Clinical Sciences

One-Year Incidence, Time Trends, and Predictors of Recurrent Ischemic Stroke in Sweden From 1998 to 2010
An Observational Study

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Background and Purpose—Recent data on the incidence, time trends, and predictors of recurrent ischemic stroke are limited for unselected patient populations.

Methods—Data for ischemic stroke patients were obtained from The Swedish Stroke Register (Riksstroke) between 1998 and 2009 and merged with The Swedish National Inpatient Register. A reference group of patients was created by Statistics Sweden. The ischemic stroke patient cohort was divided into 4 time periods. Recurrent ischemic stroke within 1 year was recorded until 2010. Kaplan–Meier and Cox regression analyses were performed to study time trends and predictors of ischemic stroke recurrence.

Results—Of 196 765 patients with ischemic stroke, 11.3% had a recurrent ischemic stroke within 1 year. The Kaplan–Meier estimates of the 1-year cumulative incidence of recurrent ischemic stroke decreased from 15.0% in 1998 to 2001 to 12.0% in 2007 to 2010 in the stroke patient cohort while the cumulative incidence of ischemic stroke decreased from 0.7% to 0.4% in the reference population. Age >75 years, prior ischemic stroke or myocardial infarction, atrial fibrillation without warfarin treatment, diabetes mellitus, and treatment with β-blockers or diuretics were associated with a higher risk while warfarin treatment for atrial fibrillation, lipid-lowering medication, and antithrombotic treatment (acetylsalicylic acid, dipyridamole) were associated with a reduced risk of recurrent ischemic stroke.

Conclusions—The risk of recurrent ischemic stroke decreased from 1998 to 2010. Well-known risk factors for stroke were associated with a higher risk of ischemic stroke recurrence; whereas, secondary preventive medication was associated with a reduced risk, emphasizing the importance of secondary preventive treatment. (***Stroke***. 2017;48:00-00. DOI: 10.1161/STROKEAHA.117.016815.)

Key Words: atrial fibrillation ◼ diabetes mellitus ◼ epidemiology ◼ myocardial infarction ◼ prognosis

Ischemic stroke continues to be an important cause of morbidity and mortality worldwide.[1] Patients with a former stroke have an elevated risk of having a recurrent stroke, a myocardial infarction, or death.[2–11] In Sweden, ischemic stroke, with an incidence of ≈25 000 cases per year, is one of the major causes of hospital admissions. About 3 of 4 strokes are first-ever events; while, one fourth are recurrent.[12] Although the incidence of ischemic stroke tends to decrease in the Western world,[1] time trends on the risk of recurrent stroke in large and unselected patient populations are less studied. Available studies indicate that the risk of stroke recurrence has declined over time in some countries.[11,13–19] For example, recent studies from the Italian region of Lombardy (years 2002–2010) and from Taiwan (years 2000–2012) found that the 1-year risk of ischemic stroke recurrence had decreased by 30% and 18%, respectively.[17,18] Most other studies have included small[13,19] or age-restricted[11,15,16] cohorts. Many studies included hemorrhagic stroke events,[11,13,14,19] and one study found diverging time trends between regions of the same country.[16]

There are several well-established risk factors for ischemic stroke, such as diabetes mellitus, atrial fibrillation, hypertension, cigarette smoking, and elevated blood lipids. To reduce the risk of recurrent ischemic stroke, secondary prevention strategies include blood pressure control, lipid-lowering drugs, and treatment with antiplatelet medication or anticoagulants.[20,21] In clinical trials, these treatments have resulted in relative risk reductions of 28%,[22] 16%,[23] 30%,[24] and 68%,[25] respectively. In Sweden, there has been increased use of secondary preventive drugs in recent years,[6] but it is unclear whether this has translated into risk reductions in clinical practice during the corresponding time period. A recurrent stroke can, at least to some extent, be considered a failure of

secondary prevention, and knowledge of predictors of ischemic stroke recurrence may improve secondary prevention measures after ischemic stroke. The aim of this study was to study the cumulative incidence, time trends, and predictors of recurrent ischemic stroke in a large and fairly unselected cohort of patients with ischemic stroke.

