Discarding Heparins as Treatment for Progressive Stroke in Sweden 2001 to 2008

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**Background and Purpose**—High-dose heparin has been used extensively to treat patients with progressive ischemic stroke, but the scientific support is poor and the current stroke guidelines advise against its use. We studied how heparin treatment for progressive stroke has been discarded in Sweden.

**Methods**—All 78 hospitals in Sweden that admit acute stroke patients participate in Riks-Stroke, the Swedish Stroke Register. During 2001 to 2008, information on the use of high-dose heparin was available for 155,344 patients with acute ischemic stroke. The determinants as to region, patient characteristics, and stroke service settings were analyzed.

**Results**—Use of heparin for progressive stroke declined from 7.5% (2001) to 1.6% (2008) of all patients with ischemic stroke. The marked regional differences present in 2001 were reduced over time. The use of heparin declined at a similar rate in all types of hospital settings, in stroke units vs nonstroke units, and in neurological vs medical wards. Independent predictors of use of heparin included younger age, first-ever stroke, independence in activities of daily living before stroke, atrial fibrillation, no aspirin treatment, and lowered consciousness on admission.

**Conclusions**—There is no immediate, stepwise effect of new scientific information and national guidelines on clinical practice. Rather, the phasing out of heparin has followed a linear course over several years, with less variation between hospitals. We speculate that open comparisons between hospitals in a national stroke register may have helped to reduce the variations in clinical practice. *(Stroke. 2010;41:2552-2558.)*

**Key Words:** acute ischemic stroke • heparin

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After efficacy and safety of a new treatment method have been established in clinical research studies, there is commonly a lag time before the method becomes implemented in routine clinical practice.1 There is also reason to believe that there is considerable lag time from when a routine method is proven to be inefficient or potentially harmful until that evidence is applied to routine clinical practice. The use of heparin for progressive ischemic stroke is a case for exploring how a widespread clinical practice changes as a result of new knowledge and clinical guidelines.

Early neurological deterioration is a frequent complication in acute stroke.2-3 If the worsening occurs after medical care begins, then the terms progressive stroke, stroke in progression, deteriorating stroke, and stroke-in-evolution have been used. This condition has no generally accepted definition, no established underlying mechanism, and no effective treatment.4 Yet, it is of great clinical significance.

Among potential reasons for progressive stroke are thrombus propagation and re-embolization from a cardiac source.4 Hence, heparin treatment would seem to be a rational approach,5 and studies performed in the early 1960s indicated some beneficial effects.6-7 Heparin came to be recommended, although there were limitations and warnings in WHO8 and other guidelines on stroke management during the 1970s and 1980s.

However, later studies failed to show efficacy of heparin to prevent stroke progression.9,10 In studies on the effect of heparin in patients with ischemic stroke, not subdivided as stable or progressing, the International Stroke Trial, TOAST, and other trials failed to demonstrate net clinical benefits of heparin.11 Instead, heparin treatment was associated with an increase in symptomatic intracranial and extracranial hemorrhages.11

By the end of the 1990s, strong scientific evidence had accumulated against the routine use of heparin in patients with ischemic stroke. However, a survey performed in 2001 showed that a large proportion of U.S. and Canadian neurologists would use heparin in several scenarios of ischemic stroke.12 For progressive stroke, 51% of U.S. and 33% of...
Canadian neurologists would use it. An additional 35% and 25%, respectively, responded “maybe.”

Swedish national stroke guidelines that went into effect from 2001 pointed out that there was “no modern scientific evidence to support the once-common use of heparin for a cerebral infarction in progress.” Revised versions of the guidelines published in 2005 and 2009 strongly advised against the use of high-dose heparin during the acute phase of ischemic stroke.

We used data from Riks-Stroke, The Swedish Stroke Register, to study how heparin (including low-molecular-weight heparins) has been discarded as treatment for progressive stroke in Swedish stroke care on national, hospital, and patient levels.

Materials and Methods

This study included patients with ischemic stroke registered in Riks-Stroke, the Swedish Stroke Register, between January 1, 2001 and December 31, 2008. Riks-Stroke was established in 1994, and since 1998 it has been covering all 78 hospitals in Sweden admitting patients with acute stroke. The coverage, ie, the proportion of all acute patients registered in Riks-Stroke, is estimated to be 83%. Basic patient characteristics (including age, gender, living conditions, history of previous stroke, and comorbidities), diagnosis, level of consciousness on arrival, pharmaceutical treatment, complications, and sequence of care (including type of stroke care organization and department) are recorded at the hospitals. Riks-Stroke also includes a 3-month and, since 2009, a 12-month follow-up that describes patient-reported outcomes and rehabilitation after stroke.

