Cost-Effectiveness of Recombinant Activated Factor VII in the Treatment of Intracerebral Hemorrhage

Stephanie R. Earnshaw, PhD; Ashish V. Joshi, MS, PhD; Michele R. Wilson, MSPH; Jonathan Rosand, MD, MSc

**Background and Purpose**—Intracerebral hemorrhage (ICH) is among the most severe and crippling forms of stroke. Intracerebral hemorrhage (ICH) is one of the most severe and debilitating forms of stroke. ICH-related mortality is very high, and only a small percentage of survivors regain functional independence.1–3 The incidence of stroke in the United States (US) is estimated to be about 337 per 100,000, with healthcare system associated with stroke.4 Functional outcomes in survivors can range from no disability to severe disability immediately after an ICH event. Nonetheless, quality of life after major stroke, the category into which ICH most often falls, can be considered by some to be worse than death.8

Currently, there are no well-proven treatment options for ICH. Recombinant activated factor VII (rFVIIa) reduces ICH mortality and improves functional outcome. In the current analysis, we examine the cost-effectiveness of early treatment with rFVIIa for ICH in the United States.

**Methods**—A decision-analytic model was developed to estimate the lifetime costs and outcomes associated with rFVIIa treatment at doses of 40, 80 and 160 μg/kg compared with current standard of care in treating ICH, from a US third-party payer perspective. The patient population was similar to that of the Phase IIb clinical trial. Model structure and inputs were obtained from published literature, clinical trial data, claims databases, and expert opinion. All costs are presented in 2005 US dollars. Outcomes included incremental cost per life-year (LY) saved and incremental cost per quality-adjusted life-year (QALY) gained. Costs and outcomes were discounted at 3% annually. Univariate and multivariate sensitivity analyses were conducted to assess model robustness.

**Results**—Compared with standard care, treatment with rFVIIa 40 μg/kg, and 160 μg/kg results in total lifetime cost-effectiveness ratios of $6308/QALY and $3152/QALY, respectively. Treatment with rFVIIa 80 μg/kg was found to be cost saving and a gain of 1.67 QALYs is achieved over a patient’s lifetime. These results are robust to changes in input parameters.

**Conclusions**—Treatment of ICH with rFVIIa 40 μg/kg and 160 μg/kg appears to be cost-effective (≤$50 000/QALY). At the 80 μg/kg dose, rFVIIa was not only cost-effective, but also cost saving. (*Stroke*. 2006;37:2751-2758.)

**Key Words:** cost-effectiveness analysis ■ economics ■ intracerebral hemorrhage ■ stroke management

Intracerebral hemorrhage (ICH) is one of the most severe and crippling forms of stroke. ICH-related mortality is very high, and only a small percentage of survivors regain functional independence.1–3 The incidence of stroke in the United States (US) is estimated to be about 337 per 100,000, with ICH representing 8% to 15% of all strokes.4

The medical resources required for ICH treatment and accommodation of functional impairment in survivors imposes a significant economic burden,5–7 contributing to the estimated $35.0 billion in annual direct costs to the US healthcare system associated with stroke.4 Functional outcome in survivors can range from no disability to severe disability immediately after an ICH event. Nonetheless, quality of life after major stroke, the category into which ICH most often falls, can be considered by some to be worse than death.8

Currently, there are no well-proven treatment options for patients with ICH. Recombinant activated factor VII (rFVIIa; NovoSeven, Novo Nordisk A/S,) is a human coagulation Factor VIIa that promotes hemostasis and is currently approved as a treatment for bleeding episodes in patients with hemophilia who have antibodies (inhibitors) to factor VIII or IX. In addition, it has been reported to reduce bleeding in patients without coagulopathy.9 In a recent phase IIb dose ranging study, clinical efficacy of rFVIIa compared with standard care was reported. In this study, ICH patients were treated within 4 hours of onset of ICH symptoms.10 Those receiving rFVIIa achieved an improved functional outcome at 90 days after initial onset of ICH and a 38% relative reduction in mortality compared with those receiving standard care.

