20-year time trends in long-term case-fatality and recurrence rates after ischemic stroke stratified by aetiology

Cover title: The population-based Erlangen Stroke Project

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Tables 4; **Figures** 2

Keywords*:* ischemic stroke, survival analysis, recurrent event, case-fatality

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Abstract

Background and Purpose-Data on long-term survival and recurrence after stroke are lacking. We investigated time trends in ischemic stroke case-fatality and recurrence rates over 20-years stratified by aetiological subtype according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification within a population-based stroke register in Germany.

Methods-Data was collected within the Erlangen Stroke Project, a prospective, population-based stroke register covering a source population of 105,164 inhabitants (2010). Case fatality and recurrence rates for 3months, 1year and 5years were estimated with Kaplan-Meier estimates. Sex-specific time trends for case-fatality and recurrence rates were estimated with Cox regression. We adjusted for age, sex and year of event and stratified for aetiological subtypes. A sensitivity analysis with competing risk analysis for time trends in recurrence were performed.

Results-Between 1996 and 2015, 3,346 patients with first ischemic stroke were included; age-standardized incidence per 100,000 was 75.8 in women and 131.6 in men (2015). Overall, 5-year survival probabilities were 50.4% (95%-CI: 47.9-53.1) in women and 59.2% (95%-CI: 56.4-62.0) in men; 5-year survival was highest in patients with first stroke due to small-artery occlusion (women: 71.8% (95%-CI: 67.1-76.9); men: 75.9% (95%-CI: 71.3-80.9)) and lowest in cardioembolic stroke (women: 35.7% (95%-CI: 31.0-41.1); men: 47.8% (95%-CI: 42.2-54.3)). 5-year recurrence rates were 20.1% (95%-CI: 17.5-22.6) in women and 20.1% (95%-CI 17.5-22.7) in men ; 5-year recurrence rate was lowest in women in stroke due to small artery occlusion 16.0% (95%-CI: 11.7-20.1) and in men in large-artery atherosclerosis 16.6% (95%-CI: (8.7-23.9); highest risk of recurrence was observed in undefined strokes (women: 22.3% (95%-CI: 17.8-26.6); men: 21.4% (95%-CI: 16.7-25.9)). Cox regression revealed

improvements in case-fatality rates over time with differences in stroke aetiologies. No time trends in recurrence rates were observed.

Conclusion-Long-term survival and recurrence varied substantially by first stroke aetiology. Survival probabilities improved over the last two decades, no major trends in stroke recurrence rates were observed.

Non-standard Abbreviations and Acronyms

CE	cardioembolism
CI	Confidence Interval
CFR	case-fatality rates
HR	Hazard Ratio
LAA	large-artery atherosclerosis
OC	stroke of other determined cause
SAO	small-artery occlusion
TOAST	Trial of Org 10172 in Acute Stroke Treatment
UND	stroke of undetermined cause

Introduction

Based on routine mortality statistics ischemic stroke mortality decreased between 1998 and 2015 about 50% in Germany[1]. It is unclear, to what extent this decline is attributable to changes in stroke incidence or to changes in case fatality and recurrence rates. Previous analysis from the Erlanger Stroke Project showed that ischemic stroke incidence in Germany decreased between 1995 to 2010 in men but not in women with substantial differences in aetiological subtypes of ischemic stroke according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification[2]. However, the burden of stroke in the population is not only influenced by incidence but also by case-fatality rates (CFR) as decreasing CFR accompanied by constant incidence rates leads to increasing prevalence[3]. Another important factor that drives the burden of stroke in the population are recurrence rates, because a second stroke is associated with a longer in-hospital stay, higher mortality and a higher degree of disability[4, 5].

Epidemiological data on the long-term time trends in CFR and recurrence rates in ischemic stroke patients are scarce. Recent publications from the population-based South London Stroke Register showed improved survival rates in all pathological subtypes of stroke[6, 7]. A systematic review showed that the 5-year stroke recurrence rates decreased over time across the 13 hospital- or community-based stroke registers included[8]. However, in the population of Perth in Australia no significant time trends in 5-year stroke recurrence rates were found[9]. CFR and recurrence rates differ substantially between aetiological subtypes of ischemic stroke based on TOAST criteria[10-12]. To the best of our knowledge, long-term data on patterns of CFR and recurrence rate from a population-based register stratified by ischemic stroke aetiology are lacking.

