Dissemination of Thrombolysis for Acute Ischemic Stroke Across a Nation
Experiences From the Swedish Stroke Register, 2003 to 2008

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Background and Purpose—We used Riks-Stroke, the Swedish Stroke Register, to explore how thrombolysis has been disseminated in Swedish hospitals since it was approved in 2003.

Methods—All 78 hospitals in Sweden admitting patients with acute stroke participate in Riks-Stroke. Between 2003 and 2008, 72,033 adult patients were hospitalized for acute ischemic stroke. We analyzed thrombolysis use by region, patient characteristics, and stroke service settings.

Results—Nationwide, the use of thrombolysis increased from 0.9% in 2003 to 6.6% in 2008. There were marked regional differences in the dissemination of thrombolysis, but these gaps narrowed over time. Nonuniversity hospitals reached treatment levels similar to university settings, although with a 2- to 3-year delay. Symptomatic intracranial hemorrhage remained at the 3% to 9% level without an apparent time trend during dissemination. Independent predictors of higher thrombolysis use included younger age, male sex, not living alone, and no history of stroke or diabetes. In 2008, patients admitted to a stroke unit were 5 times more likely to receive thrombolysis than those admitted to general wards.

Conclusions—Nationwide implementation of thrombolysis has been slow but has accelerated mainly due to increased access outside university hospitals. The increased use has been achieved safely, but access has been unequal. (Stroke. 2010;41:1115-1122.)

Key Words: acute ischemic stroke ■ implementation ■ thrombolysis

Although thrombolysis has been amply shown to have a beneficial benefit-to-risk ratio as treatment for acute ischemic stroke,1 its dissemination in routine clinical practice has been slow. Although there are examples of local successes in the promotion of thrombolysis,2–4 the large-scale implementation at the population level mostly has been disappointing. It has been estimated that the proportion of patients with ischemic stroke treated with recombinant tissue plasminogen activator (rtPA) remains <2% in most countries.5 In the United States, where rtPA was approved for this indication in 1996, the proportion treated with rtPA was estimated to be approximately 2% in 2004 with an increase of <0.1% per year during the early 2000s.6 The implementation of thrombolysis for acute ischemic stroke mostly has been studied at the local level or in selected patient populations, and there is limited information at the national level on how thrombolysis for acute ischemic stroke is disseminated.7

In 2003, rtPA was conditionally approved for treatment of acute ischemic stroke within 3 hours of onset by the regulatory authorities in the European Union countries, including Sweden. In this article, we have applied a national perspective on the dissemination of thrombolysis for acute ischemic stroke over the years 2003 to 2008. We describe and analyze how the treatment has been applied in different patient groups and in various regional and hospital settings.

Patients and Methods

Riks-Stroke, the Swedish Stroke Register

Patients included in this article were recorded in Riks-Stroke, the Swedish Stroke Register, during the years 2003 to 2008. 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 admitting acute stroke patients (78 hospitals in 2008). Riks-Stroke has been approved by the Regional Ethical Review Board at Umeå University and the data-handling procedures by the National Computer Data Inspection Board.

Information is collected during the acute phase and at follow-ups 3 and 12 months after stroke. In the present study, only acute-phase
information was included. Details on what information is collected are available at the Riks-Stroke web site (www.riks-stroke.org).

Definitions

Riks-Stroke has developed several simple instruments to be used for large-scale data collection. Level of consciousness is used as a proxy for stroke severity on admission to the hospital. It is recorded using 3 levels based on the Reaction Level Scale. Patients with Reaction Level Scale 1 are defined as alert, Reaction Level Scale 2 to 3 as drowsy, and Reaction Level Scale 4 to 8 as unconscious. The level of consciousness recorded in Riks-Stroke is a very strong predictor of short- and long-term survival and functional outcome (documentation available at the Riks-Stroke web site, www.riks-stroke.org).

