Effects of Extending the Time Window of Thrombolysis to 4.5 Hours
Observations in the Swedish Stroke Register (Riks-Stroke)

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Background and Purpose—The European Cooperative Acute Stroke Study (ECASS) III trial and Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register (SITS-ISTR) data were published in 2008. Riks-Stroke, the Swedish Stroke Register, was used to explore how thrombolysis in the 3- to 4.5-hour window has been spread in different hospitals and patient groups and what effects this has had on treatment within 3 hours.

Methods—All 76 hospitals in Sweden admitting patients with acute stroke participate in Riks-Stroke. During the study period, January 2003 to June 2010, 92 150 18- to 80-year-old patients were hospitalized for acute ischemic stroke.

Results—After the publication of the ECASS III results in the third quarter of 2008, thrombolysis in the 3- to 4.5-hour window increased from 0.5% before publication to 2.1% in 2010. Thrombolysis in the 3- to 4.5-hour window spread somewhat faster in men than women (P=0.04) but at a similar rate in different age groups. The use of thrombolysis within 3 hours after onset of symptoms increased successively from 0.9% in 2003 to 6.6% in late 2008 and then it stabilized at 6%. The median time from arrival to the hospital to start of treatment remained unchanged at 66 to 69 minutes before and after 2008 (P=0.06).

Conclusions—Since the end of 2008, there has been a rapid nationwide dissemination of thrombolysis in the 3- to 4.5-hour window, whereas rates in the <3-hour window have leveled off. The extended time window has not affected door-to-needle time. (Stroke. 2011;42:2492-2497.)

Key Words: acute ischemic stroke ■ delay of treatment ■ implementation ■ rtPA ■ thrombolysis

Although thrombolysis has been amply shown to have a beneficial benefit-to-risk ratio as treatment for acute ischemic stroke, its large-scale dissemination in routine clinical practice has usually been slow. In the United States and most west European countries, the proportion of patients with ischemic stroke receiving thrombolytic treatment has been reported to be 1% to 7%, although higher percentages have been reported among patients treated in stroke units in Austria and Helsinki.

Up to 2008, time restrictions hampered the implementation of thrombolysis, because the scientific documentation was very limited for thrombolysis performed later than 3 hours after onset of stroke symptoms. The European Cooperative Acute Stroke Study (ECASS) III trial assessed the efficacy and safety of intravenous recombinant tissue-type plasminogen activator (rtPA) administered between 3 and 4.5 hours after the onset of acute ischemic stroke and found that it significantly improved clinical outcomes with an acceptable benefit-to-risk ratio. In addition, the observational Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register (SITS-ISTR) study concluded that rtPA remained safe when given at 3 to 4.5 hours after ischemic stroke. A meta-analysis confirmed the efficacy and safety of thrombolysis performed in the 3- to 4.5-hour interval after stroke and so did the second pooled analysis.

When the ECASS III trial and SITS-ISTR results became publicly available in September 2008, the proportion of patients with ischemic stroke that were eligible for thrombolytic treatment increased, and it was anticipated that there would be a significant increase in the number of patients who would receive the treatment. In an updated analysis of SITS-ISTR, it was observed that the proportion of patients treated in the 3- to 4.5-hour interval increased 3-fold within 1 year after publication of the ECASS III and SITS-ISTR results. Admission-to-treatment time did not increase. After publication of the key studies in September 2008, there was an early rise not only of patients treated in the 3- to 4.5-hour interval, but also a rise in patients treated in the 0- to 3-hour interval. Similar increases were also observed in a study including 2 French hospitals.

We have previously reported how thrombolytic treatment for acute ischemic stroke in Sweden was slowly disseminated...
across the country to reach 6.6% in 2008.\textsuperscript{11} In February 2009, updated national stroke guidelines recommended, with a high priority level, rtPA treatment in the 3- to 4.5-hour window.\textsuperscript{12} Riks-Stroke, the Swedish Stroke Register, covers all hospitals in the country and permits monitoring of the nationwide implementation of new methods in stroke care. We describe and analyze, in a national perspective, how thrombolysis in the 3- to 4.5-hour interval has been applied in different patient groups and in various types of hospitals. We also tested the hypotheses that the extended time window affects door-to-needle time and the proportion of patients with stroke receiving thrombolytic treatment at 0 to 3 hours.