Methods

The Swedish Stroke Register (Riksstroke) is a national quality register where Swedish hospital admissions because of stroke are recorded. From 1998, all hospitals in Sweden report to Riksstroke, and the coverage gradually improved to 85% in 2009.[6,26] The Swedish National Inpatient Register (IPR) contains data about diagnoses and dates of discharge from hospitalizations in Sweden. The register has been validated with respect to the sensitivity and specificity of stroke events.[27,28] Patients with ischemic stroke, *10th revision of the International Classification of Diseases* (*ICD-10*) code I63, registered in Riksstroke from 1998 to 2009 were included in this study. The first recording for ischemic stroke in the database was used. The Riksstroke database was amalgamated with the IPR to identify recurrent ischemic stroke within 1 year from the admission date registered in Riksstroke (the index stroke). In the IPR, ischemic stroke was defined according to the *ICD* codes 433 (*ICD-9*) and I63 (*ICD-10*). In addition, we chose to count unspecified stroke events (codes 433 and I64) as recurrent ischemic strokes. Recurrent events were recorded from the day after hospital discharge until 364 days after admission. To avoid double registrations referring to the same index stroke, we excluded any ischemic stroke diagnosis registered at a rehab facility immediately after the index stroke hospitalization.

The Riksstroke database was also combined with the Swedish Cause of Death Register that includes all deaths in Sweden. This information was used to identify deaths occurring from the day of admission for the index stroke until 364 days after admission.

Information about age, sex, hospitalization time, treatment, and risk factors (smoking and concomitant diseases) was gathered from the Riksstroke database. Data on previous ischemic stroke or myocardial infarction occurring within 7 years before the index stroke event were collected from the IPR. Data about medication at discharge were collected from the Riksstroke database.

To compare the cumulative incidence of ischemic stroke in the study group with that in a population representative of the general population in Sweden, data for a reference population were obtained from the governmental agency, Statistics Sweden. The reference subjects were randomly selected 1:1 after matching for age, sex, and county with the ischemic stroke subjects and then linked to the IPR and to the Swedish Cause of Death Register by the same algorithms as the study population. We did not exclude reference subjects with prior stroke or other comorbidities to preserve the representativeness of the general population. The reference group was matched with the stroke cohort by January 1 of the year the stroke patient experienced the index stroke. Some subjects in the reference group died before the date of the corresponding index stroke (n=5763), and it was impossible to find a matching control in some cases (n=845); therefore, the reference group was somewhat smaller than the stroke cohort. The study was approved by the Regional Ethics Committee, Umeå.

Statistics

Patients were divided into 4 groups depending on the year of inclusion in Riksstroke (1998–2000, 2001–2003, 2004–2006, and 2007–2009). The reference group was stratified correspondingly. Results are presented as mean values with SD for continuous variables and as percentage for categorical variables. Incidences are presented as cumulative incidences estimated by the Kaplan–Meier method, with the day of admission set as day 0.

Comparisons between groups were made using Student *t* test for continuous variables and Pearson χ^2 test for categorical variables. $P<0.05$ was considered significant. Because some data are missing, especially in the early time periods of the study, the number of patients included in the analysis is presented for each variable. Some descriptive variables were not available for all time periods, and there were also variables with missing data. The valid number of subjects is therefor presented for each variable.

Kaplan–Meier curves with censoring for deaths were calculated on recurrent ischemic stroke for the above-mentioned 4 time periods, both for the ischemic stroke cohort and for the reference group, with the difference that ischemic stroke events in the reference group can be either first-ever or recurrent stroke. Comparisons between time periods were made by the log-rank test.

Multivariate Cox regression was used to identify predictors of ischemic stroke recurrence within 1 year. In the multivariate model, previously established predictors of risk were included together with factors that were found to be of potential importance in a univariate analysis ($P<0.10$). Patients included during 2004 to 2009 and discharged alive were used in the regression analyses. Patients included during the earlier time periods (1998–2003) could not be included because of lack of sufficient data on medication at discharge.

Because Cox regression analyses assume that the associated risk is proportionate over time, the assumption of proportional hazards was verified using Kaplan–Meier curves for the individual risk factors and scaled Schoenfeld residuals. For several variables, the associated risk differed significantly from the assumption of proportionality during the first 27 days from admission for the index event, and the data were therefore truncated to <28 days. This time limit also conforms with previous epidemiological studies. In the final regression analysis, 89 691 patients with stroke were included. The Holm–Bonferroni method was used to control multiple comparisons. IBM SPSS Statistics (version 22) and SAS, SAS institute Inc (version 9.4) were used for the statistical analyses.