Therefore, by updating a prior analysis from the Erlangen Stroke Project from 1994-1996, we investigated long-term time trends in CFR and stroke recurrence rates by ischemic stroke aetiology over a 20-year time period based on data from the population-based Erlangen Stroke Project[11].

Methods

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

Erlanger Stroke Register

The Erlanger Stroke Project is an ongoing prospective population-based stroke register in Germany, covering a source population of 105,164 inhabitants (2010). Within this source population incidence and outcome of stroke is continuously monitored since 1994. The methodology of the study has been described in detail elsewhere[13]. All hospitalized and non-hospitalized stroke patients with registered residence in Erlangen were identified by regular checks of hospital admission, discharge records, nursing homes and general practices using standardized criteria to ensure completeness of case ascertainment[13]. Every patient is followed-up 3 months, 12 months and annually until death. Patients are contacted for follow-up by study nurses and research assistants. In case the patient could not be contacted for follow-up, the Population Register of the City of Erlangen is checked for a possible change of address or death. If the patient died during the follow-up period, the death certificates is reviewed, and the cause of death is ascertained from all available medical records.

Stroke was determined according to the WHO criteria[14]. Classification of pathological subtypes of stroke was determined based on brain CT or MRI scan, with 95% imaging rate[13].

For the present analysis, patients with first-ever ischemic stroke from 1996 to 2015 were included.

Aetiological subtype of ischemic stroke was defined according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification[15]. We used the five major categories of TOAST: large-artery atherosclerosis (LAA) including large-artery thrombosis and artery-to-artery embolism, cardioembolism (CE), small-artery occlusion (SAO), stroke of other determined cause (OC) and stroke of undetermined cause (UND) comprising stroke of undefined and concurrent aetiology. Interrater reliability of the classification of TOAST for the present analysis was good (kappa=0.65 [95%-CI 0.35-0.96] between 1995 and 1998 and 0.63 [95%-CI 0.43-0.83] between 1999 and 2010) as previously published[2, 11]. Recurrent stroke was defined as new neurological deficit at least 24 hours after the incident stroke according to the WHO definition excluding oedema, mass effect, brain shift syndrome or hemorrhagic transformation and procedure-related strokes[16].

Statistical Analysis

Incidence rates were age-standardized according to the European standard population[17]. Recurrent stroke was defined as first recurrent stroke after the index event (ischemic stroke) regardless of the pathological subtype (ischemic, hemorrhagic stroke or other) of recurrent stroke. Crude 3 months, 1 year and 5 years CFR and recurrence rates at were estimated with Kaplan-Meier and stratified by sex and according to TOAST classification. Age-adjusted CFR and recurrence rates were estimated using Cox regression. Sex-specific time trends for CFR and recurrence rates were estimated Cox proportional hazard regression models. The Cox regression models were adjusted for age, sex and year of event and stratified by aetiological subtypes according to the TOAST classification. Due to the small sample size,

stroke of other determined cause was excluded in survival analysis. Competing risk analysis were performed as sensitivity analysis for time trends in recurrence rates[18] with death from any cause being used as a competing event and recurrent stroke as an event of interest. Competing risk calculates the probability of getting a recurrent stroke under the condition that no recurrent event occurred before or that the person might have died. We used Aalen Johansen estimator to estimate the cumulative incidence as a function of recurrent stroke[19]. The subdistribution hazard regression from Fine and Gray was used to investigate time trends in the cumulative risk of recurrent stroke under competing risks adjusted for age, sex and stratified for aetiological subtype according to TOAST classification[20].

Ethics

Written informed consent to participate was given by patients or their legal representatives. The study was approved by the Ethics Committee of the Medical Faculty of FAU Erlangen-Nürnberg (Reference number: 249_15 Bc).

Results

Overall, 3,346 ischemic stroke patients were registered in the Erlanger Stroke Project between January 1996 to December 2015. Mean age was 74±13 years, 53.2% were women. Distribution of subtypes was as follows: LAA 8.4 %; CE 23.0%; SAO 28.0 %; OC 2.1%; and UND 38.5%. Mean age in years was 71±12 in LAA, 77±11 in CE, 71±12 in SAO, 58±17 in OC and 75±13 in UND; 41.5% of LAA, 56.7% of CE, 50.1% of SAO, 55.5% of SAO, 55.9% of OC and 55.5% of UND were women. The average annual age-standardized incidence rate of total ischemic stroke from 1996-2015 was 109.7 per 100,000 overall, 75.8 in women and

131.6 in men; average annual age-standardized incidence rate per stroke subtypes per 100,000 was as follows: 11.2 in LAA; 22.7 in CE; 32.2 in SAO; 4.4 in OC; and 39.5 in UND.