Variable Definitions

In this study, heparin denotes both unfractionated heparin and low-molecular-weight heparins. The use of heparin as progressive stroke treatment during the acute phase has been recorded in Riks-Stroke since 2001. A single question that changed in formulation in 2004 has been used. Between 2001 and 2003, it was formulated, “Anticoagulants, injection or infusion, heparin, and low-molecular-weight heparin (eg, [brand name of dalteparin]) as treatment for stroke,” and from 2004 as, “Heparin and [brand names of dalteparin, enoxaparin, and tinzaparin, the 3 low-molecular-weight heparins substances available on the Swedish market] as treatment for progressive stroke.” Riks-Stroke did not define precise criteria for progressive stroke.

Hospitals were categorized into university, large nonuniversity, and community hospitals. Large nonuniversity and community hospitals were differentiated by their degree of specialization. Type of department on hospital admission (medicine, neurology, geriatrics/rehabilitation, or other type) and type of stroke organization (stroke unit, general ward, or other ward) were also recorded.

Riks-Stroke’s definition of a stroke unit corresponds with the definitions used by the Stroke Unit Trialists’ Collaboration, a dedicated inpatient facility that exclusively (or nearly exclusively) cares for stroke patients and includes a multidisciplinary team of professionals with special skills in stroke management.

Level of consciousness is registered using 3 levels in which alert corresponds to level 1 on the reaction level scale, drowsy to reaction corresponds to level 2 to 3, and unconscious to reaction corresponds to level 4 to 8. Patients who managed clothing, toileting, and walking were defined as being independent in activities of daily living.

Relevant questions essentially have been the same throughout the study period. Case record forms can be found on the Riks-Stroke web page (www.riks-stroke.org).

Statistical Methods

Proportions of patients with heparin as progressive stroke treatment are presented for groups defined by gender, age (18–59, 60–69, 70–79, 80 and older), year of stroke onset, living in institution, living alone, smoking, dependent in activities of daily living, previous stroke, atrial fibrillation, history of diabetes, antihypertensive medication, aspirin or other antiplatelet agent at onset, level of consciousness on admission, type of hospital, type of department, and type of stroke organization. Multiple logistic regression was used to simultaneously test the effect of several predictors on the probability to receive heparin. To adjust for the dependence between patients treated at the same hospital, patients were handled as repeated observations within hospitals in the statistical analysis. An exchangeable correlation structure was used, and the logistic regression parameters were estimated by generalized estimation equations using SAS/STAT software’s procedure GENMOD. Because neurology departments, with a few exceptions, were only available at university hospitals, type of department was not included in the multiple regression model.

The rate at which heparin was phased out in different groups was mainly analyzed graphically by plotting the proportion of heparin-treated patients by year. In addition, the 2-way interaction terms (year*age group, year*gender, year*type of hospital, year*department, and year*organization) were added to this model to test if the rate of dissemination differed.

Statistical analysis was performed using IBM SPSS statistics 18.1 and SAS software 9.1 (SAS Institute Inc., Cary, NC). Maps were produced with GIS software ArcGis 9.3 (ESRI).

Results

National Level

During 2001 to 2008, 158744 ischemic stroke patients (79693 men and 79051 women) were registered in Riks-Stroke. Of these, 155344 had valid information on heparin treatment for progressive stroke.

In 2001, 1275 of 17068 (7.5%) patients received heparin as progressive stroke treatment. The proportion decreased linearly during subsequent years (Figure 1) and reached 325 of 20597 (1.6%) during 2008.
Hospital Level

Sweden has a decentralized health care system, and each of the 20 administrative regions in the country is responsible for health care in its region. There are no private hospitals that receive acute stroke patients. The rate at which heparin was phased out varied considerably between regions (Figure 2) and hospitals. In 2001, there were large variations between hospitals in the use of heparin for progressive ischemic stroke. Thus, in 20 out of 78 hospitals, heparin was used in >10% of the patients, and in 3 hospitals it was used in >20% (maximum 50%). It was used in <3% of the patients in 13 hospitals. In 2008, 5 hospitals still treated >5% of their patients with heparin (maximum 7%), whereas 61 hospitals used high-dose heparin for progressive stroke in <3% of the patients.

Heparin was phased out at a similar rate independently of type of hospital ($P=0.115$; Figure 3) or organization ($P=0.757$). Throughout the observation period, heparin was used somewhat more commonly in departments of neurology than in departments of medicine ($P<0.001$; Table), but the use of heparin in progressive stroke declined at similar rates ($P=0.236$).