Patients and Methods

Patients presenting with ischemic stroke between January 1, 2003, and June 30, 2010, who were recorded in the Swedish Stroke Register (Riks-Stroke) before October 20, 2010, and were 18 to 80 years old were included in the study. The primary aim of this national register is to monitor and support improvement of quality of stroke care in Sweden. Riks-Stroke, established in 1994, covers all hospitals in the country that admit patients with acute stroke (76 hospitals in 2009). It is funded by a grant from The National Board of Health and Welfare and The Swedish Association of Local Authorities and Regions. Riks-Stroke has been approved by the Regional Ethical Review Board at Umeå University and the data-handling procedures have been approved by the National Computer Data Inspection Board.

The proportion of patients recorded in Riks-Stroke of all patients discharged from a hospital with a diagnosis of acute stroke was 85% in 2009; because acute stroke is overdiagnosed in routine administrative registers, the actual coverage of the register is probably higher. Details on what information is collected are available at the Riks-Stroke Web site (www.riks-stroke.org).

Variable Definitions

In this study, thrombolysis was defined as rtPA administration and did not include thrombectomy or other catheter-based (endovascular) treatments for stroke.

Delay to treatment (onset-to-needle time) was defined as minutes from onset of symptoms (or last time known without stroke symptoms) if time of onset was unknown until start of thrombolytic treatment. Door-to-needle time was defined as minutes from hospital arrival until time of thrombolytic treatment.

Hospitals admitting patients with acute stroke were categorized as university hospitals (n=9; mean number of patients reported to Riks-Stroke in 2009, 580; range, 328 to 775), specialized nonuniversity hospitals (n=22; mean, 500 patients; range, 255 to 1234), and community hospitals (n=45; mean, 197 patients; range, 38 to 453). The delineation between specialized nonuniversity and community hospitals was based on their degree of specialization; community hospitals had only basic inpatient specialties and lacked advanced diagnostic and interventional technology.

Statistical Analyses

Basic characteristics were presented by means or proportions with 95% CIs for patients not treated with rtPA, treated within 3 hours, or treated between 3 and 4.5 hours. A $\chi^2$ test was used for comparisons of proportion of patients treated during the third quarter (Quartile [Q] 3) 2007 to Q3 2008 versus Q4 2008 to Q4 2009. The Breslow-Day statistic was used to test if the implementation rate between Q3 2007 to Q3 2008 versus Q4 2008 to Q4 2009 was homogenous across subgroups of patients.

Log-linear joinpoint regression\textsuperscript{13} was used for identification of changes in thrombolytic treatment trends (joinpoints). The dependent variable, proportion treated with thrombolysis, was calculated for each quarter of the year and assumed to have a nonconstant variance. The model allowed up to 4 joinpoints, not closer than 2 quarters apart or 2 quarters from beginning or end of the study. The estimated annual trends (%) are presented with 95% CIs.

| Table 1. Basic Characteristics (95% CIs) of 18- to 80-Year-Old Patients With Acute Ischemic Stroke Not Treated With rtPA, Treated With rtPA Within 3 Hours, or Treated Within 3 to 4.5 Hours* |
|-----------------|-----------------|-----------------|
| Variable        | No rtPA         | 0 to 3 H        | 3 to 4.5 H      |
| Mean age, y     | 69.0 (69.0–69.1) | 66.5 (66.2–66.9)| 66.2 (65.2–67.2)|
| Women, %        | 41.7 (41.4–42.0)| 37.9 (36.2–39.5)| 40.7 (36.4–45.0)|
| Institutional living, % | 4.5 (4.4–4.6) | 1.2 (0.8–1.6) | 2.0 (0.8–3.2) |
| Living alone, % | 39.3 (38.9–39.6)| 23.5 (22.1–25.0)| 28.3 (24.3–32.2)|
| Dependent in p-ADL, % | 6.7 (6.5–6.8) | 1.4 (1.0–1.8) | 1.8 (0.6–3.0) |
| Previous stroke, % | 25.3 (25.0–25.6)| 12.9 (11.7–14.0)| 15.3 (12.1–18.5)|
| TIA, %          | 8.0 (7.7–8.2)   | 6.2 (5.2–7.3)   | 8.7 (6.0–11.4)  |
| Atrial fibrillation, % | 20.5 (20.3–20.8)| 25.3 (23.8–26.7)| 22.3 (18.7–26.0)|
| Diabetes, %     | 23.3 (23.0–23.6)| 14.2 (13.0–15.4)| 18.3 (14.9–21.7)|
| Treatment for high BP, % | 55.4 (55.1–55.8)| 50.4 (48.7–52.1)| 50.2 (45.8–54.6)|
| Current smoker, % | 22.3 (22.0–22.5)| 21.4 (20.0–22.9)| 21.7 (18.0–25.5)|
| Not fully conscious, % | 10.9 (10.7–11.1)| 16.0 (14.7–17.2)| 11.7 (8.9–14.5)|