Whether a patient is dependent in activities of daily living (ADL) or not is based on the responses to 3 questions: does the patient need assistance with toileting, clothing, and walking? This simplified measurement of ADL dependency has a 92% sensitivity and a 91% specificity when compared with the Barthel Index <90 and correlates well with the modified Rankin score.

rtPA-related symptomatic intracranial hemorrhage is defined as deterioration of neurological symptoms within 36 hours after thrombolytic treatment when brain imaging shows intracranial bleeding. The time limit is in accordance with that used by the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST). Hospitals admitting patients with acute stroke are categorized as university hospitals (n=9; mean number of patients reported to Riks-Stroke in 2008 was 553; range, 326 to 839), large nonuniversity hospitals (n=22; mean 483 patients; range, 236 to 1210), and community hospitals (n=47; mean 188 patients; range, 26 to 420). The delineation between large nonuniversity and community hospitals is by their degree of specialization; community hospitals have only basic inpatient specialties and they lack advanced diagnostic and interventional technology.

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

Statistical Analyses

The associations between different types of stroke care organizations, patient characteristics, and thrombolysis were described by proportions with corresponding 95% CIs and univariately tested using the Pearson χ² test. Multiple logistic regression was used to simultaneously test the effect of several predictors on the chance to receive thrombolytic therapy. A multilevel approach was used in which patients were considered repeated observations within counties. An exchangeable correlation structure was assumed, and the logistic regression parameters were estimated by generalized estimation equations using SAS procedure GENMOD. Two-way interaction terms (year*age group and year*sex) were included to test if the rate of dissemination differed between groups of patients defined by sex and age. Statistical analyses were performed using SAS 9.1.

Results

During the years 2003 to 2008, a total of 146 374 patients were recorded in Riks-Stroke. Of those, 72 033 were in the possible target group for thrombolysis, that is, they had a diagnosis of ischemic stroke and were 18 to 80 years old. For 1328 of them, there was no information on thrombolytic therapy. Of the remaining 70 705 patients with valid information on thrombolytic therapy, 2535 (3.6%) were treated with thrombolysis. Of patients treated with thrombolysis, 2215 (87.4%) were treated within 3 hours of onset of symptoms (the approved indication during these years), an additional 186 (7.3%) within 4.5 hours, and 44 (1.7%) were treated later. For 90 patients (3.6%), there was no information on the delay between symptom onset and thrombolysis.

Dissemination Across the Country

At the national level, there has been a gradual but slow increase in the use of thrombolysis for acute ischemic stroke from 0.9% in 2003 to 6.6% in 2008 (Figure 1).

Swedish health care is provided by 21 counties. The uptake by the counties has been skewed (Figure 2). During 2003, the year rtPA was approved for stroke by the regulatory authority, 3 counties reached at least 2% treatment among 18- to 80-year-old patients with ischemic stroke. The last county to reach this level did so in 2008. As illustrated in Figure 2, there are examples of late-adopting counties that exceeded the national average within 2 years after introduction of thrombolysis. In 2008, there remained a belt of low-frequency counties (<5%) across mid-Sweden (Figure 2). In general, the gaps between the counties decreased over time, but a more than 7-fold gradient between high- and low-frequency counties remained in 2008.

Dissemination Across Patient Groups

Table 1 presents the proportions treated with thrombolysis in subgroups of patients. Women, older patients, patients living alone or in institution, being dependent in ADL before the stroke event, having had a previous stroke, a history of diabetes or hypertension, being treated with an antiplatelet agent or being unconscious on admission to the hospital received thrombolysis less frequently. Patients with atrial fibrillation were more likely to receive thrombolysis.

Independent predictors of thrombolysis were analyzed by multiple-adjusted logistic regression analyses. As shown in Table 2, women had a 6% lower chance than men to be treated. Age had an important impact: compared with patients <60 years of age, the chance of receiving thrombolysis was reduced by 16% for patients aged 60 to 69 years and by 34% for patients aged 70 to 80 years. The year*sex and year*age group interactions did not differ.
significantly, indicating a similar dissemination rate in men and women of all ages. Patients with stroke who were cohabitant were twice as likely as those living alone to be treated. Nonsmokers had a somewhat higher chance than smokers to receive thrombolysis.