Results

Descriptive Data

A total of 196 765 patients with ischemic stroke were included in this study. The mean age was 76.0 (±11.4) years, and 50.0% were women. In total, 43 494 (22.1%) of the patients died during the year of follow-up, of which 38 198 (19.4%) died without experiencing a recurrent ischemic stroke and 16 376 patients (8.3%) died during hospitalization. The mortality rate was similar for all 4 time periods (Table I in the online-only Data Supplement). The reference group consisted of 190 157 individuals, and 1 year from the corresponding index event, 11 152 individuals (5.9%) had died.

Baseline patient characteristics and treatment at discharge are shown in Tables 1 and 2. Patients with stroke who experienced a recurrent ischemic stroke more often had a history of ischemic stroke (17.7% versus 14.2%; $P<0.001$) or myocardial infarction (13.8% versus 12.1%; $P<0.001$) before the index event compared with patients with ischemic stroke without recurrent stroke. Patients with recurrent stroke more often had atrial fibrillation (29.4% versus 27.1%; $P<0.001$), diabetes mellitus (22.5% versus 20.2%; $P<0.001$), and treatment with antihypertensive therapies at admission (57.3% versus 52.8%; $P<0.001$). In addition, they were slightly younger (75.4 versus 76.1 years; $P<0.001$) and more often men (51.6% versus 49.8%; $P<0.001$).

In the reference population, the mean age among those experiencing an ischemic stroke was 82.3 (±7.0) compared with 75.4 (±11.5) years among the Riksstroke patients who had a recurrent ischemic stroke ($P<0.001$). The characteristics of stroke patients stratified by time period and occurrence of recurrent ischemic stroke within 1 year are shown in Table II in the online-only Data Supplement. The prevalence of prior

Table 1. Baseline Characteristics for Patients in the Ischemic Stroke Cohort

	% (n)	Missing Values % (n)
No. of subjects	196 765	
Age (years), mean±SD	76.0±11.4	0
Women	50.0 (98 425)	0
Prior ischemic stroke	14.6 (28 697)	0
Prior myocardial infarction	12.3 (24 248)	0
Atrial fibrillation	27.4 (52 169)	3.1 (6067)
Diabetes mellitus*	20.5 (30 568)	1.1 (1601)
Antihypertensive drugs at admission*	53.3 (78 809)	2.0 (2995)
Smoking*	16.2 (21 273)	12.8 (19 298)
Thrombolysis*	2.4 (3599)	2.6 (3912)

*Time periods 2000–2003, 2004–2006, and 2007–2009 (n=150 873).

myocardial infarction and atrial fibrillation increased over time and was persistently higher among patients who had a recurrent stroke during follow-up. Similarly, diabetes mellitus was more prevalent among patients with recurrent ischemic stroke, but the proportions were maintained during the study period. In contrast, there was a decrease in the number of prior ischemic strokes throughout the study period, but this was a methodological consequence because only the first ischemic stroke recorded in Riksstroke was included in this study.

Antihypertensive treatment became more common during the study period, and patients with recurrent ischemic stroke more often received these treatments (Table III in the online-only Data Supplement). In general, there was increased use of

Table 2. Secondary Preventive Treatment at Discharge After the Index Stroke Event

	% (n)	Missing Values % (n)
Warfarin*	12.1 (16 113)	3.5 (4767)
Antiplatelet drug(s)*	76.7 (105 824)	
ASA	65.8 (87 964)	3.2 (4354)
ASA+dipyridamole	16.3 (14 734)	34.5 (47 563)
Clopidogrel	5.9 (5296)	34.5 (47 641)
Lipid-lowering drug†	45.7 (41 213)	4.0 (3737)
Antihypertensive drug(s)†	72.1 (67 692)	
Calcium channel blocker	21.0 (18 905)	4.1 (3824)
β-Blocker	42.8 (38 527)	4.0 (3824)
ACE inhibitor	33.7 (30 285)	4.1 (3834)
ARB	12.6 (5808)	50.9 (47 776)
Diuretics	34.5 (31 070)	4.0 (3766)

For the composite treatment variables antiplatelet drug(s) and antihypertensive drug(s), the proportions presented are conservative estimates of patients on treatment, assuming that patients were not treated with drugs for which they had missing information. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; and ASA, acetylsalicylic acid.