Currently, limited economic analyses of ICH are available in the published literature. Several analyses of stroke have been published,5,6,11–14 but these analyses tend to focus mainly on ischemic stroke. No economic analyses have been performed specifically for treatments of ICH. We hypothesize that if rFVIIa were introduced as a treatment for ICH it would have a substantial impact on drug costs, medical resource costs, quality-adjusted life years (QALYs) and possibly cost-effectiveness. The goal of this article is to estimate the cost-effectiveness of treating patients with ICH with the novel treatment, rFVIIa, versus standard of care.
Subjects and Methods

Overview
A decision-analytic model was developed to examine the cost-effectiveness of treating acute ICH patients with rFVIIa compared with current standard of care (ie, placebo). The model simulates treatment and outcomes for a cohort of patients presenting to the emergency department with ICH. The patient population was assumed to have similar age distribution as that of a typical patient population with ICH observed in the published literature and as estimated from analyses of data from the Healthcare Cost and Utilization Project (HCUP) and Medicare data.

Input Parameters
Input parameters were drawn from clinical trial data and published clinical studies and include the following critical elements:

Patient Characteristics
To maximize generalizability, age distribution of the patient population was assumed to be that as observed in clinical practice based on an analysis of the HCUP and Medicare data as well as published literature. The average age of the patient population was estimated to be 69.6 years which is slightly older than that observed in the clinical trial (66 years of age). Average patient weight was assumed to be 70 kg.

Clinical Efficacy
Data on treatment efficacy for patients on 40, 80, or 160 µg/kg of rFVIIa and standard care were obtained from the clinical trial. Clinical efficacy for each treatment-branch was measured by the percentage of patients achieving specific mRS scores at day 90 (Table 1).

Short-Term Costs
Resource use and costs for the first 90 days after ICH were estimated from the clinical trial, Medicare data, and published literature. Specifically, per-day hospital costs were estimated from a 5% sample of the Medicare database. These costs were applied to the mean length of stay (LOS) in the hospital observed in the clinical trial (Table 1) to estimate the average cost of hospitalization for patients in each category of functional outcome. Additional 90-day medical costs included medication management and outpatient physician visits after hospital discharge for all surviving patients. Durable medical equipment and skilled nursing facility/rehabilitation/home health care after the initial hospitalization were assumed to be incurred only for those with severe disability (mRS 5). All costs, when appropriate, were adjusted to 2005 US dollars using the medical Consumer Price Index. Cost inputs and their sources are provided in Table 2.
Mortality was allowed to increase as a function of patient’s age in the model. Death hazard ratios were estimated by Gage and colleagues. These all-stroke utility weights have been used in a previous cost-effectiveness analysis in patients with ICH and are presented in Table 2. Because several studies have been performed in which utilities have been derived for each of the mRS groups, we performed a sensitivity analysis around these estimates given the likelihood that there may be a difference in utility between functional status health states. In addition, it has been noted that being severely disabled (mRS 5) could be considered worse than death (ie, a negative utility score) by some patients.

### Sensitivity Analysis

To test the robustness of the model assumptions and specific parameters, we examined the effect of changing several parameters in one-way sensitivity analyses. Parameters analyzed include the cost multipliers; death hazard rates; hospital LOS; distribution of patients among the various functional outcome groups; cost of medication management, outpatient physician visits, and durable equipment; utility weights; and discount rates. The effect of varying individual parameters was examined using plausible ranges of values (Table 2) from the literature, 95% CIs, or by varying the estimates by up to 20% in each direction.

In addition to one-way sensitivity analyses, we also performed probabilistic sensitivity analyses (second-order Monte Carlo simulation) in which all parameters are varied simultaneously. The parameters that we varied in these analyses included the distribution of patients among the various functional outcome groups, mortality, hospital LOS, cost multipliers, death hazard ratios, and utility weights. We assumed that parameter estimates followed a triangular distribution. The effect of varying individual parameters was examined using plausible ranges of values (Table 2) from the literature, 95% CIs, or by varying the estimates by up to 20% in each direction.