rtPA indicates recombinant tissue-type plasminogen activator; p-ADL, personal activities of daily living; TIA, transient ischemic attack; BP, blood pressure; Q, quartile; CI, confidence interval.

*Riks-Stroke Q1 2003 to Q2 2010.

In 2002, rtPA was conditionally approved by European regulatory authorities for treatment of acute ischemic stroke. During the period January 2003 to June 2010, a total of 186 605 patients were recorded in Riks-Stroke. Of these, 92 150 were in the possible target group for thrombolysis, that is, they had a diagnosis of ischemic stroke and were 18 to 80 years old; 1462 of them had no information on thrombolytic therapy. Of the remaining 90 688 patients, 4057 (4.4%) were treated with intravenous rtPA; 3298 (81.3%) within 3 hours of onset of symptoms, 499 (12.3%) in the 3- to 4.5-hour time interval, and 80 (2.0%) were treated later. Information on delay to treatment was missing in 180 patients (4.4%) treated with rtPA.

Characteristics of patients treated with rtPA within 3 hours, in the 3- to 4.5-hour interval, and not treated are shown in Table 1. Women, older patients, patients living in an institution or living alone, dependent in activities of daily living before stroke, having had a previous stroke, diabetes, or hypertensive treatment were less likely to be treated with rtPA. The differences between the 3-hour and 3- to 4.5-hour treatment groups were small. However, patients treated within 3 to 4.5 hours were more often fully conscious (Table 1).
Figure 1 shows, quarterly, the proportion of patients in the target group that were treated with thrombolysis in Sweden from the first quarter (Q1) of 2003 to the second quarter (Q2) of 2010 by time from onset of symptoms to start of thrombolytic treatment. There was a gradual but slow increase in the total proportion of patients undergoing thrombolytic treatment from 0.4% in Q1 2003 to 8.7% in Q2 2010. Figure 1 suggests a close to linear increase with 3 possible exceptions. There was an apparent but short-lived surge after the strong recommendation of thrombolysis in the national stroke guidelines published in early 2005. A new surge occurred during 2008, when the ECASS III and SITS-ISTR results became known and then were published. The rate of increase appears to have leveled off during 2009 and 2010. Joinpoint analysis estimated that the proportion treated with thrombolysis increased at a constant rate, by 26.4% (95% CI, 22.9 to 30.0) per year, between 2004 and 2010.

Up to Q3 2008, thrombolysis in the 3- to 4.5-hour interval was infrequent (Figure 1). Between Q3 2008 and Q4 2008, it increased rapidly from 0.5% to 1.2%. The proportion then increased at a slower rate (P=0.011 for change in rate) to reach 2.1% in Q2 2010, corresponding to an annual increase of 49.8% (95% CI, 13.4 to 98.0). In the last quarter, it accounted for 24.7% of all thrombolytic treatments.

From Q4 2008 onward, the proportion treated later than 4.5 hours remained at a low level (0.1% to 0.3%), but the proportion treated without recorded information on timing increased (Figure 1).

