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Cost-Effectiveness of Intravenous Thrombolysis With Alteplase Within a 3-Hour Window After Acute Ischemic Stroke

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Background and Purpose—The aim of this study was to assess the costs and cost-effectiveness of intravenous thrombolysis treatment with alteplase (Actilyse) of acute ischemic stroke with 24-hour in-house neurology coverage and use of magnetic resonance imaging.

Methods—A health economic model was designed to calculate the marginal cost-effectiveness ratios for time spans of 1, 2, 3 and 30 years. Effect data were extracted from a meta-analysis of six large-scale randomized and placebo-controlled studies of thrombolytic therapy with alteplase. Cost data were extracted from thrombolysis treatment at Aarhus Hospital, Denmark, and from previously published literature.

Results—The calculated cost-effectiveness ratio after the first year was $55 591 US per quality-adjusted life-year (base case). After the second year, computation of the cost-effectiveness ratio showed that thrombolysis was cost-effective. The long-term computations (30 years) showed that thrombolysis was a dominant strategy compared with conservative treatment given the model premises.

Conclusions—A high-quality thrombolysis treatment with 24-hour in-house neurology coverage and magnetic resonance imaging might not be cost-effective in the short term compared with conservative treatment. In the long term, there are potentially large-scale health economic cost savings. **(*Stroke*. 2007;38:85-89.)**

Key Words: acute care ■ economics ■ health policy ■ stroke ■ thrombolysis

A number of basic cardiovascular diseases may trigger a stroke, which in 85% of the cases will include cerebral thromboembolism and in the remaining cases cerebral hemorrhage. Treatment of acute ischemic stroke with intravenous thrombolysis was approved in the United States in 1996 and shortly after in Canada and Germany. In Denmark, intravenous thrombolysis treatment (rt-PA) of selected patients with stroke is now recommended if treatment can be started within 3 hours after symptom onset.[1] The incidence of a first stroke is two per 1000 individuals, corresponding to approximately 12 000 annual cases in Denmark. To this should be added recurrence of stroke in approximately 25% of all stroke cases corresponding to approximately 4000 recurrent strokes per year.[1]

International health economic studies of intravenous thrombolysis treatment for acute ischemic stroke indicate that the intervention might be cost-effective in the short term and in the long term.[2–9] In all these studies patients, are assumed to receive the standard computed tomography-based approach to treatment.

There is no evidence of an improved quality-adjusted life-year outcome in thrombolysis-treated patients by MRI selection, but MRI imaging could help identify patients who could benefit from treatment and an MRI-based selection approach is safe and effective within the rigid 3-hour time window.[10] This health economic analysis is designed to assess the cost-effectiveness of implementing high-quality thrombolysis treatment with rt-PA (Actilyse) with 24-hour in-house neurology coverage and prompt and frequent MRI imaging.

Method

A health economic model was created replicating previous international cost-utility analyses.[2–6] The model is designed in the program TreeAge Pro Health Care Module as a decision tree with Markow modeling of the long-term consequences.[11,12]

The model assumes that the patient can receive either thrombolysis or conservative treatment (see Figure). Depending on the treatment instituted, the patient is exposed to a risk of intracranial hemorrhage of 5.9% on thrombolysis and 1.1% on conservative treatment.[13] The assumptions about the clinical effectiveness of thrombolysis treatment with rt-PA within 3 hours after symptom onset were derived from a meta-analysis of six large randomized, placebo-controlled studies,[13] which demonstrated the importance of time from symptom onset to start of intravenous thrombolysis with rt-PA for the time window 0 to 90 minutes and 91 to 180 minutes (see Table 1).