### Results

#### Base Case Analysis

A summary of results are presented in Table 3. Treatment with rFVIIa at a dose of 80 μg/kg results in a reduction of total lifetime medical costs ($153 264 compared with $167 160, $163 730, and $159 055 for patients on 40 μg/kg, 80 μg/kg, and standard care respectively). Although the initial cost of administering rFVIIa is high, this analysis demonstrates that these drug costs are only a small portion of the overall cost ($159 055 for rFVIIa compared with $167 160 for standard care).

### Utility Weights

Utility weights range from 0.0 to 1.0, where a utility value of 1.0 represents perfect health and a value of 0.0 represents death. These utility values are used to estimate QALYs by multiplying the number of life years within a particular health state by that health state’s utility weight.

Utility weights by mRS group status were obtained from a study by Gage and colleagues. These all-stroke utility weights have been used in a previous cost-effectiveness analysis in patients with ICH and are presented in Table 2. Because several studies have been performed in which utilities have been derived for each of the mRS groups, we performed a sensitivity analysis around these estimates given the likelihood that there may be a difference in utility between functional status health states. In addition, it has been noted that being severely disabled (mRS 5) could be considered worse than death (ie, a negative utility score) by some patients.

### Long-Term Costs

Estimates for costs incurred beyond 90 days were based on data from the Medicare analysis and published literature. Specifically, the Kaplan Meier Sampling Averages method was used to estimate medical costs accrued up to 4 years after ICH. Costs incurred for each state of functional recovery were determined by applying age-specific all-cause mortality was estimated from the US National Vital Statistics Reports. This mortality risk was adjusted by death hazard ratios reported by Samsa et al. to estimate mortality rates for ICH survivors, stratified by mRS at 90 days. Mortality was allowed to increase as a function of patient’s age in the model.

<table>
<thead>
<tr>
<th>Table 1. Distribution of Patients at 90 Days and Initial Hospital Length of Stay by Disease Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model Parameter</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Efficacy (90-day disease severity by mRS score)*</td>
</tr>
<tr>
<td>mRS 0</td>
</tr>
<tr>
<td>mRS 1</td>
</tr>
<tr>
<td>mRS 2</td>
</tr>
<tr>
<td>mRS 3</td>
</tr>
<tr>
<td>mRS 4</td>
</tr>
<tr>
<td>mRS 5</td>
</tr>
<tr>
<td>mRS 6</td>
</tr>
</tbody>
</table>

*Distribution of disease severity was estimated 90 days after initial onset of ICH. †Distribution of disease severity and initial hospital length of stay were obtained from a phase IIb clinical trial. Initial hospital length of stay is presented as mean days (SD).

Utility weights range from 0.0 to 1.0, where a utility value of 1.0 represents perfect health and a value of 0.0 represents death. These utility values are used to estimate QALYs by multiplying the number of life years within a particular health state by that health state’s utility weight.
Patients treated with 40, 80, and 160 μg/kg gain 1.41, 1.67, and 1.45 LYs respectively over patients on standard care. Furthermore, treatment with 40, 80, and 160 μg/kg confers 1.28, 1.72, and 1.48 more QALYs compared with standard care. Treating with 80 μg/kg is therefore cost saving (ie, less costly and more effective) whereas the incremental cost per QALY when treating with 40 μg/kg and 160 μg/kg is $6308 and $3152 respectively compared with standard care. Treating with rFVIIa is cost-effective, assuming the standard $50 000 cost per QALY threshold,28–30 at any dose.

### Sensitivity Analyses

One-way and multiway probabilistic sensitivity analyses showed base case results to be robust to variations in most input parameters. Figure 2 illustrates one-way sensitivity of the incremental cost-effectiveness ratio (ICER) results in response to variations in several model parameters. The model was most sensitive to changes in cost multipliers for mRS 5, death hazard ratios for mRS 5, improvement in functional outcome, hospital LOS, and 90-day mortality. Varying these parameters resulted in a greater deviation in ICER from the base case ICER. However, in all analyses,
treatment with 80 μg/kg remained a cost-effective strategy compared with standard care.

Additional one-way sensitivity analyses were performed on changes in initial hospital LOS and improvement in functional outcome at individual mRS groups. In these analyses, the model was set up so that the hospital LOS for patients on all treatments was fixed to the LOS observed by patients in each mRS group on standard care. Changes in LOS by ±20% at each mRS group were then examined. This variation had little effect on the cost-effectiveness.

