Survival, causes of death and recurrence up to 3 years after stroke: A population-based study

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Abstract

Background and purpose: Up-to-date population-based information about long-term survival, causes of death and recurrence after stroke is needed.

Methods: Four hundred consecutive individuals in a population-based cohort of first-ever stroke between 2015 and 2016 in Lund, Sweden, were followed up to 3 years regarding (i) survival (Swedish Population Register); (ii) causes of death (Swedish Causes of Death Register); and (iii) stroke recurrence (interview and medical chart review). Index and recurrent ischaemic stroke cases were classified using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) and Oxfordshire Community Stroke Project; and comorbidities were classified using the Charlson Comorbidity Index. Cox regression was used to determine predictors for 3-year mortality. Survival rates were compared with three local studies over a 30-year timespan.

Results: Amongst 400 first-ever stroke patients, 265 (66%) survived 3 years post-stroke. Age (hazard ratio [HR] 1.09; 95% confidence interval [CI] 1.06–1.11), stroke severity (HR 1.11; 95% CI 1.08–1.13) and comorbidities (HR 1.36; 95% CI 1.22–1.53) were independently related to 3-year mortality. Amongst index ischaemic stroke patients, survival was lowest amongst those with cardio-aortic embolism (51/91; 56%). Cerebrovascular disease (54/135; 40%) and ischaemic heart disease (25/135; 19%) were the most common causes of death. Within 3 years, 30 (8%) had recurrent stroke. Amongst patients with index ischaemic stroke, 16/29 (55%) had a different TOAST pathogenetic mechanism or hemorrhagic stroke upon recurrence. Stroke survival improved between 1983–1985 and 2015–2016 (p = 0.002), but no significant change was observed between 2001–2002 and 2015–2016 (p = 0.48).

Conclusions: Stroke survival rates are relatively high, but their improvement over recent decades may be slowing down, possibly due to the composition of the first-ever stroke population. The common occurrence of changed pathogenetic mechanisms between first-ever and recurrent stroke highlights the value of reassessment in recurrent stroke.

Keywords
outcome, recurrent stroke, stroke, survival
INTRODUCTION

Stroke continues to be the second most common cause of death and a leading cause of disability worldwide [1]. Although the stroke incidence is declining in high-income countries, the burden of stroke has been projected to increase globally in the coming decades [2–6].

Previous estimates of survival after first-ever stroke range between 47% and 59% at 3 years after stroke in hospital-based studies in high-income countries [7,8], with higher mortality rates amongst patients with intracerebral hemorrhage (ICH) than amongst those with ischaemic stroke (IS). Recently, a European population-based study reported 65% 3-year survival after first-ever stroke [9], but many studies on long-term stroke survival are hospital-based, which may entail selection bias [10].

Mortality after first-ever stroke has been reported to be predominantly due to cardiovascular disease (including stroke mortality), but with excess mortality also amongst other non-cardiovascular causes of death compared with a general population [11]. However, recent population-based studies of causes of death after first-ever stroke are scarce.

In a 2011 meta-analysis, stroke recurrence rates were estimated at 26% at 5 years after first-ever stroke, but with substantial heterogeneity between studies [12]. A recent population-based study of stroke recurrence reported a 5-year recurrence rate of 10% and suggested that stroke recurrence rates declined until the mid-2000s and have since remained unchanged [13].

Since the global burden of stroke is projected to increase [5], and new treatment options such as non-vitamin K oral anticoagulants and recanalization therapies may have altered the prognosis after first-ever stroke in recent decades [14], up-to-date population-based studies are required. In the present study, the aim was to investigate 3-year survival, causes of death and stroke recurrence amongst a population-based cohort of first-ever stroke patients in southern Sweden, and also to compare survival with prior studies from the same area.

METHODS

This study was approved by the Regional Ethical Committee in Lund, Sweden (diary number 2018/393). Participating stroke survivors provided informed consent to participate. If they were unable to give consent, this was sought through their next-of-kin.

