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

Lars Ehlers, PhD, MSc (econ); Grethe Andersen, DMSc, PhD, MD; Lone Beltoft Clausen, MSc; Merete Bech, MSc; Mette Kjølby, PhD, DDS

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 Scale14: no symptoms (R0), no significant disability (R1), minimal disability (R2), moderate disability

Received March 13, 2006; final revision received September 11, 2006; accepted September 12, 2006.

From the HTA Unit (L.E., M.B., M.K.), Aarhus University Hospital, Aarhus, Denmark; the Department of Neurology (G.A.) and the Planning Department (L.B.C.), Aarhus Hospital, Aarhus, Denmark.

Correspondence to Lars Ehlers, PhD, HTA Unit, Aarhus University Hospital, Olof Palmes Allé 17, 8200 Aarhus N, Denmark. E-mail: le@ag.aaa.dk

© 2006 American Heart Association, Inc.

Stroke is available at http://www.strokeaha.org

DOI: 10.1161/01.STR.0000251790.19419.a8

85
After index hospitalization, the patients are assumed to be discharged to their own home, 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. 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.

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. 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. 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. 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. 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 stable.

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. 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

<table>
<thead>
<tr>
<th>(Base case) Total Modified Rankin Scale 0 to 180 minutes</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=465)</td>
<td>0.13</td>
<td>0.16</td>
<td>0.11</td>
<td>0.14</td>
<td>0.20</td>
<td>0.07</td>
<td>0.18</td>
</tr>
<tr>
<td>Thrombolysis (n=463)</td>
<td>0.20</td>
<td>0.22</td>
<td>0.08</td>
<td>0.14</td>
<td>0.12</td>
<td>0.07</td>
<td>0.18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(Best case) Modified Rankin Scale 0 to 90 minutes</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=150)</td>
<td>0.10</td>
<td>0.19</td>
<td>0.13</td>
<td>0.12</td>
<td>0.21</td>
<td>0.05</td>
<td>0.21</td>
</tr>
<tr>
<td>Thrombolysis (n=161)</td>
<td>0.22</td>
<td>0.19</td>
<td>0.08</td>
<td>0.14</td>
<td>0.13</td>
<td>0.05</td>
<td>0.19</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(Worst case) Modified Rankin Scale 91 to 180 minutes</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=315)</td>
<td>0.16</td>
<td>0.14</td>
<td>0.10</td>
<td>0.17</td>
<td>0.20</td>
<td>0.09</td>
<td>0.16</td>
</tr>
<tr>
<td>Thrombolysis (n=302)</td>
<td>0.18</td>
<td>0.25</td>
<td>0.07</td>
<td>0.14</td>
<td>0.11</td>
<td>0.08</td>
<td>0.17</td>
</tr>
</tbody>
</table>

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

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)