After 5 years of steady increase, the levels of thrombolysis in the 0- to 3-hour interval peaked at 6.6% during Q4 2008 and then stabilized at the 6% level from Q1 2009 onward (Figure 1). Joinpoint regression analysis confirmed 2 significant changes in time trends, Q1 2004 and Q4 2008. The annual increase in patients treated with thrombolysis at 0 to 3 hours was 405.5% (95% CI, 55.6 to 1542.3) in 2003, 27.9% (95% CI, 22.1 to 34.0) between Q1 2004 and Q4 2008, and −4.4% (95% CI, −20.9 to 15.6) thereafter. The stagnation in implementation of thrombolysis treatment at 0 to 3 hours was most prominent in university hospitals and departments of neurology (Table 2).

From Q4 2008 to Q2 2010, there was no significant correlation between proportions of patients treated in the 0- to 3-hour and 3- to 4.5-hour intervals across the 21 healthcare regions (county councils) of Sweden (r=0.25, P=0.266). The increase of thrombolysis in the 3- to 4.5-hour time interval was significant in both men and women (P<0.001), but the implementation was significantly faster in men than in women (P=0.041). Thrombolytic treatment increased significantly (P<0.001) in all age groups up to the age limit of 80 years approved by the regulatory authorities with no significant difference between age groups (Table 2; P=0.166). The implementation rate of thrombolysis at 3 to 4.5 hours did not differ between university hospitals and other hospitals (P=0.202) nor between departments of neurology and internal medicine (P=0.248).

As shown in Figure 2, except for the early introductory years 2003 and 2004, the median time from arrival in hospital to start of treatment (door-to-needle time) for patients receiving thrombolysis remained constant throughout the study period. It was seemingly unaffected by the extension of the treatment interval to 4.5 hours in late 2008. Thus, during January 2007 to September 2008, median (interquartile) door-to-needle time was 69 minutes (range, 53 to 90 minutes) and during October 2008 to December 2009, it was 66 minutes (range, 50 to 90 minutes; P=0.062, Mann-Whitney U test). The proportion of patients treated within 60 minutes from hospital admission was 22% in 2003, increased to 35% in 2005, and reached 40% in 2010.

The median (interquartile) door-to-needle time was 72 minutes (range, 55 to 96 minutes) in patients arriving within 1 hour and 63 minutes (range, 48 to 82 minutes) in patients arriving later. The inverse correlation between onset-to-door and door-to-needle time was highly significant (Spearman correlation 0.22; P<0.001).

**Discussion**

Thrombolysis for acute ischemic stroke is increasingly implemented in routine clinical practice in Sweden. However, since the end 2008, the increase is restricted to patients...
treated in the 3- to 4.5-hour time interval after onset of stroke symptoms, and this interval now accounts for one fourth of all thrombolytic treatments for stroke. The previous gradual rise in the proportion of patients receiving thrombolysis within 3 hours has leveled off, especially in university hospitals and departments of neurology. This cannot be ascribed to prolonged door-to-needle times.

A strength of Riks-Stroke is that it covers all Swedish hospitals that admit patients with acute stroke. The register is estimated to cover at least 85% of all patients with acute stroke in Sweden. A detailed case-by-case validation of Riks-Stroke has indicated that patients who die early after admission to hospitals and who are not treated in a stroke unit are less likely to be recorded. The corollary would be that the frequency of thrombolysis reported here is slightly inflated. Riks-Stroke is not primarily a research register; it was established to serve as a national register monitoring the quality of stroke care and to stimulate improvements by benchmarking across all hospitals in the country. Therefore, the quality of individual data may vary. However, validation studies have found good agreement (95%) between medical records and patient information in the Riks-Stroke register.

### Table 2. Proportion (%) of Patients Treated With rtPA Within 3 Hours or in the 3- to 4.5-Hours Interval, Before (Q3 2007 to Q3 2008) and After (Q4 2008 to Q4 2009) ECASS III and SITS-ISTR*