Study sample

The population-based cohort in the present study has been described in detail previously [3]. Case ascertainment was based on suggested gold standard criteria for epidemiological stroke studies [15]. Both prospective and retrospective methods of case ascertainment were used. Consecutive first-ever stroke patients between March 2015 and February 2016 in the catchment area of Skåne University Hospital in Lund, Sweden, were recruited prospectively in the primarily hospital-based local stroke study Lund Stroke Register and the nationwide hospital-based stroke register the Swedish National Stroke Register (Riksstroke). Furthermore, retrospective searches based on International Classification of Diseases 10 (ICD-10) diagnosis codes were performed in local databases for primary care, outpatient clinic visits and autopsy registers, and patients’ medical records were reviewed for potential inclusion in the present study. Stroke was defined according to the World Health Organization criteria [16]. Due to a small number of subarachnoid hemorrhage (SAH) cases in the cohort, only cases with index IS and ICH (and not SAH) are included in the present study.

Baseline characteristics

Data were collected at baseline on stroke risk factors including (i) hypertension (>140/90 at discharge, or antihypertensive treatment during the last 2 weeks); (ii) diabetes mellitus (prior diagnosis, or fasting plasma glucose levels >6.1 mmol/l, or non-fasting plasma glucose level >11 mmol/l); (iii) heart disease (ischaemic heart disease including myocardial infarction, angina pectoris, percutaneous coronary intervention or cardiac bypass surgery; heart failure; cardiac surgery; cardiac arrythmias); and (iv) hypercholesterolemia (prior diagnosis, lipid-lowering treatment in last 2 weeks, total cholesterol blood levels ≥5 mmol/l or low-density lipoprotein cholesterol blood levels ≥3 mmol/l). Data were also collected on medication at baseline and at discharge from medical records, including anticoagulant therapy (direct oral anticoagulants or warfarin) and anti-platelet therapy (aspirin, ADP receptor inhibitors, adenosine reuptake inhibitors or thromboxane inhibitors).

Stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS) [17,18]. Pathogenetic mechanisms of IS were assessed with the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification [19] as follows: cardio-aortic embolism (CE); large artery atherosclerosis (LAA); small artery occlusion (SAO); other causes (OC); and undetermined cause (UND-IS). Clinical IS syndromes were categorized with the Oxfordshire Community Stroke Project (OCSP) classification as lacunar infarct (LACI); partial anterior circulation infarct (PACI); total anterior circulation infarct (TACI); and posterior circulation infarct (POCI) [20]. Comorbidities at baseline were also assessed with the Charlson Comorbidity Index (CCI) [21,22] by reviewing medical records.

Mortality and causes of death

Data on survival status were obtained from the Swedish Population Register and the Swedish Cause of Death Register [23], using unique Swedish personal identification numbers for case validation.

Cause of death data were evaluated by using ICD-10 diagnosis codes in the Swedish Cause of Death Register. In this study, underlying causes of death were categorized into (i) cerebrovascular...
disease (ICD-10: I60–I69); (ii) ischaemic heart disease (ICD-10: I20–I25, including patients with cardiac arrest with no other apparent cause); (iii) cancer (ICD-10: C00–D48); (iv) infectious diseases (ICD-10: A00–B99, G00–G09, I38–I39, J09–J22, J85–J86); (v) trauma (ICD-10: S00–T32, V01–X59); and (vi) other causes. In cases where categorization could not be completed using the underlying cause of death, the contributing causes of death and medical records were used as additional information and cases were discussed by two of the authors (J.A. and H.D.) for a consensus decision.

Recurrence

Stroke recurrence within 3 years after first-ever stroke was evaluated by review of the participants’ hospital-based electronic medical records for the region of Skåne, Sweden. Primary-care-based electronic medical records and autopsy registers were not assessed or screened for recurrent stroke. Participants who attended follow-up visits were also asked if they had suspected or been diagnosed with a recurrent stroke after their first-ever stroke, in which case supporting documentation was sought in medical records. Recurrent stroke was defined as any new acute focal (or global in the case of subarachnoid hemorrhage) neurological event with no apparent cause other than vascular, lasting 24 h or leading to death that occurred after the initial ictus (including acute worsening of an established non-progressive deficit that was not considered to be caused by edema, brain shift, hemorrhagic transformation, concurrent illness or drug toxicity) [24]. Uncertain cases were discussed by two of the authors (J.A. and H.D.) for a consensus decision. Identified recurrent stroke events were also assessed with NIHSS [18], TOAST [19] and OCSP [20] via medical record review. A stroke diagnosis code registered as cause of death in the Swedish Cause of Death Register, without supporting documentation in medical records, was not regarded as a stroke recurrence [25].