<table>
<thead>
<tr>
<th>Type of Resource</th>
<th>Assumptions About Changed Quantities of Resources (average per patient)</th>
<th>Unit</th>
<th>Change Worst Case</th>
<th>Change Expected</th>
<th>Change Best Case</th>
<th>Basis for Assumptions About Changed Quantities of Resources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in treatment costs per patient (average)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>Length of stay 1.5 days shorter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[11, 15, 16]</td>
</tr>
<tr>
<td>Costs of rt-PA</td>
<td>70 mg Actilyse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[9, 17]</td>
</tr>
<tr>
<td>Extra consultant time</td>
<td>4 hours extra</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Data from Dept. Of Neurology, Aarhus Hospital</td>
</tr>
<tr>
<td>Extra nursing time</td>
<td>8 hours extra</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Data from Dept. Of Neurology, Aarhus Hospital</td>
</tr>
<tr>
<td>Extra MRI scanning (80% have full MRI on admission and MRI on control after 24 hours)</td>
<td>1.6 scanning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[17]</td>
</tr>
<tr>
<td>Saving in computed tomography scanning on admission</td>
<td>0.8 scanning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[17]</td>
</tr>
<tr>
<td>Extra minutes of sick transportation attributable to centralized thrombolysis treatment (average)</td>
<td>Approximately 13 minutes extra per rt-PA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Data from Falck and Dept. of Health Services, The County of Aarhus</td>
</tr>
<tr>
<td>Other (medicine, blood test, electrocardiogram)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[16]</td>
</tr>
<tr>
<td>Implementation costs on introduction of treatment modalities at Aarhus Hospital</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Training of personnel (ambulance, emergency room, and so on)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Data from Dept. Of Neurology, Aarhus Hospital</td>
</tr>
<tr>
<td>Approx. 200 patients who will not receive rt-PA are transported to the Aarhus Hospital for diagnosis instead of to a local hospital</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[16]</td>
</tr>
<tr>
<td>Approximately 200 patients are diagnosed on MRI compared with normal diagnosis by computed tomography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[16, 17]</td>
</tr>
<tr>
<td>New duty schedule at Department of Neurology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[16]</td>
</tr>
<tr>
<td>Extra need for admission rooms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Data from The Planning Dept., Aarhus Hospital</td>
</tr>
<tr>
<td>Extra duty at Department of Neuroradiology?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[16]</td>
</tr>
<tr>
<td>Need for new MRI scanner? (discounting and annuitization of capital expenditures)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Data from The Planning Dept., Aarhus Hospital</td>
</tr>
<tr>
<td>Need for more beds?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[16]</td>
</tr>
<tr>
<td>Cost increase compared with conservative treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ehlers et al Cost-Effectiveness of rt-PA 87
economic costs, but the picture changes after 2 years, when, given
3 shows that short-term thrombolysis (first year) increases health
Table 2 features the direct costs of thrombolysis treatment calcu-
expected value (first year) of the ICER drops
The assumptions about effect and costs, thrombolysis becomes
cost-effective.
In the long term (30 years), intravenous thrombolysis treat-
ment with rt-PA is the dominant strategy compared with con-
servative treatment.
Sensitivity Analysis
Table 2 shows that the short-term cost of thrombolysis can vary
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>
<thead>
<tr>
<th>Time horizon</th>
<th>Costs (US $)</th>
<th>Quality-Adjusted Life-Years</th>
<th>ICER (US $ per quality-adjusted life-year)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(A)</td>
<td>(B)</td>
<td>(C)</td>
</tr>
<tr>
<td>Expected value (first year)</td>
<td>29,079</td>
<td>26,934</td>
<td>26,219</td>
</tr>
<tr>
<td>Expected value (second year)</td>
<td>37,635</td>
<td>35,480</td>
<td>34,775</td>
</tr>
<tr>
<td>Expected value (third year)</td>
<td>45,373</td>
<td>43,229</td>
<td>42,513</td>
</tr>
<tr>
<td>Expected value (30 years)</td>
<td>97,922</td>
<td>95,776</td>
<td>95,061</td>
</tr>
</tbody>
</table>

* (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.

Results
Table 2 features the direct costs of thrombolysis treatment calcu-
lated 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
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. 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.

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. 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 likely be used for thrombolysis. If, however, such arrangements are

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. For a discussion of the use of discounting and quality-adjusted life-years in health economic analysis, see reference 23. This could mean that short-term costs of thrombolysis shown in Table 2 should be even higher.

Acknowledgments
The authors thank Vibeke Porsdal, PhD, clinical research physician, Ei Lilly Demark A/S, Jakob Hjort, data manager, The Department of Public Health, The County of Aarhus, and Anne Brucker, managing clerk, the Health Technology Assessment Unit, The County of Aarhus.

Disclosures
None.

References
20. The Planning Department. Analysis of Operating Economy—Concerning HTA of Thrombolysis in Patients With Acute Ischemic Stroke [in Danish]. Aarhus: HTA Unit, Aarhus University Hospital, Department of Public Health, The County of Aarhus, Denmark, 2005.
Cost-Effectiveness of Intravenous Thrombolysis With Alteplase Within a 3-Hour Window After Acute Ischemic Stroke
Lars Ehlers, Grethe Andersen, Lone Beltoft Clausen, Merete Bech and Mette Kjølby

Stroke. 2007;38:85-89; originally published online November 22, 2006;
doi: 10.1161/01.STR.0000251790.19419.a8
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/38/1/85

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/