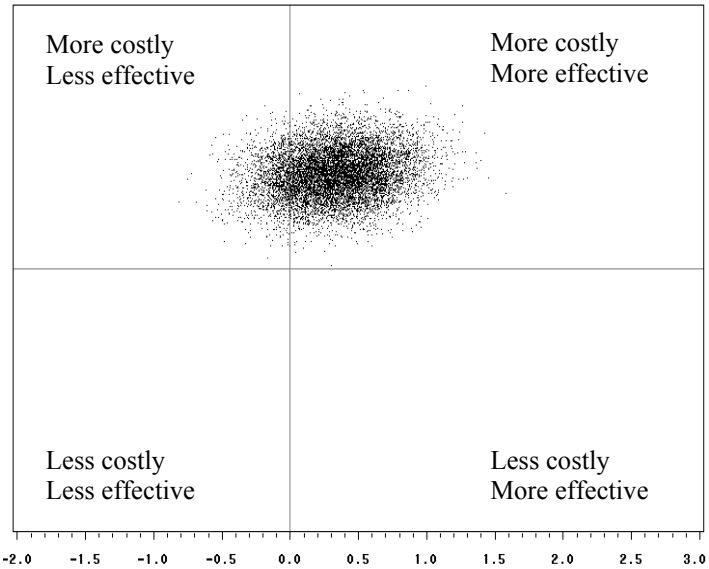


Figure 3. Cost-effectiveness acceptability curves of rhAPC

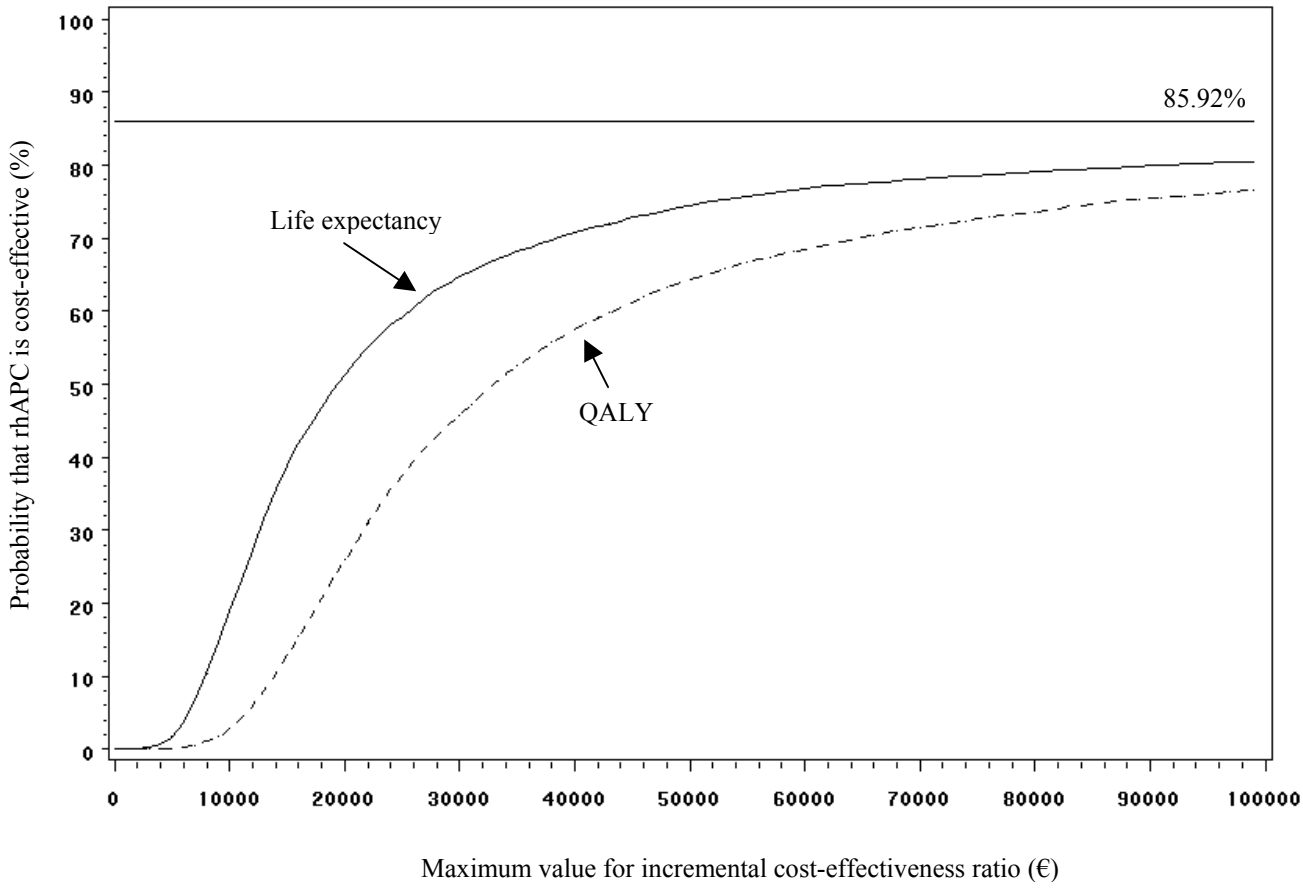


Figure 3