The patients could undergo transition between seven poststroke disability states in the model according to functional outcome after 3 months based on a modified Rankin Scale[14]: no symptoms (R0), no significant disability (R1), minimal disability (R2), moderate disability

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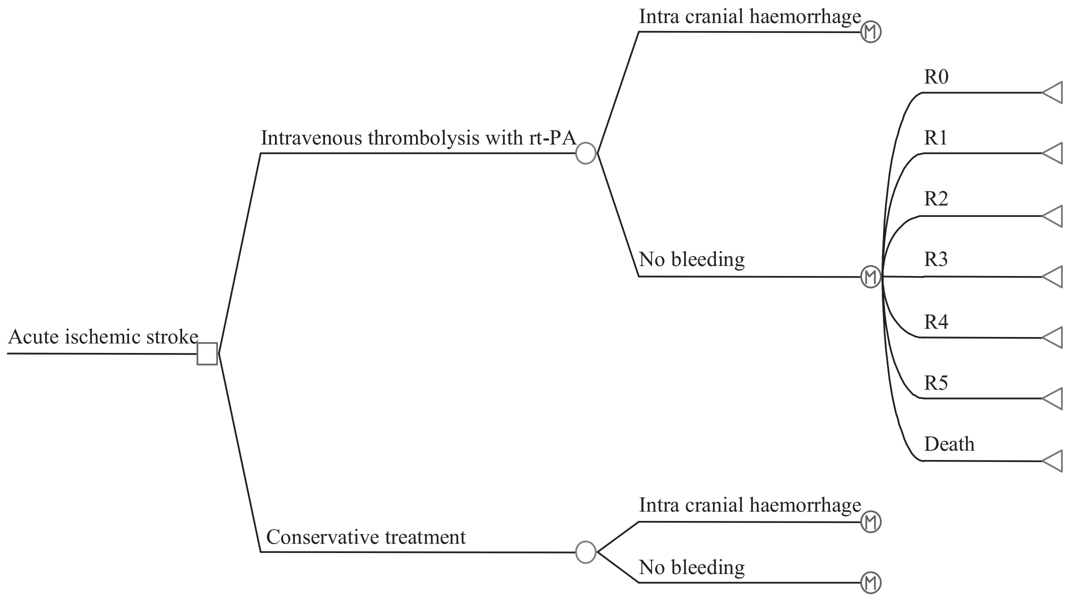

Markov decision analytic model for intravenous thrombolysis with rt-PA.

(R3), moderate to severe disability (R4), severe disability (R5), and dead.

After index hospitalization, the patients are assumed to be discharged to their own home, to rehabilitation, or to a nursing home. We used data on hospital discharge location for stroke patients from the County of Aarhus deploying the inclusion and exclusion criteria for receiving thrombolysis treatment on the basis of the data from the Danish Stroke Register for a full year for the period April 1, 2004, to March 31, 2005.[15] To allow for the possibility that thrombolysis treatment reduces the likelihood of discharge to nursing home and rehabilitation facilities, we assumed the same drop in discharge to rehabilitation and nursing homes after thrombolysis as obtained in other countries.[2,3,16]

After discharge, the patients may have a risk of another stroke and to be readmitted to the hospital. Death (by stroke or other causes) is the only absorbing stage, after which the patient is excluded from the model. We used epidemiologic data for 2005 from the Statistics Denmark's database death register.[17] All patients were assumed to be 68 years of age at the time of the index stroke. The overall death rate after the first year was assumed to exceed that of the average population approximately 2.5 times.[6] The number of patients who died from all causes was calculated by multiplying 2.5 times the age-specific mortality rate specified in the mortality tables. The risk of recurrence was assumed to be 5.2% per year.[1,3,16,18] For survival after first year and recurrence, we assumed an equal rate in all patients.

To adjust life years gained by the survivors after a stroke, each health state (Rankin category) was assigned a utility value. In the absence of Danish preference data within this field, we used American quality-of-life assumptions previously used in American and Canadian health economic studies.[2,3,19] The number of gained quality-adjusted life-years was calculated as gained life years in each Rankin category multiplied by the allotted utility value for each category assuming that the effect of treatment after 3 months is stabile.[13]

Thrombolysis cost data were extracted from implementing high-quality thrombolysis treatment with 24-hour in-house MRI imaging and neurology coverage at the Aarhus Hospital. The calculations in Table 2 were performed in collaboration with The Planning Department and Department of Neurology at the Aarhus Hospital.[18,20,21] The cost calculations are based on the assumption that employment of extra health professionals was needed to supply thrombolysis