<table>
<thead>
<tr>
<th></th>
<th>rtPA 0 to 3 H</th>
<th></th>
<th>rtPA 3 to 4.5 H</th>
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<tr>
<td></td>
<td>No. Before</td>
<td>After</td>
<td>P&lt;sub&gt;change&lt;/sub&gt;</td>
<td>P&lt;sub&gt;homog&lt;/sub&gt;</td>
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<td>29 849</td>
<td>5.1 6.0</td>
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<td>Large nonuniversity hospital</td>
<td>13 102</td>
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<td>0.4 1.7</td>
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<tr>
<td>Community hospital</td>
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<td>4.2 4.8</td>
<td>0.148</td>
<td>0.4 1.0</td>
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<td>Type of department†</td>
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<tr>
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<td>&lt;0.001</td>
<td>0.4 1.8</td>
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<tr>
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<td>17 657</td>
<td>5.5 6.0</td>
<td>0.184</td>
<td>0.4 1.6</td>
</tr>
<tr>
<td>Women</td>
<td>12 192</td>
<td>4.6 6.0</td>
<td>0.001</td>
<td>0.5 1.3</td>
</tr>
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<td>18–64 y</td>
<td>8590</td>
<td>6.9 6.6</td>
<td>0.538</td>
<td>0.7 1.8</td>
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<tr>
<td>65–74 y</td>
<td>11 074</td>
<td>5.4 6.2</td>
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<td>0.3 1.3</td>
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<tr>
<td>75–80 y</td>
<td>10 185</td>
<td>3.3 5.1</td>
<td>&lt;0.001</td>
<td>0.3 1.3</td>
</tr>
</tbody>
</table>

rtPA indicates recombinant tissue-type plasminogen activator; Q, quartile; ECASS, European Cooperative Acute Stroke Study; SITS-ISTR, Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register.

*P value for change (P<sub>change</sub>) was tested using Pearson χ² test and homogeneity of implementation rate (P<sub>homog</sub>) was tested using the Breslow-Day statistic.

†In university and other large nonuniversity hospitals.

Figure 2. Door-to-needle time for 18- to 80-year-old patients with acute ischemic stroke treated with thrombolysis from 2003 to 2010. The box represents the interquartile range, and the band near the middle represents the median. Data from Riks-Stroke. Q indicates quartile.
our study is that the proportion of patients without information on delay time has increased since mid-2008. It may be that attending physicians have estimated that the time elapsed since onset of stroke has definitely been <4.5 hours but that the exact delay time has been difficult to assess.

The proportion of patients with ischemic stroke ≤80 years receiving thrombolysis was 8.5% to 9.0% during Q3 2009 to Q2 2010. This is above the 1% to 7% reported from several other North American and west European countries. Some of the low reported proportions are from studies early during the implementation.

Results from The National Sentinel Stroke 2008 Audit data set in the United Kingdom suggest that the proportion eligible for stroke thrombolysis would only increase marginally if the time window was extended from 3 to 4.5 hours. The implementation of 0- to 3-hour thrombolysis in Sweden was gradual over several years, whereas the 3- to 4.5-hour thrombolysis started to be applied within a few months after the scientific documentation became available. The fast implementation rate of thrombolysis in the extended time window agrees with what has been reported in the multinational SITS-ISTR study. It is likely that already existing infrastructures for thrombolytic treatment of patients with stroke helped to rapidly implement thrombolysis in the extended interval. The fact that more stroke physicians now have personal experience with the administration of rtPA and can better assess risks has probably contributed to the rapid implementation of the 3- to 4.5-hour thrombolysis.

Implementation of 3- to 4.5-hour thrombolysis was as fast in specialized nonuniversity hospitals as in university hospitals. This implementation pattern was different from that when 0- to 3-hour thrombolysis was first introduced and there was an apparent 2-year delay in specialized nonuniversity hospitals as compared with university hospitals.

The somewhat slower implementation of thrombolysis in the 3- to 4.5-hour timeframe in women than in men concurs with previous observations that new interventions in cardiovascular medicine are often applied earlier to men than to women. The difference seemed to be a matter of an initial delay of implementation in women; 1 year after the publication of the 2 key studies on thrombolysis in the 3- to 4.5-hour interval, the sex difference had reduced to 0.1% units.