*Time periods 2000–2003, 2004–2006, and 2007–2009 (n=138 031).

†Time periods 2004–2006 and 2007–2009 (n=93 829).

acetylsalicylic acid combined with dipyridamole, lipid-lowering medication, calcium channel blockers, and angiotensin receptor blockers; whereas, there was a decrease in the use of acetylsalicylic acid as single antiplatelet agent at discharge.

Cumulative Incidence and Time Trends
In total, the cumulative incidence of recurrent ischemic stroke within the first year was 13.1% (Table 3). In the reference population, the cumulative incidence of ischemic stroke was 0.5% during the corresponding year. The cumulative incidence of recurrent stroke decreased from 15.0% to 12.0% in the ischemic stroke patient cohort during the study period 1998 to 2010 (Figure; Table 3), corresponding to a relative risk reduction of 20.0%. The survival curves for censored events (ie, death before the occurrence of a recurrent stroke event) were similar for the 4 time periods (data not shown), and the time trend in cumulative incidence of recurrent stroke was maintained when patients with an ischemic stroke before the index event were excluded from the analysis (Figure I in the online-only Data Supplement). In the reference population, the cumulative incidence of ischemic stroke decreased from 0.7% to 0.4% during the same time period (Figure; Table 3).

Predictors
In the multivariate Cox regression analysis (Table 4), age >75 years, prior ischemic stroke, prior myocardial infarction, diabetes mellitus, atrial fibrillation without warfarin treatment at discharge, and treatment with diuretics or β-blockers at discharge were associated with an increased risk of recurrent ischemic stroke. The risk associated with the oldest age category had a tendency toward nonproportional risk during the year of follow-up. Warfarin treatment for atrial fibrillation, lipid-lowering medication, and treatment with acetylsalicylic acid with or without dipyridamole were associated with a decreased risk of ischemic stroke recurrence. No interaction was found between sex and age.

Discussion
In this study, we found that the 1-year risk of recurrent ischemic stroke has decreased in Sweden between the time periods 1998 to 2001 and 2007 to 2010. Well-known risk factors for stroke were important contributors to the risk of recurrent ischemic stroke, whereas several secondary preventive drugs were associated with a lower risk. This is one of the largest

Table 3. Kaplan–Meier Estimates of the 1-Year Cumulative Incidences of Recurrent Ischemic Stroke in the Riksstroke Cohort and of Ischemic Stroke in a Matched Reference Population

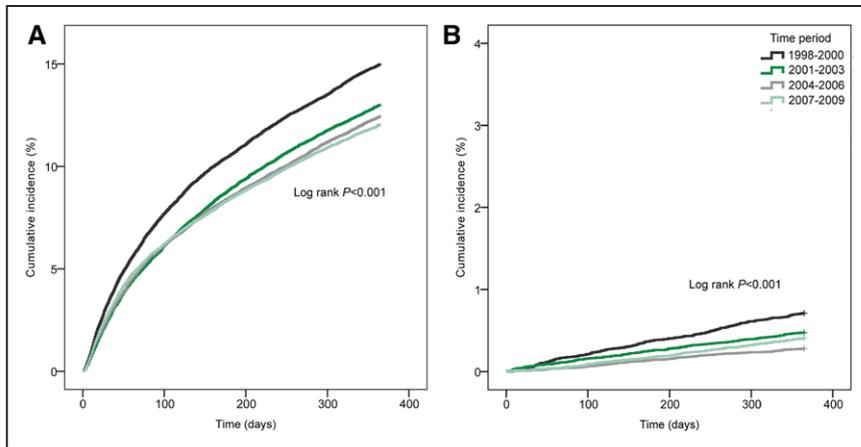| Year of Index Event	Riksstroke Cohort, % (n)	Reference Population, % (n)
1998–2000	15.0 (5970)	0.7 (315)
2001–2003	13.0 (5388)	0.5 (222)
2004–2006	12.4 (5540)	0.3 (140)
2007–2009	12.0 (5300)	0.4 (201)
Total	13.1 (22 198)	0.5 (878)