Case-fatality rates

Overall, 3 month, 1-year and 5-year survival probabilities by sex and TOAST subtype are shown in Table 1 and Figure 1; 5-year survival probability was highest in patients with stroke due to SAO (73.8%, 95%-CI: 70.4-77.3) and lowest in CE stroke (40.9%, 95%-CI: 37.2–45.0): Table 2 shows time trends determined by Hazard Ratios (HR) for the year of event of the adjusted Cox proportional hazard regression for death for the entire observation period as well as censored after 3 months, 1 year and 5 years. The same linear trends were observed in Kaplan-Meier survival estimates stratified for the year of event in 5-year groups with 1996-2000 having the lowest and 2011-2015 having the highest survival rates (for details, please see https://www.ahajournals.org/journal/str, Figure I). Overall, Cox regression showed a trend for declining stroke mortality during the entire time period (HR for year of event 0.98, 95%-CI: 0.97–0.99, p-value: <0.001). Stratified Cox regression revealed a significant decrease in stroke mortality over time in men as well as in women. Further significant decreases over time in stroke mortality were observed in CE in total as well as for men. In SAO we observed statistically significant declining stroke mortality rates in all for all and in women. In UND stroke mortality decreased significantly over time in total and in men.

Stroke Recurrence

Pathological subtypes of second strokes were as follows: 84.5% ischemic stroke; 5.7% intracerebral haemorrhage; 0.2% subarachnoid haemorrhage; and 9.6% stroke pathology not specified or missing. Overall, 3 month, 1-year and 5-year recurrence rates by sex and TOAST

subtype were shown in Table 3 and Figure 2. Undefined strokes had the highest (21.9%, CI:18.7-25.0) and SAO in women (16.0%, 95%-CI:11.7-20.1) and LAA in men (16.6%, 95%-CI:8.7-23.9) the lowest rate of stroke recurrence after 5 years. There were no significant trends for decline in stroke recurrence estimated with Cox Regression (Table 4). In the sensitivity analysis taking death as competing risk into account the UND had the highest risk of recurrent stroke followed by SAO (for details please see https://www.ahajournals.org/journal/str , Table I). After considering death as competing risks, there were significant trends for a decline in stroke recurrence in all the patients. Stratified competing risk analysis showed significant decreases in risk of recurrent stroke in women and in women with UND (for details please see https://www.ahajournals.org/journal/str Table II). There was no linear trend in recurrence rates stratified for 5-year groups of year of event (for details please see https://www.ahajournals.org/journal/str Figure II).

Discussion

In our population-based sample, nearly every second patient died 5 years after the first event. There were substantial variations in survival rates across aetiological subtypes observed with highest rates for CE and lowest for SAO, respectively. CFR decreased over the 20 years of observation, showing similar trends across stroke aetiological subtypes except for LAA. About every fifth patient suffered from a recurrent stroke within 5 years after the first event with the highest recurrence rates observed in CE and UND. Cox Regression revealed no significant decrease in long-term recurrence rates over time. Competing risks analysis showed similar patterns with additional decreasing patterns in stroke recurrence overall and in women.

Our 3-month CFR of 13% are lower than the mean weighted CFR of 21.8% reported from the European Registers of Stroke (EROS) collaboration of six population-based stroke registers in Europe in 2004-2006, but similar to the lowest rate across the participating registers observed in Dijon[21]. On the other hand, the 1-year (63.7%) and 5-year survival rates (42.8%.) for ischemic and haemorrhagic stroke in the South London Stroke Register were lower compared to our study[22]. This might be caused by the fact that haemorrhagic strokes were included in the South London Stroke Register which had lower survival rates than ischemic strokes. Only few studies investigated time trends in long-term CFR, most of them showing decreasing CFR. For example, in a Danish population-based cohort found a decrease in 30-day and 5-year mortality rates after IS between 1994-2011[23]. In addition, in the Netherlands in a linkage study of national registries, age-and sex-specific 30-day and 1-year (excluding the first 30 days) CFR decreased between 1997 and 2005 in most age-groups[24]. Controversially, 90-days CFR increased in the Swedish Stroke Registry between 1995 to 2010, which the authors referred to the higher proportion of more severe strokes[25].