In a multiple logistic regression model adjusting for case-mix (Table), the probability of heparin treatment did not differ significantly between university hospitals, large non-university hospitals, and community hospitals. There was no difference between patients admitted to a stroke unit or to another type of ward.

Patient Level

The rate at which heparin was phased out was similar in men and women ($P=0.654$) in all age groups ($P=0.912$; Figure 1). Younger age, living at home, not living alone, independence in activities of daily living, atrial fibrillation, first-ever stroke,
Table. Frequencies and Proportions of Patients With Acute Ischemic Stroke Who Were Treated With Heparin for Progressive Stroke in Different Subgroups of Patients

<table>
<thead>
<tr>
<th>Year</th>
<th>Non-Missing Observations</th>
<th>Treated Frequency</th>
<th>Proportion (%)</th>
<th>Odds Ratio</th>
<th>95% CI of Odds Ratio</th>
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<td>Year</td>
<td>Ref</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>1275</td>
<td>7.5</td>
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<td>2002</td>
<td>18 123</td>
<td>1048</td>
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<td>0.764</td>
<td>0.642</td>
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<td>2003</td>
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<td>2004</td>
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<td>866</td>
<td>4.5</td>
<td>0.568</td>
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<tr>
<td>2005</td>
<td>20 613</td>
<td>595</td>
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<tr>
<td>2006</td>
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<td>497</td>
<td>2.4</td>
<td>0.312</td>
<td>0.236</td>
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<tr>
<td>2007</td>
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<td>328</td>
<td>1.6</td>
<td>0.210</td>
<td>0.157</td>
</tr>
<tr>
<td>2008</td>
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<td>325</td>
<td>1.6</td>
<td>0.197</td>
<td>0.143</td>
</tr>
</tbody>
</table>

Stroke care characteristics

Type of hospital
- University hospital: 30 705, 1139, 3.7, 0.769, 0.480, 1.233
- Large non-university hospital: 65 766, 2385, 3.6, 0.802, 0.521, 1.235
- Community hospital: 58 873, 2378, 4.0, Ref

Type of department (all hospitals)
- Medicine: 109 792, 4022, 3.7, ... ...
- Neurology: 21 542, 874, 4.1, ... ...
- Geriatric: 16 690, 604, 3.6, ... ...
- Other: 5782, 335, 5.8, ... ...

Type of department (university hospitals)
- Medicine: 9476, 238, 2.5, ... ...
- Neurology: 18 739, 766, 4.1, ... ...
- Geriatric: 189, 3, 1.6, ... ...
- Other: 2277, 131, 5.8, ... ...

Type of stroke organization
- Stroke unit: 103 686, 3883, 3.7, 1.082, 0.933, 1.255
- General ward: 32 781, 1219, 3.7, Ref
- Other ward: 18 823, 798, 4.2, 1.084, 0.922, 1.274

Patient characteristics before stroke/on admission

Gender
- Men: 78 027, 3157, 4.0, 1.048, 0.997, 1.03
- Women: 77 317, 2745, 3.5, Ref

Age
- 18–59: 14 302, 938, 6.6, 2.717, 2.292, 3.221
- 60–69: 24 502, 1074, 4.4, 1.757, 1.560, 1.979
- 70–79: 47 400, 1947, 4.1, 1.442, 1.299, 1.599
- 80 and above: 69 140, 1943, 2.8, Ref

Institutional living
- No: 140 425, 5489, 3.9, 1.143, 1.002, 1.304
- Yes: 14 147, 377, 2.7, Ref

Living alone
- No: 77 512, 3293, 4.2, 1.094, 1.033, 1.158
- Yes: 76 727, 2563, 3.3, Ref

(Continued)
hypertensive medication, no aspirin treatment, and lowered consciousness on admission were factors related to a higher probability of receiving heparin for progressive stroke (Table).

### Discussion

In 2001, the use of high-dose heparin for progressive stroke was introduced as a variable and as an indicator of patient risk in Riks-Stroke, the Swedish national quality register. Before 2001, any use of high-dose heparin in patients with ischemic stroke was recorded, irrespective of the reason.