Survival comparisons with prior studies

Three-year survival data from the present study were compared with prior studies from the same geographical area for 1983–1985, 1993–1995 and 2001–2002 [26–28]. These studies include data on 3-year stroke survival that have been incorporated in the present study [26–28]. The cohorts from 1983–1985 and 1993–1995 were predominantly hospital-based, whilst the two later time periods were population-based. Raw data from all four time periods were analyzed with Kaplan–Meier curves and the log-rank test. For comparisons with the current study, SAH cases were excluded in all time periods.

Statistics

Baseline characteristics were analyzed for between-group differences using the chi-squared test for categorical variables and the Mann–Whitney U test for ordinal variables. Kaplan–Meier curves were generated for stroke survival and recurrence with censoring at 3 years (1095 days). The log-rank test was used to detect between-group differences in survival/recurrence status over time, provided that the number of censored cases was acceptably similar in each group. Cox regression was used to determine associations with survival as well as with recurrence, and univariable and multivariable analyses were performed separately using pre-defined variables. When analyzing predictors for 3-year survival amongst all stroke subtypes the following baseline variables were included: age; sex (female as reference category); index stroke subtype (IS as the reference category); CCI; NIHSS; hypertension (no hypertension as the reference category); hypercholesterolemia (no hypercholesterolemia as the reference category); and active smoking (no smoking as the reference category). When analyzing predictors for 3-year mortality amongst index IS cases, the following baseline variables were included: age; sex; TOAST classification of index stroke (CE as the reference category); OCSP classification of index stroke (LACI as the reference category); CCI; NIHSS; hypertension; hypercholesterolemia; and active smoking. Forest plots of hazard ratios for multivariable Cox regression analyses were produced in Microsoft Excel. Bonferroni corrections of p values were calculated based on the number of simultaneous variables being tested. Statistical analyses were performed using SPSS version 25.

RESULTS

The population-based cohort included 400 first-ever stroke patients (335 IS; 60 ICH; 5 UND). Since a previous study of this cohort [3], one additional patient with IS has been retrospectively detected. All 400 participants were followed up regarding survival status. Four (1%) patients were not screened for stroke recurrence through medical record review because of non-consent. In all, 376 (94%) were hospitalized. Amongst 335 IS patients, 324 (97%) underwent acute computed tomography imaging, 181 (54%) underwent magnetic resonance imaging, 199 (59%) underwent intracranial vascular diagnostics and 262 (78%) underwent extracranial vascular diagnostics.

Three-year stroke survival

At 3 years, 34% (135/400) had died. Patients with index ICH had a lower 3-year survival rate than those with IS (55% vs. 69%; log-rank test p = 0.01). In all, age (hazard ratio [HR] 1.09; 95% confidence interval [CI] 1.06–1.11), CCI at baseline (HR 1.36; 95% CI 1.22–1.53) and NIHSS at baseline (HR 1.11; 95% CI 1.08–1.13) were independently related to worse 3-year survival. Baseline characteristics of all first-ever stroke patients are presented in Table 1. Kaplan–Meier diagrams of 3-year survival amongst stroke subtypes are presented in Figure 1. Univariable and multivariable analysis results are presented in Table 2 and Figure S2.

Amongst those with index IS, no patients with the TOAST classification OC died within 3 years after first-ever stroke. Three-year
Survival was lower amongst those with index CE (51/91; 56%) compared to LAA (35/44; 80%) and SAO (35/40; 88%) (log-rank test \( p = .01 \) and \( p = 0.001 \), respectively). Compared with LACI as the reference category, PACI and POCI stroke syndromes were independently associated with higher 3-year mortality (HR 2.81; 95% CI 1.46–5.41; and HR 4.66; 95% CI 2.12–10.27, respectively). Patients with TACI at baseline received acute recanalization therapy in 36% of cases, compared to between 9% and 15% for PACI, LACI and POCI (\( \chi^2 \) test: \( p = 0.008 \)).

Kaplan–Meier diagrams of 3-year mortality amongst pathogenetic mechanisms of IS are presented in Figure 2. Univariable and multivariable analyses are presented in Table 3 and Figure S3.