To the best of our knowledge, our study is the first to investigate long-term time trends in CFR stratified by aetiological stroke subtypes according to standardized mechanism-based classification scheme such as the TOAST classification. The patterns of the stratified 5-year CFR by TOAST are in line with previously published data from our group reporting survival up to 2 years[11]. In the Nanjing Stroke Registry, highest one-year survival rates were reported for patients with SAO (92.7%), followed by UND (89.4%), CE (88.1%) and LAA (84.2%)[26]. Most CFRs in our study were lower compared to this data, and we found the lowest 1-year survival rates in CE (67.9%). Furthermore, the Dijon Stroke Registry analyzed 28-days CFR stratified by aetiology (defined as macroartheromics, microatheroma and cardioembolic).

They reported significantly improvements CFR in stroke due to microatheroma from 1985 to 2004, similar to our findings[27].

The decrease in CFR might be caused by improvements in stroke management and treatment. For example, after the introduction of stroke units in 1994/1995 the number of stroke units, one of the most effective options in stroke management[28], increased in Germany up to 255 in 2012[29]. Also, an increased uptake in acute therapies, such as thrombolytic therapy and improved overall care, might have led to the observed reduction in CFR in Germany. For example, based on German administrative hospital data proportion of stroke patients being admitted to a stroke unit increased between 2005 and 2010 from 15% to 52%[30]. The decrease in CFR might also be attributed to changes over time in patient characteristics affecting outcome such as stroke severity, comorbidities or frequency of early complications. For example, in the Austrian Stroke Unit Registry the stroke severity significantly decreased by 1 Point in the National Institutes of Health Stroke Scale between 4 and 3 in men and between 5 to 4 in women[31].

The recurrence rates observed in our study are in line with the pooled estimates of a recent meta-analysis based on population-based studies[8]. There are only a few studies reporting recurrence rates stratified by stroke aetiology. We found that patients with LAA have a high risk to get a second stroke within the first year, whereas after five years the risk in the LAA subgroup was relatively small in comparison to the other stroke subtypes. This higher risk might be because the CFR after 5 years in patients with LAA is high and, therefore, a substantial proportion of the patients died before they can get a second stroke. The rates in SAO are relatively low over the whole observation period. A previous systematic review

found lower recurrence rates up to 1 month in lacunar vs. non-lacunar infarctions, however, these differences were not statistically significant in time period up to 12 months[32]. The risk of a recurrent stroke in CE and UND remains high after the first year after the event. The high risk in CE might be attributable to patients with atrial fibrillation having a higher risk of recurrence[33]. The high risk of recurrent stroke in the UND group might be caused by a substantial proportion of patients with undetected AF in this group as recent studies revealed that intensified monitoring for AF in this group yield to a proportion of 16.1% patients with potential cardioembolic stroke[34].

We found no clear time trends in overall stroke recurrence rates as well after stratification for sex or stroke subtype in our main analysis using Cox regression, whereas we found a few significant time trends in stroke recurrence rates after taking competing risks into account. Our main analysis is in line with a systematic review from 2018 comprising 34 RCT, hospital-based and community-based studies published before December 11, 2016, which also found no statistically significant time trends in stroke recurrence rates after ischemic stroke or transient ischemic attack[35]. The authors concluded that this might partly be due to heterogeneity in stroke aetiology as no stratification for stroke subtype was performed[35]. However, after stratification for ischemic stroke aetiology in our study, we did not find any clear time trend in recurrence rate in our main analysis despite substantial heterogeneity in stroke recurrence rates by aetiological subgroups. We only found a decrease in stroke recurrence rates over time in patients in the UND group, when we considered competing risks. One possible reason might be, that, although new medication for stroke prevention are available such as non-vitamin K oral anticoagulants, the control of cardiovascular risk factors (e.g. hypertension, atrial fibrillation) after a stroke is still not optimal in Germany[36]. Besides, adherence to secondary preventive measures might decrease during follow-up, leading to a

decrease in the effect of secondary prevention. An alternative explanation could be that our study was underpowered to detect a small decrease in stroke recurrence rates due to the small sample size, especially in the later years. Another reason might be that people die before they can get a second stroke. Therefore, we included as a sensitivity analysis an analysis accounting for competing risks, where we observed a significant decrease in stroke recurrence in total and in women.