Figure. Kaplan–Meier analysis of the cumulative incidence of (**A**) recurrent ischemic stroke within 1 year after admission and (**B**) ischemic stroke in a matched reference population during the same year.

population-based studies assessing the temporal trends in risk of recurrent ischemic stroke. The population-based approach without age restriction is a major strength of this study. Age is an important contributor to higher stroke risk,[29] and the mean age of this stroke population was >75 years, markedly higher than several other time trend studies of stroke recurrence.[11,15,30] Thus, the characteristics of the patients in this study fairly well reflect the clinical reality of ischemic stroke patients in stroke care facilities. In addition, the large population size was important because it enabled assessment of predictors through multivariate analysis.

Table 4.   Multivariate Cox Regression Analysis of Predictors of Recurrent Ischemic Stroke Within 1 Year After Ischemic Stroke

	Hazard Ratio (95% CI)
Age 18–65 y	Ref.
Age 66–75 y	1.04 (0.97–1.12)
Age 76–85 y	1.13 (1.06–1.21)
Age ≥86 y	1.16 (1.07–1.25)
Sex (woman)	0.96 (0.91–1.00)
Prior ischemic stroke	1.28 (1.20–1.37)
Prior myocardial infarction	1.26 (1.18–1.34)
Diabetes mellitus	1.18 (1.12–1.25)
Atrial fibrillation, no warfarin at discharge	1.59 (1.50–1.68)
Atrial fibrillation, warfarin treatment at discharge	0.80 (0.73–0.88)
Acetylsalicylic acid	0.91 (0.85–0.97)
Acetylsalicylic acid+dipyridamole	0.85 (0.79–0.93)
Clopidogrel	1.06 (0.97–1.17)
Lipid-lowering drug	0.88 (0.84–0.93)
Calcium channel blockers	1.04 (0.98–1.09)
β-Blockers	1.21 (1.16–1.27)
Diuretics	1.07 (1.02–1.12)
ACE inhibitors	0.99 (0.95–1.04)

Events occurring during <28 days from admission were excluded from this analysis. The model included previously established risk factors for stroke and factors with a $P<0.10$ in a univariate analysis. ACE indicates angiotensin-converting enzyme; and CI, confidence interval.

The cumulative incidence of recurrent ischemic stroke within 1 year was 13.1%, similar to the 1-year cumulative incidence of 12.0% and 11.0% reported from Rochester during 1975 to 1990[5] and Erlangen during 1994 to 1999.[2,31] The cumulative incidence in our study was, however, higher than the 1-year incidences of 7.7%, 6.9%, 8.9%, and 5.7% found in Northern Manhattan (1993–1997),[8] South London (1995–2002),[4] North Dublin (2006–2007),[10] and South Korea (2010–2014),[9] respectively. The lower cumulative incidences reported in these studies could, at least partly, be because of more recent study time periods,[9,10] exclusion of events occurring during the first 21 days,[4] or because of demographic differences, such as lower mean age than in our study.[4,8–10] In addition, stroke recurrence should always be viewed in relation to all-cause mortality during the time period studied because death is a competing risk event that effects the Kaplan–Meier estimates of cumulative incidence. In Rochester and South London, 27.2% and 36.3% died within 1 year, respectively, which is higher than the 22.1% observed in our population.[4,5] For the other studies mentioned, 1-year mortality was not reported, and no study reported the proportion of participants censored from the survival analysis because of death before the end of follow-up.

The risk of ischemic stroke recurrence decreased by 20% between time periods 1998 to 2001 and 2007 to 2010. This is similar to the relative risk reductions reported from Taiwan[17] and Lombardy.[18] The same trend was true for ischemic stroke incidence in our reference population, and this is in accordance with the general decrease in incident stroke seen in most high-income countries during the last decades.[1,17,18] In Sweden, recent studies have reported a decline in early and long-term ischemic and ischemic/hemorrhagic stroke recurrences in later years for the age groups 18 to 54 years[15] and 25 to 74 years.[11] Our study confirmed a decline in the 1-year recurrence of ischemic stroke in a Swedish population without age restrictions.