A concern about the extended time limit for thrombolysis has been that the hospital staff would lose some of its sense of urgency when a possible candidate for thrombolysis arrives in the hospital. An analysis based on the Austrian Stroke Unit Registry showed that early hospital arrival translated into a significant delay in the application of thrombolysis among patients with acute stroke. Confirming this observation, we found an inverse relationship between onset-to-door versus door-to-needle times. However, we found no change in median door-to-needle time as the number of patients treated in the 3- to 4.5-hour interval increased. This is in accordance with observations in the SITS-ISTR study. The median door-to-needle time in this study was also consistent with findings in the SITS-ISTR study, but considerably longer than the 50 minutes reported from the Austrian Stroke Unit Registry or 20 minutes reported from the Helsinki Stroke Thrombolysis Registry. Although the proportion of Swedish stroke thrombolysis patients receiving treatment within 1 hour from hospital admission has increased markedly since thrombolysis was introduced for stroke in 2003, it reached only 40% in 2010. Except for the initial years of thrombolysis, improvement in door-to-needle time has been modest and there seems to be room for further improvement. A large-scale national campaign to reduce all components of the onset-to-needle delay is now being launched in Sweden.

Since the end of 2008 there has been a definite, significant break in the previous upward trend of rtPA administration within 3 hours of stroke onset. This coincides temporally with the increase in thrombolysis in the 3- to 4.5-hour window. Although suggestive, it does not prove a definite cause–effect relationship.

If door-to-needle time has not been negatively affected, what is the reason for the recent break in the upward trend of 0- to 3-hour thrombolysis? One possible explanation would be that a saturation level has been approached in many hospitals, that is, the great majority of patients that is possible to treat within 3 hours is actually treated. The fact that many Swedish hospitals have reached the 10% to 15% range of thrombolysis, well above the national average, speaks against this explanation. However, there is a possibility that the proportion of patients treated with thrombolysis may vary by the extent to which hospitals adhere to the European product label for rtPA.

Thrombectomies were not included in this analysis. Thrombectomies have been registered in Riks-Stroke since 2009, and since then, 88 thrombectomies have been performed in patients who did not receive intravenous rtPA. If thrombectomies were included, the total proportion treated would have increased from 7.9% to 8.3% in 2009 and from 8.7% to 9.5% in 2010. Catheter-based treatments may have replaced intravenous thrombolysis in some patients and this may partially explain why no further increase in intravenous 0- to 3-hour thrombolysis was observed.

Thrombolysis in the 3- to 4.5-hour interval has not yet been formally approved by the European Medicines Agency and, yet, our data show that the extended time window has been widely accepted in clinical practice. Instead, it seems that a major driving force has been the very publication of key scientific studies in the second half of 2008 and during 2009 and 2010. It is reasonable to assume that the dissemination has been reinforced by professional guidelines and recommendations. A high-priority recommendation to apply rtPA treatment in the 3- to 4.5-hour interval in appropriate patients included in the early 2009 update of the guidelines may have contributed to the increase of thrombolysis in the extended time window during 2009 to 2010.

Appendix: Hospitals Participating in Riks-Stroke and Contact Persons

Aknowleds: Brita Eklund and Birgitta Norrjö Östman; Angelholm: Dorit Christensen and Inger Hallenberg; Arvika: Anna Lena Wall; Avesta: Åsa-Lena Koivisto and Else-Marie Larsson; Bollnäs: Maj Fröjd and Lena Parhans; Borås: Inger Högardh, Hillevi Grändby, and Carina E. Persson; Danderyd/Stockholm: Berit Eriksson, Ann-Charlott Laska, Magnus Von Arbin, and Owe Schill; Ekmöping: Gunilla Ingerud and Johanna Linder; Falköping: Ann Charlotte Sunnergren; Falun: Helen Eriksson; Finspäng: Carola Oskarsson
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References


Sources of Funding

Riks-Stroke, the Swedish Stroke Register, is funded by the National Board of Health and Welfare and Swedish Association of Local Authorities and Regions. This study was supported by the VINNVÅRD research program.

Disclosures

K.A. has formerly been employed by The National Board of Health and Welfare, a governmental agency funding Riks-Stroke. The other authors declare that they have no conflict of interest in relation to this study.
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Stroke. 2011;42:2492-2497; originally published online July 28, 2011; doi: 10.1161/STROKEAHA.111.618587
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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