### Causes of death

The most common cause of death at 3 years after first-ever stroke was cerebrovascular disease (54/135; 40%), followed by other causes (34/135; 25%) and ischaemic heart disease (25/135; 19%).
In total, 50 (37%) participants died due to the index stroke event, whereas four (3%) individuals died due to recurrent stroke (two recurrent IS and two recurrent ICH). Other causes included death due to cardiac arrhythmias, acute vascular pathology and kidney failure. In all, the estimated 3-year cerebrovascular mortality after first-ever stroke was 14% (54/400) whereas the estimated 3-year cardiovascular mortality (cerebrovascular and ischaemic heart disease) was 20% (79/400). Causes of death over the follow-up time are presented in Figure 3 and Table S2. Cumulative mortality by stroke subtype and pathogenetic mechanisms of IS is presented in Table S1.

**Three-year stroke recurrence**

The total 3-year stroke recurrence rate was 8% (30/400), and 9% (29/335) amongst those with IS at baseline. Four of these individuals had a fatal stroke recurrence. After first-ever IS, 29% (98/335) were discharged with anticoagulant therapy and 60% (200/335) were discharged with anti-platelet therapy.

Amongst IS patients with any recurrent stroke within 3 years, UND-IS was the most common baseline pathogenetic mechanism (15/29; 52%), followed by CE (8/29; 28%) and SAO (4/29; 14%). No stroke recurrences occurred within 3 years amongst those with OC at baseline.

In 13 cases (45%), the pathogenetic mechanism of index IS was the same as the pathogenetic mechanism of recurrent stroke. In another 13 cases (45%) there was a recurrent IS with a different pathogenetic mechanism than the index IS. In three cases (10%), there was a recurrent stroke with a different stroke subtype (i.e. hemorrhagic stroke) than the index IS. The most common combination of baseline and recurrent stroke pathogenetic mechanism or subtype was UND-IS at baseline and UND-IS upon recurrence (6/30; 20%), followed by CE at baseline and CE upon recurrence (4/30; 13%). The most common change from pathogenetic mechanism of index stroke to recurrent stroke mechanism was from UND-IS to CE (4/30; 13%).

Stroke recurrence patterns amongst pathogenetic mechanisms of baseline stroke are presented in Table 4. Kaplan–Meier analysis of stroke recurrence is presented in Figure S1.

### TABLE 2 Univariable and multivariable Cox regression analyses of 3-year mortality in 400 patients with first-ever stroke

|                          | Univariable analysis |          | Multivariable analysis |          |
|--------------------------|----------------------|----------|------------------------|----------|
|                          | HR       | 95% CI   | p         | HR       | 95% CI   | p         |
| Age                      | 1.07     | 1.05–1.09| <.001     | 1.09     | 1.06–1.11| <0.001    |
| Sex, female              | 1.53     | 1.09–2.14| .01       | 0.75     | 0.51–1.10| 0.13      |
| Stroke subtype, ISa      | –        | –        | –         | –        | –        | –         |
| Stroke subtype, ICH      | 1.72     | 1.13–2.63| .01       | 1.60     | 0.99–2.60| 0.06      |
| Stroke subtype, UNDb     | 3.34     | 1.06–10.53| 0.04     | –        | –        | –         |
| CCI                      | 1.35     | 1.22–1.50| <.0001    | 1.37     | 1.22–1.53| <.0001    |
| NIHSS                    | 1.10     | 1.08–1.11| <.0001    | 1.11     | 1.08–1.13| <.0001    |
| Hypertension             | 0.83     | 0.58–1.19| 0.30      | 1.11     | 0.73–1.67| 0.63      |
| Hypercholesterolemia     | 1.62     | 1.15–2.29| 0.01      | 1.24     | 0.83–1.85| 0.30      |
| Current smoking          | 1.65     | 0.98–2.79| 0.06      | 1.21     | 0.84–1.73| 0.77      |

**Notes:** For dichotomous variables, “no” was used as the reference category. Bonferroni-adjusted p value for multiple comparisons 0.007.

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; ICH, intracerebral hemorrhage; IS, ischaemic stroke; NIHSS, National Institutes of Health Stroke Scale; UND, undetermined.

*a*Reference category.

*b*UND stroke subtype not evaluated in multivariable analysis due to the small number of cases leading to extreme CIs.

![Figure 2](image-url)
Amongst those with ICH at baseline, only one recurrent stroke (1/60, 2%) was observed at the 3-year follow-up (recurrent IS with CE pathogenetic mechanism).