Treatment with secondary preventive drugs was associated with a lowered recurrent ischemic stroke rate. Lipid-lowering after ischemic stroke is supported by clinical trials, such as the SPARCL study (Stroke Prevention by Aggressive Reduction in Cholesterol Levels),[23] and given high priorities in guidelines of secondary stroke prevention.[20,21] Antiplatelet therapy for non-embolic ischemic stroke is known to prevent recurrent stroke, and oral anticoagulation significantly reduces the risk of

recurrent ischemic stroke in patients with atrial fibrillation.[24,25] Although treatment data should be cautiously interpreted in observational studies because of inevitable confounding related to treatment decisions, our real life data add to the evidence of benefit associated with these well-established treatments. In the studies from Taiwan and Lombardy, the decrease of recurrent ischemic stroke events coincided with an increased use of secondary preventive drugs.[17,18] An increased use of secondary preventive drugs might have contributed to the decrease of recurrent stroke events in our study. We only had data to confirm an increased use during the last 2 time periods, whereas most of the reduction in recurrent stroke risk was observed during the earlier part of the study. We lacked important variables related to the treatment, such as patters of adherence and persistence to the medications and achievements on modifiable risk factor levels. There might also be other factors that contributed to the decrease in risk. For example, the decline in stroke incidence observed in the reference population during the study period could be a reflection of a lowered burden of cardiovascular risk factors in the general population, which might have contributed to an altered risk of recurrent events.

Treatment with β-blockers or diuretics was associated with an increased recurrent ischemic stroke rate. Diuretics tend to lower the visit-to-visit blood pressure variability, whereas β-blockers may increase this variability.[32] The importance of this is not yet fully known. No other antihypertensive treatment in our study was associated with a decrease in the risk of recurrent stroke, and the increased risk associated with treatment with β-blockers and diuretics may solely reflect that hypertension is a risk factor for recurrent ischemic stroke.

Limitations

Our study had some limitations. The Riksstroke register does not include variables to distinguish between different subtypes of ischemic strokes, and we could, therefore, not account for this factor in our analysis.

The coverage in Riksstroke improved over time. Because selection for registration was probably systematic, we cannot rule out that this could have affected the results. Patient baseline characteristics, such as age, sex distribution, and mortality, were, however, fairly consistent throughout the study period. We could not adjust for loss to follow-up because of emigration.

The use of IPR to identify recurrent ischemic stroke events probably overestimated the true incidence because the *ICD-10* manual allows use of the acute stroke diagnosis up to 12 months after a stroke event. To minimize the problem, we excluded ischemic stroke diagnosis registered at a rehabilitation facility immediately after the index hospitalization. Because it can be presumed that this inherent problem with the register was constant over time, excess registrations should not alter our results on time trends.

Our method did not catch events that were not admitted to hospital or early recurrent events occurring during the index hospitalization or at rehab immediately thereafter. Because of varying duration of hospitalization, the actual follow-up time in which early events could be detected differed between patients.

Because of properties of the data, the early time period after the index event could not be included in the multivariate model. Although we used a multivariate Cox regression model, there is a risk of residual confounding.

Summary

Recurrent ischemic stroke is common during the first year after an ischemic stroke, but the risk decreased from the years 1998 to 2001 to 2007 to 2010. Well-known risk factors for stroke, such as prior stroke or myocardial infarction, diabetes mellitus, and atrial fibrillation without warfarin treatment, are important predictors of recurrent ischemic stroke. The use of lipid-lowering medication, warfarin treatment for atrial fibrillation, acetylsalicylic acid, and dipyridamole was associated with a lower risk of ischemic stroke recurrence. Although our study was observational and the treatment data were not complete, it is reasonable to think that an increased use of secondary preventive drugs may have contributed to the decrease in stroke recurrence.

Disclosures

None.