Comorbidity was an important determinant of the likelihood of receiving thrombolysis (Table 2). A history of previous stroke or of diabetes markedly reduced the chance of being treated, and patients who were dependent in ADL before stroke had a substantially reduced chance of receiving thrombolysis. Ongoing treatment with aspirin, other antiplatelet agents, or antihypertensive therapy at stroke onset had little impact on the chance of receiving thrombolysis. The presence of atrial fibrillation independently increased the likelihood of thrombolysis by 51%.

Stroke severity at stroke onset was a major determinant of thrombolysis. Thus, patients who were drowsy on admission to the hospital were more than twice as likely to be treated as compared with patients who were alert. Unconscious patients had the lowest chance of being treated with thrombolysis.

**Dissemination by Stroke Care Setting**

Over the years 2003 to 2008, the chance of being treated with thrombolysis was significantly greater in university hospitals than in community hospitals after adjustment for differences in case-mix in the logistic regression model (Table 2). As shown in Figure 3A, thrombolysis was adopted 2 to 3 years later in nonuniversity hospitals as compared with university hospitals. In 2003, the chance of receiving thrombolysis at specialized nonuniversity hospitals was at the same level as in community hospitals. However, that chance increased over time and reached a level close to that in the university hospitals by 2008.

Of 18- to 80-year-old patients with acute ischemic stroke reported to Riks-Stroke in 2003 to 2008, 15% were admitted to a neurological department and 70% to a department of internal medicine. Departments of neurology took up thrombolysis earlier than departments of internal medicine (Figure 3A). Over the 6-year period, patients admitted to a department of neurology had twice the chance of being treated with thrombolysis than those admitted to a department of internal medicine (Table 1). Within university hospitals, after adjustments for other characteristics, the OR of receiving thrombolysis in a department of neurology versus internal medicine was 2.5 (95% CI, 2.0 to 3.1). Similarly, patients admitted to a stroke unit were considerably more likely to receive thrombolysis than those admitted to a general ward (Table 2; Figure 3C).

**Safety**

As shown in Figure 4, dissemination of thrombolysis across the country and across different hospital settings was
<table>
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<td>Yes</td>
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(Continued)
achieved with apparent preservation of safety. Thus, the proportion of patients with a symptomatic intracranial bleeding varied between 3.3% and 8.9% (mean 6.2%) without an apparent time trend ($P/\text{H}11005 0.72$). In a logistic regression model, adjusting for age, there were no significant differences in the frequency of symptomatic intracranial bleedings between men and women (6.3% versus 6.8%; $P/\text{H}11005 0.78$), different types of hospitals (5.6% in university hospitals, 7.5% in large nonuniversity hospitals, and 5.8% in community hospitals; $P/\text{H}11005 0.23$), or between departments of neurology versus internal medicine (5.4% versus 7.0%; $P/\text{H}11005 0.22$). Neither was there a significant time trend in 90-day case fatality in patients treated with thrombolysis ($P/\text{H}11005 0.97$), which varied between 6.1% and 9.3% (mean 8.3%). The case fatality rate was 8.2% in men and 8.4% in women ($P/\text{H}11005 0.93$), 7.8% in university, 9.7% in specialized nonuniversity, 6.7% in community hospitals ($P/\text{H}11005 0.10$), and 7.6% versus 8.5% at departments of neurology versus medicine ($P/\text{H}11005 0.61$).

**Discussion**

The present results show that thrombolysis for acute ischemic stroke can be implemented in different hospital settings with preserved safety. However, the data also show that the dissemination has been unequal across Sweden as to geography, patient groups, and healthcare settings.

**Limitations and Strengths**

To make it possible for all hospitals to take part in the voluntary Riks-Stroke collaboration, the strategy has been to keep data collection simple. The complete coverage of Swedish hospitals admitting patients with acute stroke is a strength of Riks-Stroke. Riks-Stroke is estimated to cover 82% of all patients with acute stroke in Sweden (for more information, see www.riks-stroke.org). 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.