Over the four periods 1983–1985, 1993–1995, 2001–2002 and 2015–2016, 3-year stroke survival increased continually (509/906, 56%; 758/1259, 60%; 282/439, 64%; and 265/400, 66%, respectively; pooled log-rank test \( p = 0.002 \)). Survival rates at 3 years over these four periods are visualized in Kaplan–Meier curves in Figure 4.

This is one of very few population-based studies examining changes in stroke survival in a specified geographical area during a time period of over 30 years. In our new study, approximately two-thirds survived 3 years after the index stroke. Most deaths were due to cerebrovascular causes. Less than one in 10 stroke patients had a recurrent stroke within 3 years. In over half of the recurrent stroke cases, pathogenetic mechanisms or stroke subtypes were different at the index stroke and the recurrent stroke event.

### Comparisons of 3-year stroke survival with prior studies

Over the four periods 1983–1985, 1993–1995, 2001–2002 and 2015–2016, 3-year stroke survival increased continually (509/906, 56%; 758/1259, 60%; 282/439, 64%; and 265/400, 66%, respectively; pooled log-rank test \( p = 0.002 \)). Survival rates at 3 years over these four periods are visualized in Kaplan–Meier curves in Figure 4.

### Discussion

This is one of very few population-based studies examining changes in stroke survival in a specified geographical area during a time period of over 30 years. In our new study, approximately two-thirds survived 3 years after the index stroke. Most deaths were due to cerebrovascular causes. Less than one in 10 stroke patients had a recurrent stroke within 3 years. In over half of the recurrent stroke cases, pathogenetic mechanisms or stroke subtypes were different at the index stroke and the recurrent stroke event.

### Table 3

Univariable and multivariable Cox regression analyses of 3-year mortality in 335 patients with first-ever ischaemic stroke

|                | Univariable analysis | Multivariable analysis |
|----------------|----------------------|------------------------|
|                | HR 95% CI p          | HR 95% CI p            |
| Age           | 1.08 1.05–1.10 <.0001 | 1.09 1.06–1.11 <.0001  |
| Sex, female   | 1.56 1.06–2.28 0.03  | 0.86 0.56–1.34 .52     |
| TOAST, SAO⁴   | – – – – – –          | – – – – – –            |
| TOAST, CE     | 4.41 1.74–11.19 0.002 | 1.11 0.40–3.10 .85     |
| TOAST, LAA    | 1.75 0.59–5.23 0.31  | 0.51 0.15–1.71 .28     |
| TOAST, OTC⁵   | – – – – – –          | – – – – – –            |
| TOAST, UND-IS | 3.16 1.26–7.92 .01   | 0.90 0.32–2.52 .85     |
| OCSP, LACI⁶   | – – – – – –          | – – – – – –            |
| OCSP, PACI    | 2.04 1.18–3.52 .01   | 2.81 1.46–5.41 .002    |
| OCSP, TACI    | 3.94 2.03–7.65 .001  | 2.27 0.83–6.20 .11     |
| OCSP, POCI    | 1.81 0.92–3.59 0.09  | 4.66 2.12–10.27 <.001  |
| CCI           | 1.36 1.21–1.53 <.001 | 1.35 1.18–1.54 <.001   |
| NIHSS         | 1.10 1.07–1.12 <.001 | 1.10 1.06–1.15 <.001   |
| Hypertension  | 1.29 0.86–1.93 0.22  | 1.30 0.82–2.08 .27     |
| Hypercholesterolemia | 1.56 1.06–2.29 0.03 | 1.22 0.79–1.89 .38     |
| Current smoking | 1.34 0.78–2.32 0.29 | 0.84 0.44–1.58 .59     |

Notes: For dichotomous variables, "no" was used as the reference category. Bonferroni-adjusted \( p \) value for multiple comparisons 0.005.

Abbreviations: CCI, Charlson Comorbidity Index; CE, cardio-aortic embolism; CI, confidence interval; HR, hazard ratio; LAA, large artery atherosclerosis; LACI, lacunar infarct; NIHSS, National Institutes of Health Stroke Scale; OCSP, Oxfordshire Community Stroke Project; OTC, other causes; PACI, partial anterior circulation infarct; POCI, posterior circulation infarct; SAO, small artery occlusion; TACI, total anterior circulation infarct; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; UND-IS, undetermined pathogenetic mechanism.

⁴Reference category.