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One-Year Incidence, Time Trends, and Predictors of Recurrent Ischemic Stroke in Sweden From 1998 to 2010: An Observational Study

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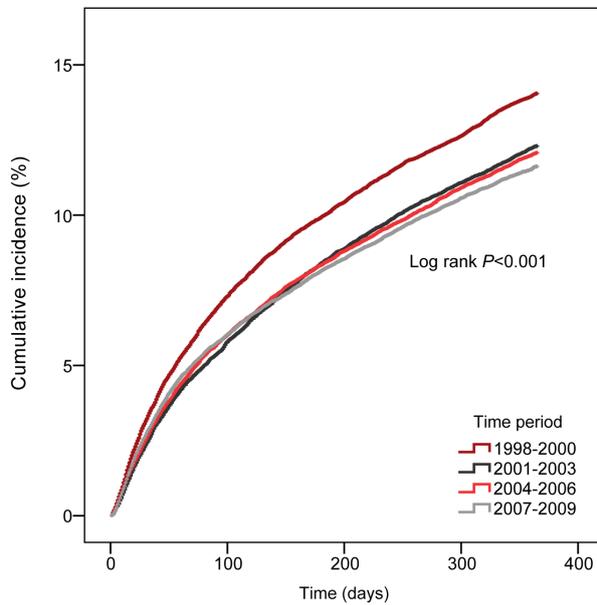http://stroke.ahajournals.org/content/early/2017/07/13/STROKEAHA.117.016815

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SUPPLEMENTAL MATERIAL

Supplementary Figure I. Kaplan-Meier analysis of the cumulative incidence of recurrent ischemic stroke within 1 year after a first-time ischemic stroke.

First-time ischemic stroke was defined as no previous ischemic stroke event registered in the In-patient Register within 7 years prior to the index event.

Supplementary Table I. In-hospital and 1-year mortality in the Riksstroke cohort, separated by time period.

Time period	Mortality	
	In-hospital, % (N)	1 year after admission, % (N)
1998-2000	7.7 (3534)	22.1 (10 132)
2001-2003	8.5 (4081)	22.5 (10 847)
2004-2006	8.4 (4322)	22.0 (11 355)
2007-2009	8.7 (4439)	21.9 (11 160)

Supplementary Table II. Baseline characteristics of ischemic stroke patients in the ischemic stroke cohort, stratified by four time periods and by occurrence of a recurrent ischemic stroke within 1 year.

	1998-2000		2001-2003		2004-2006		2007-2009	
	Recurrent ischemic stroke, % (N)							
	Yes	No	Yes	No	Yes	No	Yes	No
Subjects	13.0	87.0	11.2	88.8	10.7	89.3	10.4	89.6
	(5970)	(39922)	(5388)	(42895)	(5540)	(46043)	(5300)	(45707)
Age, mean (SD)	75.0	75.8	75.4	76.2	75.8	76.2	75.6	76.1
	(10.7)	(10.7)	(11.3)	(11.1)	(11.7)	(11.5)	(12.2)	(12.0)
Women	47.7	49.4	48.8	50.7	48.7	50.6	48.2	50.1
	(2846)	(19738)	(2630)	(21752)	(2700)	(23300)	(2557)	(22902)
Prior ischemic stroke	23.7	19.1	19.6	15.6	14.4	12.6	12.5	10.2
	(1417)	(7615)	(1054)	(6702)	(797)	(5793)	(662)	(4657)
Prior myocardial infarction	12.1	11.0	13.2	11.9	14.9	12.6	15.4	12.8
	(722)	(4410)	(711)	(5097)	(824)	(5805)	(817)	(5862)
Atrial fibrillation	27.4	26.7	28.6	26.0	30.5	27.5	31.1	28.0
	(1516)	(9920)	(1491)	(10796)	(1672)	(12499)	(1627)	(12648)
Diabetes mellitus	-	-	22.5	21.0	22.1	20.0	22.8	19.8
			(1194)	(8827)	(1217)	(9133)	(1201)	(8996)
Antihypertensive drugs at admission	-	-	51.9	48.0	58.6	53.3	61.4	56.7
			(2720)	(19934)	(3203)	(24185)	(3215)	(25552)
Smoking	-	-	17.9	16.6	16.4	16.0	15.8	15.8
			(820)	(5939)	(798)	(6489)	(756)	(6471)
Thrombolysis	-	-	0.6	0.4	2.9	1.9	5.9	4.6
			(32)	(170)	(158)	(859)	(312)	(2068)

SD, standard deviation.

Supplementary Table III. Secondary preventive treatment at discharge after the index stroke events, stratified by four time periods and by occurrence of a recurrent ischemic stroke within 1 year.