In examining variations in functional outcome among survivors (ie, mRS 0 to 5), the percentage of patients within each mRS group was varied ±20%, with the remaining percentage of patients in the respective mRS groups moved down/up to the next mRS group.

TABLE 3. Lifetime Costs and Outcomes Associated With Treating ICH via Standard Care and rFVIIa

<table>
<thead>
<tr>
<th>Outcome (per Patient)</th>
<th>Standard Care</th>
<th>rFVIIa 40 μg/kg</th>
<th>rFVIIa 80 μg/kg</th>
<th>rFVIIa 160 μg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other medical cost</td>
<td>$159,055</td>
<td>$164,696</td>
<td>$148,336</td>
<td>$153,874</td>
</tr>
<tr>
<td>Cost of drug</td>
<td>$0</td>
<td>$2,464</td>
<td>$4,928</td>
<td>$9,856</td>
</tr>
<tr>
<td>Total costs</td>
<td>$159,055</td>
<td>$167,160</td>
<td>$153,264</td>
<td>$163,730</td>
</tr>
<tr>
<td>Life years</td>
<td>6.12</td>
<td>7.54</td>
<td>7.80</td>
<td>7.58</td>
</tr>
<tr>
<td>QALYs</td>
<td>2.80</td>
<td>4.08</td>
<td>4.52</td>
<td>4.28</td>
</tr>
<tr>
<td>$/QALYs</td>
<td>...</td>
<td>$6,308</td>
<td>Cost saving*</td>
<td>$3152</td>
</tr>
</tbody>
</table>

*Cost saving means treatment resulted in lower costs and a greater number of QALYs than standard care.

Figure 2. One-way sensitivity analysis: effect of parameter variation on the incremental cost per QALY for rFVIIa 80 μg/kg compared with standard care. The tornado chart illustrates the effect on the ICER ($/QALY) comparing rFVIIa 80 μg/kg to standard care, when input parameter values are varied. Baseline ICER is $3,364. Lower bound for the input parameter is a 20% decrease in the input parameter, or the lower estimate of the plausible range listed in Table 2. Upper bound is a 20% increase in input value, or the higher estimate of the plausible range listed in Table 2.
Discussion

ICH, with its high acute mortality and its devastating effect on functional recovery among survivors, is a costly disease for society. Our analysis indicates that treatment with rFVIIa at a dose of 80 μg/kg is not only cost-effective but also a cost-saving strategy compared with the current standard of care in the treatment of ICH. From a third-party payer perspective, increases in cost incurred because of the administration of rFVIIa are offset by decreases in expected lifetime medical costs associated with ICH. More importantly, patients treated with rFVIIa are expected to see a significant improvement in functional outcome, LYs, and QALYs.

Treatment with the 80 μg/kg dose remains a cost-saving treatment in nearly all one-way sensitivity analyses, and assuming an acceptable incremental cost per QALY of $50,000, treatment with rFVIIa is cost-effective even when not cost-saving. Model results are robust to one-way changes in parameters. In the probabilistic sensitivity analysis, results show that the 80 μg/kg dose is cost-effective in 99.7% of cases. Treating with 40 μg/kg is cost-effective compared with standard care in 96.0% of cases and the 160 μg/kg dose is cost-effective in 98.4% of cases.

Treating with 80 μg/kg outperforms treatment with 40 μg/kg or 160 μg/kg. The key reason is the improvement in functional outcome after 90 days from onset of ICH for patients receiving the 80 μg/kg. In the clinical trial, a higher proportion of patients receiving 80 μg/kg (50.5%) obtained mRS 0 to 3 than did patients on either the 40 μg/kg (45.4%) or 160 μg/kg (45.6%) doses. Because patients in these mRS states are assumed to incur fewer costs and greater life-expectancy and quality of life, it is logical that the 80 μg/kg dose produces the most favorable results. However, it is noted that within the trial, differences in improvements in functional outcome among rFVIIa doses did not reach statistical significance.