⁵OTC TOAST classification HR and 95% CI not presented in multivariable analysis due to the small number of cases leading to extreme CIs.
Recently, a nationwide hospital-based study of long-term stroke survival in Sweden from the Swedish National Stroke Register reported a 3-year survival rate of 59% [8], whilst a population-based study from a high-income setting presented an observed survival of approximately 64% [9]. Our finding of 66% 3-year survival is closer to the latter population-based study than the recent Swedish hospital-based study, which may be attributable to different methodologies [10].

Mortality after first-ever stroke has declined in high-income settings over the last decades [29]. It has been suggested that this improvement is due to enhanced secondary prevention treatment, including increased prescription of oral anticoagulants in IS with concomitant atrial fibrillation [14], decreased smoking prevalence, decreased systolic blood pressure in the population [30] and improved acute therapies for IS [31]. However, in certain regions, survival rates have stagnated or worsened at the beginning of the 2010s [32]. In our study area, previous studies demonstrated a 3-year survival rate of 60% in the early 1990s and 65% in the early 2000s [26–28]. Upon analysis of survival over three decades in our area using data from these prior studies, excluding SAH, there has been a significant increase in 3-year survival after first-ever stroke in our area since the 1980s (Figure 4). Since the early 1990s, stroke survival has improved but the rate of improvement appears to be slowing down, where there was no statistically significant difference between 2001–2002 and 2015–2016 (although the numerical trend was in favor of 2015–2016). In the study populations from 1983–1985, 1993–1995 and 2001–2002 and our present study, 30-day case fatality (excluding SAH) also decreased numerically since the earliest time period (14%, 15%, 14% and 12%, respectively; log-rank test \( p = 0.72 \)), most markedly in 2015–2016, suggesting that the recent possible decline in survival improvement rate is driven primarily by differences in longer-term survival. Moreover, the proportions of first-ever stroke patients over 75 years of age in the four time periods were 44%, 46%, 59% and 46%, respectively. Thus, the observed tendency of stagnating survival improvement after first-ever stroke is not clearly due to continually increasing age amongst first-ever stroke patients. During the same time frame, the stroke incidence decreased in our region, primarily amongst those older than 65 years [3]. Speculatively, a greater decrease in incidence amongst otherwise healthy individuals with fewer comorbidities could lead to a lower life expectancy in the first-ever stroke population, leading to a stagnation of stroke survival improvement.

Amongst pathogenetic mechanisms of IS, CE was associated with higher 3-year mortality than LAA and SAO, with a 3-year survival rate of just over 50%. However, no survival difference remained upon regression analysis, which probably reflects that patients with index CE were older (median age 80 vs. 77, 74 and 75 years for LAA, SAO and UND-IS, respectively) and had more comorbidities (median CCI = 2 vs. CCI = 1 for LAA, SAO and UND-IS). Notably, it was found

| TABLE 4 | Recurrent stroke patterns within 3 years of index stroke, by pathogenetic mechanism of stroke (TOAST) |
|---|---|---|---|---|---|---|
| | All index IS \(^b\) | Index CE \((n = 91)\) | Index LAA \((n = 44)\) | Index SAO \((n = 40)\) | Index UND-IS \((n = 153)\) |
| Any recurrent stroke, n (%) | 29 (9) | 8 (9) | 2 (5) | 4 (10) | 15 (10) |
| Recurrent CE, n (%) | 8 (28) | 4 (50) | 0 | 0 | 4 (27) |
| Recurrent LAA, n (%) | 4 (14) | 0 | 2 (100) | 0 | 2 (13) |
| Recurrent SAO, n (%) | 3 (10) | 0 | 0 | 1 (25) | 2 (13) |
| Recurrent UND-IS, n (%) | 10 (34) | 3 (38) | 0 | 1 (25) | 6 (40) |
| Recurrent HS \(^a\), n (%) | 4 (14) | 1 (13) | 0 | 2 (50) | 1 (7) |

Abbreviations: CE, cardio-aortic embolism; HS, any hemorrhagic stroke (ICH or subarachnoid hemorrhage); ICH, intracerebral hemorrhage; IS, ischaemic stroke; LAA, large artery atherosclerosis; SAO, small artery occlusion; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; UND-IS, undetermined pathogenetic mechanism of ischaemic stroke.

\(^a\)One patient with index SAO had recurrent subarachnoid hemorrhage; all other HS cases were ICH.

