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

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Background

- Intracerebral hemorrhage (ICH) is the deadliest form of stroke[1] resulting in mortality and severe disability among survivors.
- ICH events impose a significant economic burden due to intense medical resource use during acute treatment as well as the cost of long-term management of survivors[2-6].
- Currently, no drug therapies have been proven effective for treatment of acute ICH.
- Recombinant activated factor VII (rFVIIa) is currently indicated for treatment of bleeding episodes and for the prevention of bleeding in surgical interventions/invasive procedures in hemophilia patients with factor VIII inhibitors and patients with congenital FVII deficiency.
- A recent Phase IIb clinical trial showed that administration rFVIIa of within 4 hours of ICH onset reduced mortality and improved 90-day functional outcome compared to standard care[7].

Objective

To determine cost-effectiveness of rFVIIa compared to current standard of care in patients with acute ICH.

Methods

Patient Population

Patients enter the hospital emergency room presenting with acute ICH within 3 hours of symptom-onset. Specific patient characteristics include:

- Age distribution typical of published patient populations with ICH[5,8].
- Characteristics (ICH severity, disease history, time of arrival after onset of ICH event) similar to those observed in the clinical trial[7].
- Patient weight of 75 kilograms.

Study Design

- A decision-analytic model was created to estimate the cost-effectiveness of rFVIIa for acute ICH (Figure 1).
- Model takes a Medicare perspective, since around two-thirds of acute ICH patients in the USA are Medicare beneficiaries[9].
- Patients entering the model receive rFVIIa 40 μg/kg, 80 μg/kg, or 160 μg/kg, or standard care within 4 hours of ICH onset (three dose arms in the Phase IIb trial). Drug costs are based on Medicare average sales prices (ASP)[10].
- Patients are followed for the first 90 days after ICH onset and annually thereafter for the remainder of lifetime.
- Functional status, measured by modified Rankin Score (mRS), is estimated at 90 days after ICH onset based on clinical trial data (Table 1)[7].
- Short-term cost calculations (90 days after ICH onset):
  - Short-term costs and outcomes are based on treatment-related clinical efficacy (Table 1) and length of stay in hospitals (Table 2) as obtained from clinical trial data and costs from an analysis of Medicare claims data (Table 3).
  - Costs include: drug cost, inpatient stay, skilled nursing facility costs, and any additional medical management costs.
- Long-term Annual Calculations:
  - Post-90 day costs and outcomes are estimated annually based on mRS score, using mRS-specific multipliers obtained from published literature (Table 4).
- Utility weights specific to each mRS score are obtained from published literature (Table 4).
- Costs and outcomes are presented in 2005 US $ and discounted at a rate of 3% per annum.

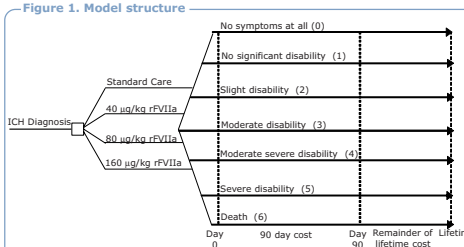
Sensitivity Analysis

- One-way sensitivity analyses were performed on key input parameters.
- Parameters were varied by +/- 20%, or based on plausible range data provided in the literature[11].

Modified Rankin Score (mRS)

mRS 0 = no disability
mRS 1 = no significant disability
mRS 2 = slight disability
mRS 3 = moderate disability
mRS 4 = moderate to severe disability
mRS 5 = severe disability
mRS 6 = death

Figure 1. Model structure



Model Assumptions

- The model assumes a permanent functional status after 90 days based on published literature[6,11].
- Long-term cost multipliers and death hazard ratios are based on ischemic stroke model[11]. The model assumes that long-term costs and outcomes are based on functional status as defined by mRS.

Table 1. Distribution of Patients by Functional Status after 90 Days

Functional Status	Patients in mRS State (%)*			
	Standard Care	rFVIIa 40 μg/kg	rFVIIa 80 μg/kg	rFVIIa 160 μg/kg
mRS 0	2.1	0.0	9.8	7.8
mRS 1	6.3	16.7	10.9	16.5
mRS 2	9.4	13.9	14.1	9.7
mRS 3	13.5	14.8	15.2	11.7
mRS 4	24.0	22.2	23.9	24.3
mRS 5	15.6	14.8	6.5	10.7
mRS 6	29.2	17.6	18.5	19.4

*Distribution of functional status was estimated 90 days after initial onset of ICH. Distribution of functional status was obtained from a phase IIb clinical trial[7]

Table 2. Initial Hospital Length of Stay for Patients by Functional Status

Functional Status	Initial Hospital LOS (days)			
	Standard Care	rFVIIa 40 μg/kg	rFVIIa 80 μg/kg	rFVIIa 160 μg/kg
mRS 0	11.0	12.1	12.1	10.9
mRS 1	14.3	21.7	14.9	16.8
mRS 2	14.3	20.3	13.6	13.9
mRS 3	14.7	17.3	14.3	15.9
mRS 4	18.8	19.5	18.5	20.1
mRS 5	21.2	26.0	12.7	33.3
mRS 6	13.5	12.8	14.4	11.3