Our study has several strength and limitations. One of the strengths is the population-based design and the long-follow up over 20 years with constant standardized data collection over the entire time period. In addition, our data is able to report data on the TOAST classification of the first event over the whole time period which allows stratifying time trends in CFR and recurrence rates by aetiological subtypes of the first event. Our study also has several limitations. First, we have a high rate of undefined causes according to TOAST classification. However, the proportion of patient with undefined stroke is within the range of other population-based registers[37, 38]. Second, no information on the aetiological subtype of recurrent stroke was available, which might influence time trends in stroke recurrence. Third no adjustment for stroke severity was possible, as stroke severity is not collected in the register by a standardized scale such as the NIHSS. Fourth, the source population of our registry is relatively small, which might limit the statistical power of the study. However, the Erlanger Stroke Project is the largest and longest running population-based stroke registry in Germany and only a limited number of other registers worldwide comprise such a long observation period.

Conclusions

Decreasing CFR over the last 20 years were observed across all stroke subtypes that might be associated by improved acute treatment options. However, there is still room for improvement secondary prevention measures in ischemic stroke survivors, as we did not observe a clear reduction in stroke recurrence rates.

References

1. Rücker V, Wiedmann S, O'Flaherty M, Busch MA, Heuschmann PU. Decline in regional trends in mortality of stroke subtypes in Germany from 1998 to 2015. *Stroke*. 2018;49:2577-2583
2. Kolominsky-Rabas PL, Wiedmann S, Weingartner M, Liman TG, Endres M, Schwab S, et al. Time trends in incidence of pathological and etiological stroke subtypes during 16 years: The Erlangen Stroke Project. *Neuroepidemiology*. 2015;44:24-29
3. Rothman K, Greenland P, Lash TL. *Modern epidemiology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
4. Sacco RL, Foulkes MA, Mohr JP, Wolf PA, Hier DB, Price TR. Determinants of early recurrence of cerebral infarction. The stroke data bank. *Stroke*. 1989;20:983-989
5. Jorgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Stroke recurrence: Predictors, severity, and prognosis. The copenhagen stroke study. *Neurology*. 1997;48:891-895
6. Wafa HA, Wolfe CDA, Rudd A, Wang Y. Long-term trends in incidence and risk factors for ischaemic stroke subtypes: Prospective population study of the south london stroke register. *PLoS medicine*. 2018;15:e1002669
7. Wang Y, Rudd AG, Wolfe CD. Trends and survival between ethnic groups after stroke: The south london stroke register. *Stroke*. 2013;44:380-387
8. Mohan KM, Wolfe CD, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve AP. Risk and cumulative risk of stroke recurrence: A systematic review and meta-analysis. *Stroke*. 2011;42:1489-1494
9. Hardie K, Jamrozik K, Hankey GJ, Broadhurst RJ, Anderson C. Trends in five-year survival and risk of recurrent stroke after first-ever stroke in the perth community stroke study. *Cerebrovasc.Dis.* 2005;19:179
10. Lavados PM, Sacks C, Prina L, Escobar A, Tossi C, Araya F, et al. Incidence, case-fatality rate, and prognosis of ischaemic stroke subtypes in a predominantly hispanic-mestizo population in iquique, chile (piscis project): A community-based incidence study. *Lancet Neurol.* 2007;6:140
11. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria - incidence, recurrence, and long-term survival in ischemic stroke subtypes: A population-based study. *Stroke*. 2001;32:2735
12. Lange MC, Ribas G, Scavasine V, Ducci RD, Mendes DC, Zetola VHF, et al. Stroke recurrence in the different subtypes of ischemic stroke. The importance of the intracranial disease. *Arquivos de neuro-psiquiatria*. 2018;76:649-653
13. Kolominsky-Rabas PL, Sarti C, Heuschmann PU, Graf C, Siemonsen S, Neundoerfer B, et al. A prospective community-based study of stroke in Germany - the Erlangen Stroke Project (ESPro) incidence and case fatality at 1, 3, and 12 months. *Stroke*. 1998;29:2501
14. Hatano S. Experience from a multicentre stroke register: A preliminary report. *Bull.World Health Organ.* 1976;54:541
15. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of org 10172 in acute stroke treatment. *Stroke*. 1993;24:35
16. Handschu R, Garling A, Heuschmann PU, Kolominsky-Rabas PL, Erbguth F, Neundorfer B. Acute stroke management in the local general hospital. *Stroke*. 2001;32:866
17. Waterhouse J, Muir CS, Correa P, Powell J, eds. Cancer incidence in five continents, volume iii. *IARC Scientific Publications*. 1976:456
18. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation*. 2016;133:601-609
19. Aalen OO, Johansen S. Empirical transition matrix for nonhomogeneous markov-chains based on censored observations. *Scand. J. Stat.* 1978;5:141-150
20. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association*. 1999;94:496-509