	1998-2000		2001-2003		2004-2006		2007-2009	
	Recurrent ischemic stroke, % (N)							
	Yes	No	Yes	No	Yes	No	Yes	No
Warfarin	-	-	11.3 (564)	11.1 (3986)	10.4 (565)	12.1 (4953)	12.2 (642)	13.2 (5403)
Antiplatelet drug(s)	-	-	69.6 (3749)	70.2 (27242)	80.5 (4462)	79.6 (33203)	79.6 (4219)	79.8 (32949)
Acetylsalicylic acid	-	-	75.0 (3748)	75.7 (27228)	65.5 (3560)	65.4 (26864)	57.9 (3049)	57.5 (23515)
Acetylsalicylic acid + dipyridamole	-	-	5.6 (1)	7.5 (10)	13.1 (675)	12.4 (4839)	18.8 (986)	20.1 (8223)
Clopidogrel	-	-	5.3 (1)	6.9 (9)	7.3 (376)	5.8 (2267)	7.1 (371)	5.6 (2272)
Lipid-lowering drug*	-	-	-	-	36.8 (1880)	37.0 (14362)	52.0 (2733)	54.4 (22238)
Antihypertensive drug(s)*					70.8 (3925)	67.6 (28216)	79.1 (4193)	76.0 (31358)
Calcium channel blockers*	-	-	-	-	19.4 (987)	19.1 (7396)	25.0 (1310)	22.6 (9212)
Beta blockers*	-	-	-	-	47.8 (2441)	41.9 (16275)	49.1 (2579)	42.2 (17232)
ACE inhibitors*	-	-	-	-	36.0 (1836)	33.5 (12990)	33.0 (1732)	33.6 (13727)
Angiotensin receptor blockers*	-	-	-	-	0.0 (0)	50.0 (1)	13.1 (685)	12.6 (5122)
Diuretics*	-	-	-	-	37.9 (1935)	35.3 (13733)	36.8 (1928)	33.0 (13474)

For the composite treatment variables, "antiplatelet drug(s)" and "antihypertensive drug(s)", the proportions presented are conservative estimates of patients on treatment, assuming that patients were not treated with drugs for which they had missing information. ASA, acetylsalicylic acid; ACE, angiotensin converting enzyme; ARB, Angiotensin receptor blocker.

Supplementary Table IV. Univariate Cox regression analysis of predictors of recurrent ischemic stroke within 1 year after ischemic stroke.

	Univariate hazard ratio (95% CI)	p-value	Missing values, %
Age 18-65	reference	-	0,0
Age 66 - 75	1.14 (1.06 - 1.22)	<0,001	0,0
Age 76 - 85	1.34 (1.26 - 1.42)	<0,001	0,0
Age ≥86	1.51 (1.41 - 1.61)	<0,001	0,0
Sex (woman)	1.01 (0.97 - 1.06)	0,527	0,0
Prior ischemic stroke	1.41 (1.32 - 1.50)	0,001	0,0
Prior myocardial infarction	1.45 (1.37 - 1.54)	<0,001	0,6
Diabetes mellitus	1.23 (1.17 - 1.29)	<0,001	0,0
Atrial fibrillation, no warfarin at discharge	1.81 (1.72 - 1.90)	<0,001	0,0
Atrial fibrillation, warfarin treatment at discharge	0.84 (0.78 - 0.91)	<0,001	1,4
Warfarin treatment, no atrial fibrillation	0.87 (0.81 - 0.93)	<0,001	10,0
Smoking	0.88 (0.83 - 0.94)	<0,001	1,1
Acetylsalicylic acid	1.05 (1.01 - 1.10)	0,021	3,6
Acetylsalicylic acid + dipyridamole	0.87 (0.82 - 0.93)	<0,001	3,7
Clopidogrel	1.19 (1.09 - 1.30)	<0,001	3,9
Lipid-lowering drug	0.83 (0.79 - 0.87)	<0,001	4,0
Calcium channel blockers	1.07 (1.01 - 1.12)	0,016	3,9
Beta blockers	1.36 (1.30 - 1.42)	<0,001	3,9
Diuretics	1.24 (1.18 - 1.29)	<0,001	4,0
ACE inhibitors	1.01 (0.97 - 1.06)	0,557	50,9
Angiotensin receptor blockers	1.00 (0.92 - 1.10)	0,949	0,0