Initial hospital length of stay was obtained from a phase IIb clinical trial[7]

Table 3. Short-term Cost Estimates by Treatment Options

Functional Status	Standard Care	rFVIIa 40 μg/kg	rFVIIa 80 μg/kg	rFVIIa 160 μg/kg
mRS 0	$16,138	$17,696	$17,696	$15,997
mRS 1	$20,812	$31,294	$21,662	$24,354
mRS 2	$20,812	$29,311	$19,821	$20,246
mRS 3	$21,739	$25,062	$20,812	$23,079
mRS 4	$39,219	$40,092	$38,845	$40,841
mRS 5	$42,213	$48,201	$31,610	$57,307
mRS 6	$57,186	$54,221	$60,999	$47,887

Costs were estimated based on initial hospital length-of-stay and costs of initial hospitalization as estimated from a Medicare claims data analysis[9]. Additionally, patients in mRS 4-5 were assumed to transition to a skilled nursing facility (SNF) after hospital discharge. The daily SNF costs were obtained from the MetLife market survey[12]

Table 4. Long-term Costs and Outcomes

Functional Status	Long-term Annual Medical Costs	Long-term Cost Multipliers[11]	Long-term Mortality Hazard[11]	Utility Values[13]
mRS 0	$5,609	1.00	1.00	0.85
mRS 1	$5,609	1.00	1.00	0.85
mRS 2	$7,123	1.27	1.11	0.85
mRS 3	$10,881	1.94	1.27	0.51
mRS 4	$22,324	3.98	1.71	0.15
mRS 5	$33,710	6.01	2.37	0.15
mRS 6	$0	0.00	0.00	0.00

Long-term annual costs estimated from a Medicare claims data analysis[9]. Costs for patients with no or minimal disability (mRS 0-1) were estimated, and then cost multipliers[11] were applied to estimate the annual costs for patients in each mRS state. Note: these costs and outcomes are based on functional status (mRS score) after 90-days from ICH onset, and are thus irrespective of treatment arm.

Results

- Expected lifetime costs per ICH patient were calculated for each treatment arm (Figure 2). Treatment with 160 μg/kg rFVIIa resulted in the highest cost, while treatment with 80 μg/kg rFVIIa resulted in the lowest cost (Figure 2).
- Cost of rFVIIa is low relative to total expected medical costs (Figure 2).
- Expected lifetime outcomes were higher for all treatment groups compared to patients who did not receive rFVIIa (Figure 3).
- Results are robust to realistic parameter variation (Table 5).

Figure 2. Expected Lifetime Costs per ICH Patient by Treatment

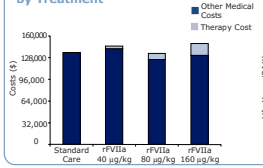


Figure 3. Expected Lifetime Outcomes per ICH Patient by Treatment

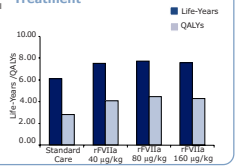


Table 5. One-way Sensitivity Analysis: Effect of Parameter Variation on the Incremental Cost per QALY for rFVIIa Compared to Standard Care

Model Parameter	rFVIIa 40 μg/kg vs Standard Care	rFVIIa 80 μg/kg vs Standard Care	rFVIIa 160 μg/kg vs Standard Care
Base-Case Analysis			
ICER ($/QALY)	$5,769	Dominant	$8,780
Sensitivity Analysis			
Cost Multiplier			
Lower Bound	$7,038	$2,579	$13,148
Baseline	$5,769	Dominant	$8,780
Upper Bound	$4,446	Dominant	$4,528
Death Hazard Ratio			
Lower Bound	$4,752	Dominant	$5,735
Baseline	$5,769	Dominant	$8,780
Upper Bound	$6,359	$381	$11,350
Clinical Efficacy 40 μg/kg			
Lower Bound	$17,585	--	--
Baseline	$5,769	--	--
Upper Bound	Dominant	--	--
Clinical Efficacy 80 μg/kg			
Lower Bound	--	$3,094	--
Baseline	--	Dominant	--
Upper Bound	--	Dominant	--
Clinical Efficacy 160 μg/kg			
Lower Bound	--	--	$20,748
Baseline	--	--	$8,780
Upper Bound	--	--	$2,022

The table illustrates the effect on the incremental cost-effectiveness ratio (ICER)($/QALY) comparing rFVIIa 40 μg/kg, 80 μg/kg, and 160 μg/kg to standard care when input parameter values are varied. Baseline ICER for rFVIIa 40 μg/kg, 80 μg/kg, and 160 μg/kg are $5,769, -$3,510, and $8,780, respectively. Lower bound for the input parameter is an actual lower bound or 20% decrease in the input parameter. Upper bound is an actual upper bound or 20% increase in the input value. Dominant means that the comparator (rFVIIa) is both more effective and less expensive than standard care.

Conclusions

- Treatment with rFVIIa 40 μg/kg and 160 μg/kg are cost-effective compared to standard care at the generally acceptable cost-effectiveness threshold of $50,000/QALY.
- Treatment with rFVIIa 80 μg/kg is not only cost-effective but is cost-saving compared to the current standard of care.

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