TABLE 1. Modified Rankin Scale Measured 90 Days After Treatment For Acute Ischemic Stroke

	(Base case) Total Modified Rankin Scale 0 to 180 minutes						
	0	1	2	3	4	5	Death
Placebo (n=465)	0.13	0.16	0.11	0.14	0.20	0.07	0.18
Thrombolysis (n=463)	0.20	0.22	0.08	0.14	0.12	0.07	0.18
	(Best case) Modified Rankin Scale 0 to 90 minutes						
	0	1	2	3	4	5	Death
Placebo (n=150)	0.10	0.19	0.13	0.12	0.21	0.05	0.21
Thrombolysis (n=161)	0.22	0.19	0.08	0.14	0.13	0.05	0.19
	(Worst case) Modified Rankin Scale 91 to 180 minutes						
	0	1	2	3	4	5	Death
Placebo (n=315)	0.16	0.14	0.10	0.17	0.20	0.09	0.16
Thrombolysis (n=302)	0.18	0.25	0.07	0.14	0.11	0.08	0.17

Source: Reproduced from ATLANTIS, ECASS, and NINDS rt-PA Study Group Investigators.[9]

TABLE 2. Direct Costs in US Dollars by Hospital on Thrombolysis Treatment (difference compared with conservative treatment calculated as average per patient on 100 patients per year)

Type of Resource	Assumptions About Changed Quantities of Resources (average per patient)	Unit Cost	Change Worst Case	Change Expected	Change Best Case	Basis for Assumptions About Changed Quantities of Resources
Change in treatment costs per patient (average)						
Hospitalization	Length of stay 1.5 days shorter	−408	0	−612	−1223	[11, 15, 16]
Costs of rt-PA	70 mg Actilyse	18	1795	1257	898	[9, 17]
Extra consultant time	4 hours extra	58	289	231	115	Data from Dept. Of Neurology, Aarhus Hospital
Extra nursing time	8 hours extra	29	261	232	116	Data from Dept. Of Neurology, Aarhus Hospital
Extra MRI scanning (80% have full MRI on admission and MRI on control after 24 hours)	1.6 scanning	805	1417	1288	1159	[17]
Saving in computed tomography scanning on admission	0.8 scanning	150	0	−120	−120	[17]
Extra minutes of sick transportation attributable to centralized thrombolysis treatment (average)	Approximately 13 minutes extra per rt-PA	4	65	52	39	Data from Falck and Dept. of Health Services, The County of Aarhus
Other (medicine, blood test, electrocardiogram)	...	...	355	284	213	[16]
Implementation costs on introduction of treatment modalities at Aarhus Hospital						
Training of personnel (ambulance, emergency room, and so on)	...	...	49	39	29	Data from Dept. of Neurology, Aarhus Hospital
Approx. 200 patients who will not receive rt-PA are transported to the Aarhus Hospital for diagnosis instead of to a local hospital	2 extra sick transportations per rt-PA	52	130	104	78	[16]
Approximately 200 patients are diagnosed on MRI compared with normal diagnosis by computed tomography	1.6 scanning	654	1309	1047	785	[16, 17]
New duty schedule at Department of Neurology	...	...	2682	2145	1609	[16]
Extra need for admission rooms	...	...	39	31	23	Data from The Planning Dept., Aarhus Hospital
Extra duty at Department of Neuroradiology?	...	...	413	0	0	[16]
Need for new MRI scanner? (discounting and annuitization of capital expenditures)	...	...	4448	0	0	Data from The Planning Dept., Aarhus Hospital
Need for more beds?	...	...	1219	0	0	[16]
Cost increase compared with conservative treatment			14 469	5978	3722	

treatment on a 24-hour basis (new duty schedule at the Department of Neurology). The patients are transferred directly to the Department of Neurology, where a neurologist will meet the patient. MRI scanning is used as the primary tool for the diagnosis of patients for thrombolysis treatment.[18] On full implementation of thrombolysis treatment at the Aarhus Hospital, it is expected that approximately 300 patients annually will reach the hospital within 3 hours, and approximately one-third are expected to qualify for thrombolysis. This amounts to 6% to 9% of all patients with stroke in the county. To improve the generalizability of the study, we calculate costs and cost-effectiveness ratio (ICER) for three different scenarios (50, 100, and 150 rt-PA patients annually).