As with any cost-effectiveness analysis, a number of assumptions were necessary in order to perform the analysis. For example, in this analysis the mRS-specific cost multipliers and mortality hazard ratios were obtained from a previously published analysis of ischemic stroke. We assume that the long-term costs and outcomes are based on functional outcome (mRS) of a patient rather than the type of stroke that initiated the patient’s steady-state functional outcome, and thus these cost multipliers and mortality hazard ratios can be appropriately applied. We also conducted extensive sensitivity analyses to examine changes in costs and mortality by functional outcome. The results of the sensitivity analyses suggest that the study findings are robust. The worst-case scenario from the sensitivity analysis resulted in an ICER of $40,510 compared with standard care.

Another limitation is that it is possible that a change in functional outcome might occur between 90 days and 180 days after ICH. We suspect that a patient with a reported mRS at 90 days would only receive a similar or better mRS at 180 days as rehabilitation would improve functional outcome over time. Therefore, the use of 90-day outcome measurements in our analysis might overestimate lifetime costs slightly. This overestimation of costs, however, is likely to be small, and would presumably affect all treatment arms and doses indiscriminately.

Currently, rFVIIa is approved in the US for treatment of bleeding episodes in hemophilia patients with inhibitors. This analysis is based on a single Phase II clinical trial of only 399 ICH patients which was powered to examine the effects of rFVIIa dose on hemorrhage growth. Functional outcome...
(likelihood of improving by 1 mRS level) in the rFVIIa groups were found to be significantly different from outcomes observed by patients on standard care. We realize that large variation of treatment effects may result from small sample sizes. Thus, we attempted to address this variation through extensive sensitivity analyses. An additional limitation of using the trial data are that the model population was restricted to patients with characteristics similar to those defined by the clinical trial. Additional studies with rFVIIa are necessary to further measure the impact of rFVIIa on functional outcome measures. However, this trial provides the only head-to-head and the most robust data available to perform an economic analysis of treatment comparators. On the completion of additional trials using rFVIIa, with more definitive data on safety and efficacy, cost-effectiveness can be re-examined.

Another limitation of this analysis is that caregiver burden, a significant cost in ICH, is not considered in this model. Assuming caregiver burden would be greater (and hence incur higher costs) for patients with higher mRS, sensitivity analyses showed that results would favor treatment with rFVIIa because of increased lifetime costs for patients in the more severe mRS groups, independent of dose. Thus, this analysis may be considered a conservative estimate of the true cost-effectiveness.

With limited healthcare resources, it is important to allocate resources to interventions that are most cost-effective (ie, have the greatest benefit per cost). The fact that this study is a modeling exercise could be stated as a limitation in itself. However, modeling techniques are widely used to calculate cost-effectiveness. These exercises enable decision-makers to examine the effects of a new therapy and its potential impact on costs and quality of life in a cost-efficient manner. Overall, in all cases where assumptions were necessary, we attempted to perform the base analysis with conservative estimates so as not to exaggerate the potential benefits of treatment with rFVIIa and then performed extensive sensitivity analyses. As more data become available, the model assumptions can be further improved.

The clinical outcomes of the double-blind, placebo-controlled trial resulted in improved functional outcome (as measured by mRS) and decreased mortality risk for patients treated with rFVIIa over placebo (ie, current standard of care). In the economic analyses performed by Samsa and colleagues, they found that “even small differences in short-term mortality and morbidity can translate into sizable long-term differences in outcomes,” and that “significant health benefits could be generated by more effective treatments for acute stroke, even if these treatments have a high short-term price.” In this study, the drug costs for treatment with rFVIIa comprise only a small portion of the total direct medical costs associated with ICH treatment.

In conclusion, this study suggests that treatment with rFVIIa within 4 hours of onset of ICH is cost-effective compared with current standard of care. Specifically, treatment with 80 µg/kg of rFVIIa appears to be cost saving. Patients receiving 40 µg/kg or 160 µg/kg doses of rFVIIa incur greater total costs. However, these costs are also associated with an improvement in functional outcome, life expectancy, and QALYs. Therefore, treating with rFVIIa is found to be cost-effective for all 3 dose results. Results of extensive sensitivity analyses support these conclusions.

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References


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