The very large number of patients in Riks-Stroke ensures a high power with precise estimates of differences. With the large numbers, the problem is rather to sort out what differences are meaningful to patients (and the healthcare system) among those that emerge as highly statistically significant. We have, therefore, in our conclusions, placed little emphasis on small differences in point estimates, even if they were statistically significant.
hospital within 3 hours of onset of symptoms is considerably
proportion of patients arrive at the hospital earlier than singles. In Riks-Stroke, the acute stroke,15 married/cohabitant people have been shown to living alone had a much lower chance of being treated with not surprising observation was that patients who had been
2008 versus 2003 1.280 1.528 3.404
2006 versus 2003 3.941 2.400 6.471
2007 versus 2003 5.758 3.736 8.874
2008 versus 2003 7.393 4.534 12.056
Living at home versus in institution 1.340 0.981 1.832
Cohabitant versus living alone 1.930 1.678 2.221
Smoking status
Unknown versus smoker 1.038 0.829 1.300
Nonsmoker versus smoker 1.124 1.037 1.219
Independent in personal ADL versus dependent 5.106 3.292 7.919
No previous stroke versus previous stroke 2.204 1.817 2.673
No atrial fibrillation versus atrial fibrillation 0.660 0.599 0.728
No diabetes versus history of diabetes 1.606 1.359 1.899
No hypertensive medication versus medication 1.051 0.928 1.190
Aspirin versus no aspirin 1.077 1.001 1.159
Other antiplatelet agent 1.022 0.873 1.197
Level of consciousness
Alert versus unconscious 2.216 1.389 3.536
Drowsy versus unconscious 5.300 3.443 8.158
Hospital type
University versus community 1.530 1.244 1.882
Large nonuniversity versus community 1.266 0.892 1.796
Organization
Stroke unit versus general ward 6.861 4.497 10.467
Other ward versus general ward 5.248 3.007 9.161

Dissemination in Different Patient Groups
We observed that younger patients were more likely to be treated than older patients and that men have a better chance to be treated than women. The age effect is in agreement with previous studies,11 but the sex difference in this study (6%) was smaller than what was observed in a meta-analysis of trials and administrative registers (30%).14 An important but not surprising observation was that patients who had been living alone had a much lower chance of being treated with thrombolysis independent of other predictors. In patients with acute stroke,15 married/cohabitant people have been shown to arrive at the hospital earlier than singles. In Riks-Stroke, the proportion of patients ≥80 years of age that arrive at the hospital within 3 hours of onset of symptoms is considerably lower in patients living alone than in cohabitant patients (19% versus 28%; Riks-Stroke, unpublished data).

Hyperglycemia or a history of diabetes10,16 and previous stroke10 is associated with a modestly increased risk of severe hemorrhagic complications to thrombolysis, and the drug regulatory agencies in Europe have classified the combination of diabetes and previous stroke as a contraindication to the treatment. Our results indicate that, in routine clinical practice, considerable vigilance is exerted when either condition is present.

Although high blood pressure10 and ongoing therapy with antiplatelet agents17 are associated with a moderately elevated risk of intracranial bleeding during thrombotic treatment, clinical guidelines do not generally advise against the use of thrombolysis in such circumstances. In agreement with this, ongoing treatment with antiplatelet or antihypertensive agents had no impact on the odds for thrombolysis in this study.

Drowsy patients were more likely to be treated with thrombolysis than patients who were alert or unconscious. The group of alert patients includes many patients with mild stroke, in whom possible benefits may be judged not to be great enough to outweigh the risks. Therefore, it is not unexpected that the frequency of thrombolysis was lower in the alert versus the drowsy patients. The low frequency of thrombolysis in patients who were unconscious on admission is in agreement with very severe stroke (and CT signs of emerging parenchymal hypodensity) being a contraindication to the treatment.

A sensitivity analysis, excluding patients with current use of oral anticoagulants, previous stroke combined with known diabetes, and patients who were dependent in ADL before stroke, did not change the interpretation of the multiple regression analysis of thrombolysis treatment (data not shown). Hence, it is unlikely that contraindications to stroke thrombolysis had any major impact on the group comparisons.