The present study shows that, already in 2001, only a minority (7.5%) of patients with ischemic stroke were treated with heparin for progressive stroke. However, there were large variations between regions and between hospitals, and heparin was used in some hospitals in >20% of the patients with ischemic stroke. After 2001, heparin therapy has become less frequent in all hospitals, and it is now used in <10% of patients with ischemic stroke in all hospitals. Although the percentages were low, almost 6000 patients were treated with heparin for progressive stroke during those 8 years, which is a substantial number considering the increased risk of hemorrhage. Based on estimated risks from the literature,11 ~45 symptomatic intracranial hemorrhages and equally many major extracranial hemorrhages may have been attributable to heparin treatment.

The rate at which heparin was discarded was unrelated to type of hospital or stroke care setting. A previous study of the dissemination of stroke thrombolysis showed that university hospitals and stroke units phased in thrombolysis earlier.1 Obviously, the pattern of phasing out an outdated low-technology method of treatment has followed a different pattern from that of introducing a new treatment that requires considerable organizational changes. We construe that phasing out an obsolete therapy has not been seen as an academic initiative as challenging as the introduction of a new exciting therapy.

<table>
<thead>
<tr>
<th>Heparin Treatment</th>
<th>Non-Missing Observations</th>
<th>Frequency</th>
<th>Proportion (%)</th>
<th>Odds Ratio</th>
<th>95% CI of Odds Ratio</th>
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<td>492</td>
<td>3.6</td>
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<tr>
<td>Alert</td>
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<td>4611</td>
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<td>4.0</td>
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</table>

The use of heparin for progressive stroke decreased uniformly in different patient groups. It is evident that hospital traditions and physicians’ attitudes played a more important role than patient subgroup characteristics in the use of heparin for progressive ischemic stroke. Strengths of this study are the high proportion of patients registered in Riks-Stroke (83%) and that it covered all hospitals in the country that admit acute stroke patients. Patients who die early after admission to hospital or who are not treated in stroke units are less likely to be registered.18,19 This may have slightly affected proportions in absolute terms, but it is unlikely that it has had any major impact on secular trends.

Another reason why the absolute percentages should be interpreted with caution is that the nominator is the number of patients treated with high-dose heparin for progressive stroke, whereas the denominator is all patients with ischemic stroke. Within the group of patients with early deterioration, the proportion treated is probably higher than the figure given, but this would not affect secular trends or analyses of subgroups by patient characteristics or hospital settings.

Yet another limitation is that our data cannot resolve if the indication for heparin has changed in absolute terms (the use of heparin is not indicated) or in relative terms (heparin is used only when progression is marked). The Swedish national stroke guidelines do not distinguish between unfractionated heparin and low-molecular-weight heparins for progressing stroke; both are considered to have insufficient scientific support and to have an unacceptable risk of adverse events. This is in agreement with other European20 and U.S.21 stroke guidelines. In accordance with the plan–do–study–act cycle to improve quality,24,25 the Swedish national stroke guidelines have been issued in Sweden in 2001, 2005, and 2009. Our results indicate that there is no immediate, stepwise effect of guidelines on clinical practice. Rather, discarding heparin has followed a linear course over many years. In its annual reports, Riks-Stroke continuously and openly discloses hospitals with practices that markedly deviate from guidelines and from practices at other hospitals. Considerable pressure is put on the divergent hospitals. We speculate that this plays a major role in promoting the acceptance and implementation of the guidelines and in reducing therapeutic differences between hospitals.

**Conclusion**

The present results show that phasing out of a potentially detrimental therapy with poor scientific support is a slow process. There are many reasons why new scientific evidence may not have immediate effects on clinical practice. When discussing the very frequent use of heparin among U.S. neurologists,12 Benatar23 proposed several possible factors: (1) relying on personal experience rather than scientific evidence, a major factor; (2) an unwavering perception that heparin should work; (3) the psychological pressure to actively treat rather than passively observe; and (4) the inertia that impedes a change in practice. We add that the fact that so few high-quality trials have been performed has left room for opinion-based use of heparin.

In accordance with the plan–do–study–act cycle to improve quality,24,25 the Swedish national stroke guidelines include a number of quality indicators that are monitored by the national quality assessment register. The Riks-Stroke reports include between-hospital comparisons, which are publicly available.15

National stroke guidelines have been issued in Sweden in 2001, 2005, and 2009. Our results indicate that there is no immediate, stepwise effect of guidelines on clinical practice. Rather, discarding heparin has followed a linear course over many years. In its annual reports, Riks-Stroke continuously and openly discloses hospitals with practices that markedly deviate from guidelines and from practices at other hospitals. Considerable pressure is put on the divergent hospitals. We speculate that this plays a major role in promoting the acceptance and implementation of the guidelines and in reducing therapeutic differences between hospitals.

**Appendix**

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Disclosures
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References
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