The costs of conservative treatment as well as the costs after hospitalization incurred in the years after stroke were extracted from

TABLE 3. Incremental Cost-Effectiveness Ratio*

	Costs (US $)				Quality-Adjusted Life-Years		ICER (US $ per quality-adjusted life-year)		
Time horizon	(A)	(B)	(C)	Cons.	rt-PA	Cons.	(A)	(B)	(C)
Expected value (first year)	29 079	26 934	26 219	23 599	0.44	0.38	91 342	55 591	43 669
Expected value (second year)	37 635	35 480	34 775	35 047	0.83	0.71	21 570	3615	Dominance
Expected value (third year)	45 373	43 229	42 513	45 322	1.17	1.01	323	Dominance	Dominance
Expected value (30 years)	97 922	95 776	95 061	112 337	3.07	2.64	Dominance	Dominance	Dominance

*(A) indicates rt-PA treatment with 50 patients per year; (B), rt-PA treatment with 100 patients per year (base case); (C), rt-PA treatment with 150 patients per year; Cons., conservative treatment.

of the Danish European Stroke Database, which contains data on all variable and fixed costs for a total of 588 patients at Hvidovre Hospital with a mean follow up of 1 year.[22] Danish European Stroke Database includes all costs of hospital care, including complications and rehospitalizations, community care, patient and family out-of-pocket expenses, and resources in other sectors summed up for patients in the three categories: patients referred to own home, patients referred to rehabilitation, or patients referred to a nursing home. In the model, we assumed that the costs of resources in other sectors such as social worker and help visits were constant after the first year after index stoke, whereas costs of hospital care and community care (outpatient attendances, general practitioner visits, and so on) drop to one-third after the first year.[22]

Incremental (marginal) cost-effect ratios were calculated as the additional costs on thrombolysis treatment per quality-adjusted life-years gained with a time horizon of 1, 2, 3, and 30 years. This variation in time horizon was chosen because it is customarily expected that thrombolysis causes hospital costs to rise in the short term but that it will entail savings in other health and social costs in the long run (savings in rehabilitation, nursing home, and so on). We accounted for the longer time horizon over which costs and health benefits may accrue by discounting outcomes and costs at an annual rate of 5%. All cost estimates are expressed in 2004 US dollars. It was assumed that the loss of utility attributable to the inability to work has been captured as a loss of quality-adjusted life-years. To count the lost earnings to the society in the numerator of the ICER would be double-counting.[23]

The robustness of the calculations was examined by means of one-way sensitivity analyses for all parameters in the model (parameter uncertainty). The long-term effect was also subjected to Monte Carlo microsimulation (multiway sensitivity analysis) to elucidate both parameter uncertainty and stochastic uncertainty (reflecting that the treated individuals were different). The hypothetical individuals were simulated through 30 Markow cycles (years) implying that almost all of the individuals would be dead at the termination of the analysis. In each simulation, all parameters were allowed to vary randomly from the defined probability distribution for each parameter. A total of 10 000 hypothetical individuals was send through the model—each time calculating costs and health outcomes for both alternatives thus giving an estimate of the robustness of the ICER. A survival curve is available in the online version.

Results

Table 2 features the direct costs of thrombolysis treatment calculated as an average per patient for 100 patients admitted annually to the Aarhus Hospital. The direct costs on the first hospitalization for thrombolytic therapy is calculated as the difference between this cost and the cost of an average conservative hospitalization course. Conservative treatment is estimated at $6271 US per patient.

Table 3 shows ICER calculated for 1, 2, 3, and 30 years. Table 3 shows that short-term thrombolysis (first year) increases health economic costs, but the picture changes after 2 years, when, given the assumptions about effect and costs, thrombolysis becomes cost-effective.

In the long term (30 years), intravenous thrombolysis treatment with rt-PA is the dominant strategy compared with conservative treatment.