Relations to Organization of Stroke Services and Region
The last county to offer thrombolysis to any significant extent (≥2%) did so 5 years after rtPA was approved by the regulatory authorities for use in patients with stroke. The fact that, in 2008, there was an obvious belt of low-frequency counties across mid-Sweden (Figure 2) indicates that regional patterns play an important role in the dissemination.

The strategy to increase the rate of thrombolysis has been different in different countries. Centralization to a few hospitals with stroke care excellence is a viable model for densely populated areas. In Sweden, with vast sparsely populated areas and a highly decentralized healthcare system, the strategy (mostly implicit) has been to implement thrombolysis for ischemic stroke in most of the hospitals admitting patients with acute stroke. Thrombolysis for acute myocardial infarction was introduced in a similar manner. University hospitals have led the implementation of thrombolysis. However, the most rapid increase in treatment frequency since 2003 was seen in specialized nonuniversity hospitals. In community hospitals, thrombolysis took an average 2 to 3 years longer than in the university hospitals. Note that several of the counties with high frequencies of...
thrombolysis are sparsely populated, for instance, the 2 northernmost counties with a total population of half a million in an area the same size as England and Wales together. Telemedicine has been launched in stroke care to enhance thrombolysis for acute stroke in remote and underserved populations, but it has not played a role in the implementation of thrombolysis in patients with stroke in Sweden.

As a whole, departments of medicine were considerably slower than departments of neurology to implement thrombolytic treatment for acute ischemic stroke. It seems that greater efforts should be made for departments of medicine to adopt thrombolysis because those are the only providers of acute stroke care in many sparsely populated parts of the country.

The likelihood of being treated with thrombolysis was higher if the patient had been admitted to a stroke unit than to a general ward or other type of ward. This is in accordance with the view that evidence-based interventions are more frequently applied in stroke units. It has been shown that certain organizational patterns may promote thrombolysis; these include informal and formal feedback, a learning culture, uncompromising, individual clinical leadership, and explicit goals. It should be noted that in many hospitals, even if a patient is admitted to a stroke unit or a general ward, the actual procedure of administering rtPA and early supervision may have been provided in an intensive care unit.

Safety
Nationwide adoption of thrombolysis, also performed in community hospitals, was achieved with apparent preservation of safety. Over time, there were no major differences in symptomatic intracranial bleeding rates or 90-day case fatality between different types of hospitals or between departments of neurology versus internal medicine. The symptomatic bleeding occurrence in the Riks-Stroke register (6.2% for the entire 2003 to 2008 period) is similar to that reported in Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST; 8.5%) and in pooled analyses of randomized controlled trials (8.6%). However, variations in definitions of symptomatic intracranial or intracerebral hemorrhage make direct comparisons difficult.

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Disclosures
B.S. is presently and K.A. was previously employed by The National Board of Health and Welfare, a governmental agency funding Riks-Stroke.

References


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Data Supplement (unedited) at:
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摘要
叶酸降低同型半胱氨酸的治疗在卒中预防中的效果：
Meta分析

Efficacy of Homocysteine-Lowering Therapy With Folic Acid in Stroke Prevention: A Meta-Analysis
Meng Lee, MD; Keun-Sik Hong, MD, PhD; Shen-Chih Chang, PhD; Jeffrey L. Saver, MD

背景和目的：虽然流行病学研究发现低血清同型半胱氨酸浓度与卒中风险的降低有相关性，但是降同型半胱氨酸治疗预防卒中的随机对照试验却未能取得一致的结果。我们进行一个随机对照试验的Meta分析，以评估补充叶酸在预防卒中上的效果。

方法：通过正式文献搜索确定重要的试验。采用相对危险度及其95%可信区间衡量补充叶酸和卒中风险之间的联系程度。汇总各试验资料后用固定效应模型分析。

结果：检索出符合条件的包括39 005个患者的13个随机对照试验，采用叶酸降低同型半胱氨酸治疗，以卒中作为结局指标。在所有试验中，补充叶酸在卒中预防方面趋向于轻度有效，但未达统计学意义（RR=0.93; 95% CI, 0.85-1.03; P=0.16）。在非二级预防的试验中相对危险度是0.89(95% CI, 0.79-0.99; P=0.03)。分层分析发现叶酸治疗在以下试验中疗效较显著: 联合叶酸和维生素B6、B12治疗的试验(RR=0.83; 95% CI, 0.71-0.97; P=0.02)，以及纳入较多男性患者的试验(男性:女性>2; RR=0.84; 95% CI, 0.74-0.94; P=0.003)。