21. Heuschmann PU, Wiedmann S, Wellwood I, Rudd A, Di Carlo A, Bejot Y, et al. Three-month stroke outcome: The european registers of stroke (eros) investigators. *Neurology*. 2011;76:159-165
22. Wolfe CD, Crichton SL, Heuschmann PU, McKevitt CJ, Toschke AM, Grieve AP, et al. Estimates of outcomes up to ten years after stroke: Analysis from the prospective south london stroke register. *PLoS medicine*. 2011;8:e1001033
23. Schmidt M, Jacobsen JB, Johnsen SP, Botker HE, Sorensen HT. Eighteen-year trends in stroke mortality and the prognostic influence of comorbidity. *Neurology*. 2014;82:340-350
24. Vaartjes I, O'Flaherty M, Capewell S, Kappelle J, Bots M. Remarkable decline in ischemic stroke mortality is not matched by changes in incidence. *Stroke*. 2013;44:591-597
25. Appelros P, Jonsson F, Asberg S, Asplund K, Glader EL, Asberg KH, et al. Trends in stroke treatment and outcome between 1995 and 2010: Observations from riks-stroke, the swedish stroke register. *Cerebrovasc Dis*. 2014;37:22-29
26. Liu X, Xu G, Wu W, Zhang R, Yin Q, Zhu W. Subtypes and one-year survival of first-ever stroke in chinese patients: The nanjing stroke registry. *Cerebrovasc Dis*. 2006;22:130-136
27. Benatru I, Rouaud O, Durier J, Contegal F, Couvreur G, Bejot Y, et al. Stable stroke incidence rates but improved case-fatality in dijon, france, from 1985 to 2004. *Stroke*. 2006;37:1674
28. Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev*. 2013;9:CD000197
29. Hillmann S, Wiedmann S, Rücker V, Berger K, Nabavi D, Bruder I, et al. Stroke unit care in germany: The german stroke registers study group (ADSR). *BMC Neurology*. 2017;17:49
30. Nimptsch U, Mansky T. Trends in acute inpatient stroke care in Germany--an observational study using administrative hospital data from 2005-2010. *Deutsches Arzteblatt international*. 2012;109:885-892
31. Teuschl Y, Brainin M, Matz K, Dachenhausen A, Ferrari J, Seyfang L, et al. Time trends in patient characteristics treated on acute stroke-units: Results from the austrian stroke unit registry 2003-2011. *Stroke*. 2013;44:1070-1074
32. Jackson C, Sudlow C. Comparing risks of death and recurrent vascular events between lacunar and non-lacunar infarction. *Brain*. 2005;128:2507-2517
33. Paciaroni M, Agnelli G, Falocci N, Caso V, Becattini C, Marcheselli S, et al. Early recurrence and cerebral bleeding in patients with acute ischemic stroke and atrial fibrillation. *Stroke*. 2015;46:2175-2182
34. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, et al. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med*. 2014;370:2467-2477
35. Boulanger M, Bejot Y, Rothwell PM, Touze E. Long-term risk of myocardial infarction compared to recurrent stroke after transient ischemic attack and ischemic stroke: Systematic review and meta-analysis. *Journal of the American Heart Association*. 2018;7
36. Heuschmann P, Kircher J, Nowe T, Dittrich R, Reiner Z, Cifkova R, et al. Control of main risk factors after ischaemic stroke across europe: Data from the stroke-specific module of the euroaspire iii survey. *European journal of preventive cardiology*. 2015;22:1354-1362
37. Krishnamurthi RV, Barker-Collo S, Parag V, Parmar P, Witt E, Jones A, et al. Stroke incidence by major pathological type and ischemic subtypes in the auckland regional community stroke studies: Changes between 2002 and 2011. *Stroke*. 2018;49:3-10
38. Li L, Yiin GS, Geraghty OC, Schulz UG, Kuker W, Mehta Z, et al. Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: A population-based study. *The Lancet Neurology*. 2015;14:903-913