Sensitivity Analysis

Table 2 shows that the short-term cost of thrombolysis can vary much as a result of local circumstances and implementation cost. Also, short-term cost-effectiveness could be sensitive to seasonality and fluctuations in patient's age, morbidity, and survival function. If the risk of intracranial hemorrhage were equal on thrombolysis or conservative treatment, the expected value (first year) of the ICER drops from $55 591 to $46 243 US per quality-adjusted life-year. None of the one-way sensitivity analyses changed the sign of the ICER at the 1-year level or the 30-year level.

Table 4 shows the result of the Monte Carlo simulation. It can be seen from Table 4 that the long-term results of the ICER are imprecise. The main reason for the large span of costs and quality-adjusted life-years is the difference in the number of years the patient lives after index stroke. It should be noted, however, that we assumed a flat distribution between minimum and maximum values for long-term costs thus giving extreme values more weight. Other distributions such as γ or normal distributions would give a narrower span of costs. In this case, the long-term estimates are based on extrapolation of data with a mean follow up of 1 year,[22] and we believe a flat distribution gives a realistic estimate of the

TABLE 4. Monte Carlo Simulation, 10 000 Iterations, 30 Cycles (years)

	Costs (US $)		Quality-Adjusted Life-Years	
	rt-PA	Cons.	rt-PA	Cons.
Base case (expected value)	95 776	112 337	3.07	2.64
Average	95 619	110 110	3.12	2.66
Minimum value	12 350	6403	−0.32	−0.32
2.5% percentile	12 350	6403	−0.14	−0.15
Median	68 283	75 641	2.28	1.89
97.5% percentile	340 965	405 125	2.28	1.89
Maximum value	531 640	517 111	14.18	14.18

Cons. indicates conservative treatment.

long-term uncertainty. Also, we allowed quality-adjusted life-years to be negative.[19]

Discussion

The additional costs of thrombolysis during the first hospitalization amount to approximately $5978 US per patient, which means that thrombolysis is approximately twice as expensive as the conventional treatment. This is much higher than reported in earlier studies.[2–8] The main explanation is the assumption of MRI imaging and a 24-hour medical service at the Department of Neurology and Department of Neuroradiology.

The short-term ICER (1 year) was calculated to $55 591 US per quality-adjusted life-year gained (see Table 3). Although an exact threshold value for the cost per quality-adjusted life-year does not exist, the calculated short-term ICER exceeds the generally accepted view of the willingness to pay per quality-adjusted life-year in the Danish Hospital sector.[24,25] This indicates that thrombolysis might not be cost-effective in the short term.

In can be argued that implementing a 24-hour neurology coverage does not, strictly speaking, belong only to rt-PA, but rather to all acute therapies for both ischemic and hemorrhagic stroke.[9] Thus, establishing new and costly duty schedules opens up for other acute treatments and only a fraction of the increased personnel costs will likely be used for thrombolysis. If, however, such arrangements are implemented, it should be calculated as a part of the costs of thrombolysis treatment and it will affect both the costs and cost-effectiveness of thrombolysis. Furthermore, because health professionals are a scarce resource in Denmark (and the supply curve for neurologists can be quite inelastic), the value to society of their work should perhaps be estimated higher than reflected by wage estimates.[23] This could mean that short-term costs of thrombolysis shown in Table 2 should be even higher.

The long-term ICER shows (Table 3) that large-scale health economic savings may be obtained in the long term. Thus, if the long-term model premises hold true, higher costs of implementing high-quality rt-PA treatment do not affect the overall long-term economic advantages of thrombolysis.

However, the modeling of the long-term cost-effect ratio is subject to both uncertainty and methodological problems.[6] For a discussion of the use of discounting and quality-adjusted life-years in health economic analysis, see reference 23. The lack of adequate long-term data in important areas therefore weakens the strength of the present study and, accordingly, the robustness with which long-term recommendations can be made. Economic studies of the long-term consequences of thrombolysis (including better evidence of the savings on rehabilitation and nursing homes) should be performed.

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Disclosures

None.

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