\(^b\)One patient with index ICH had a recurrent IS of CE pathogenetic mechanism.
that, amongst clinical syndromes of IS, TACI was not associated with a higher risk of stroke mortality compared to LACI. TACI has previously been associated with the highest mortality and morbidity amongst OCSP stroke syndromes [20]. In our cohort, 35% of individuals with TACI upon presentation received acute recanalization therapy, compared to 15%, 13% and 9% amongst participants with LACI, PACI and POCl, respectively. Recanalization therapy is likely to have affected the short- and long-term mortality of first-ever IS patients with TACI.

The proportion of cardiovascular mortality in our study was 57% compared with approximately two-thirds in a prior study from 2001 [11]. It is difficult to draw conclusions on patterns in mortality over time because the validity of diagnostic accuracy in death certificates both worldwide and in Sweden has been questioned [33,34]. However, death certificates are practically more useful for studying cause of death data compared to the gold standard clinical autopsy, due to declining clinical autopsy rates [34]. Nonetheless, most patients who died within 3 years in the present study died due to cardiovascular disease, which emphasizes the importance of secondary cardiovascular prevention after first-ever stroke.

At 3 years after first-ever stroke, the recurrence rate was 8% in our cohort. Recurrence rates of 10% at 5 years have recently been published, as well as trend data showing that recurrence rates have stagnated since 2005 after declining for several decades [12]. No significant predictors for stroke recurrence were identifiable in the present study, probably due to the small number of events leading to suboptimal power. Over half of the patients in our cohort changed pathogenetic mechanism or subtype of stroke between the index and recurrent events, and the majority of these changes were from the UND-IS mechanism at baseline—perhaps indicating a need for a broader investigation of stroke risk factors in first-ever stroke patients. A detailed analysis of the extent of investigation performed after first-ever stroke lies outside the scope of the present study, and rates of long-term cardiac monitoring were not registered—which may have affected the classification of recurrent strokes. Furthermore, in the present study, 46% of IS cases had the UND-IS mechanism at baseline, compared with 20% in the aforementioned study [12] which also had a correspondingly higher proportion of SAO stroke. It is therefore possible that the prevalence of change of pathogenetic mechanism in recurrent stroke in our study is somewhat inflated by lack of initial clinical or radiological investigation, for instance acute magnetic resonance imaging studies (which were performed after 54% of index IS in our cohort) to visualize subcortical stroke.

The present study’s strengths include the population-based methodology, low loss-to-follow-up rates and reliable linkage of mortality data due to the unique personal identification numbers in Sweden, as well as several decades of available data for analysis of survival trends. Limitations include the low absolute number of cases, few recurrent stroke events, solely patient- and hospital-based methodology for detecting recurrent stroke, limited generalizability due to case ascertainment in a small geographical area, and cause of death data based on death certificates that may be unreliable. It is also notable that differences in case ascertainment may have affected our estimates of time trends in survival, since the cohorts from 1983-1985 and 1993-1995 were predominantly hospital-based [26,27], whilst the cohorts from 2001-2002 and 2015–2016 used a similar population-based methodology.

In conclusion, our study provides new population-based data describing a relatively low stroke mortality and recurrence rate and demonstrates that cardiovascular disease is the predominant cause of death after first-ever stroke in a high-income country setting. Stroke survival rates in our area have increased since the 1980s, but the rate of this improvement appears to be slowing down. Subsequent studies with the present cohort will further examine morbidity and complications after stroke.

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CONFLICT OF INTEREST

Arne Lindgren: Personal fees from Bayer, Astra Zeneca, BMS Pfizer and Portola. The other authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Joseph Aked: Conceptualization (equal); data curation (lead); formal analysis (lead); funding acquisition (supporting); investigation (equal); methodology (equal); project administration (lead); visualization (lead); writing—original draft (lead); writing—review and editing (equal). Hossein Delavaran: Conceptualization (equal); data curation (supporting); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (supporting); supervision (equal); validation (supporting); writing—original draft (supporting); writing—review and editing (equal). Arne Lindgren: Conceptualization (equal); data curation (supporting); formal analysis (supporting); funding acquisition (lead); investigation (equal); methodology (equal); project administration (equal); resources (lead); software (lead); supervision (equal); validation (equal); visualization (equal); writing—original draft (supporting); writing—review and editing (equal).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

Fig S2
Fig S3
App S1
App S2

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