结论：虽然叶酸在瑞典的普及较慢，但是普及速度已经逐渐加快，主要归因于非大学医院溶栓比率增加。在溶栓普及过程中，安全地实现了溶栓率的提高，但是患者接受溶栓的机会尚不平等。

关键词：急性缺血性脑卒中，实施，溶栓

急性缺血性脑卒中溶栓治疗在全国的普及情况：
瑞典卒中登记2003-2008年的经验

Dissemination of Thrombolysis for Acute Ischemic Stroke Across a Nation: Experiences From the Swedish Stroke Register, 2003 to 2008
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背景和目的：根据瑞典卒中登记Riks-Stroke的数据，分析自2003年瑞典批准溶栓以来，溶栓治疗在瑞典医院的普及情况。

方法：Riks-Stroke登记了瑞典所有78家医院的急性卒中住院患者。2003-2008年期间，共登记72 033例成人急性缺血性脑卒中住院患者。我们根据地区、患者特征和医疗机构性质分析溶栓的使用情况。

结果：瑞典全国范围内的溶栓率在2003年是0.9%，截至2008年提高到6.6%。瑞典的溶栓普及存在明显的地区差异，但是该差异在逐渐减少。非大学医院的溶栓治疗水平与大学医院类似，但溶栓在非大学医院的普及要比大学医院晚2-3年。在溶栓普及过程中，症状性颅内出血发生率保持在3%-9%未呈明显的增加趋势。年轻患者、男性、与他人一起生活、无卒中或糖尿病史是高溶栓率的独立预测因素，2008年，入住卒中单元患者接受溶栓的几率是入住普通病房患者的5倍。

结论：虽然溶栓在瑞典的普及较慢，但其普及速度已经逐渐加快，主要归因于非大学医院溶栓比率增加。在溶栓普及过程中，安全地实现了溶栓率的提高，但是患者接受溶栓的机会尚不平等。

关键词：急性缺血性脑卒中，实施，溶栓

叶酸降低同型半胱氨酸的治疗在卒中预防中的效果：Meta分析

Efficacy of Homocysteine-Lowering Therapy With Folic Acid in Stroke Prevention: A Meta-Analysis
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背景和目的：虽然流行病学研究发现低血清同型半胱氨酸浓度与卒中风险的降低有相关性，但是降同型半胱氨酸治疗预防卒中的随机对照试验却未能取得一致的结果。我们进行一个随机对照试验的Meta分析，以评估补充叶酸在预防卒中上的效果。

方法：通过正式文献搜索确定重要的试验。采用相对危险度及其95%可信区间衡量补充叶酸和卒中风险之间的联系程度。汇总各试验资料后用固定效应模型分析。

结果：检索出符合条件的包括39 005个患者的13个随机对照试验，采用叶酸降低同型半胱氨酸治疗，以卒中作为结局指标。在所有试验中，补充叶酸在卒中预防方面趋向于轻度有效，但未达统计学意义（RR=0.93; 95% CI, 0.85-1.03; P=0.16）。在非二级预防的试验中相对危险度是0.89(95% CI, 0.79-0.99; P=0.03)。分层分析发现叶酸治疗在以下试验中疗效较显著: 联合叶酸和维生素B6、B12治疗的试验(RR=0.83; 95% CI, 0.71-0.97; P=0.02)，以及纳入较多男性患者的试验(男性:女性>2; RR=0.84; 95% CI, 0.74-0.94; P=0.003)。

结论：目前暂无证据显示补充叶酸对卒中预防起重要作用，但是在卒中一级预防上有轻度益处，尤其是叶酸和B族维生素联合治疗以及针对男性患者的治疗，值得进一步研究。

关键词：同型半胱氨酸，叶酸，卒中，预防，Meta分析

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