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Supplemental Materials

Table I-III

Figure I-IV

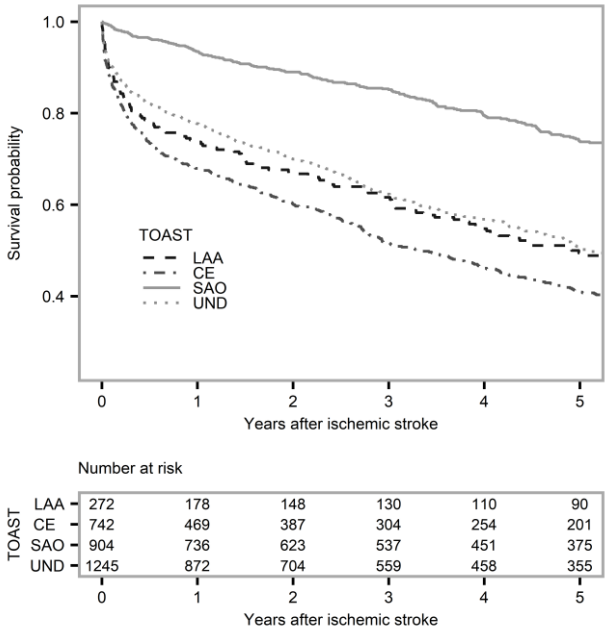

Figure 1. Survival probabilities (Kaplan-Meier estimates) after incident ischemic stroke between 1996–2015 stratified by aetiological subtype.

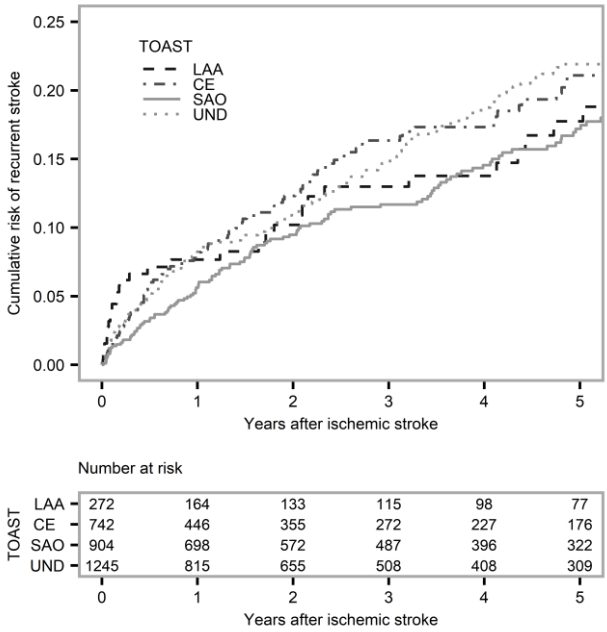

Figure 2. Cumulative risk of recurrent stroke (1-Kaplan-Meier estimates) after incident ischemic stroke between 1996–2015 stratified by aetiological subtype.

Table 1. Survival probabilities for death after ischemic stroke stratified according to TOAST classification and sex

TOAST categories	Number at risk	Survival probability in % (95%-CI)		
		3 months	1 year	5 years
All	3346	87.0 (85.9-88.2)	79.0 (77.7-80.5)	54.4 (52.5-56.4)
Men	1563	90.7 (89.3-92.2)	82.8 (80.9-84.7)	59.2 (56.4-62.0)
Women	1780	83.8 (82.1-85.5)	75.9 (73.9-77.9)	50.4 (47.9-53.1)
LAA	272	82.4 (78.0-87.1)	73.7 (68.6-79.3)	49.4 (43.3-56.5)
Men	159	84.4 (78.8-90.3)	75.5 (68.9-82.7)	53.8 (45.7-63.3)
Women	113	79.6 (72.5-87.4)	71.3 (63.4-80.2)	43.7 (34.9-54.8)
CE	742	80.0 (77.2–83.0)	67.9 (64.6-71.4)	40.9 (37.2–45.0)
Men	321	86.1 (82.4–90.0)	74.0 (69.3–79.0)	47.8 (42.2-54.3)
Women	421	75.5 (71.5-79.7)	63.4 (58.9-68.2)	35.7 (31.0-41.1)
SAO	904	97.7 (96.8-98.7)	93.5 (91.9-95.2)	73.8 (70.4-77.3)
Men	451	98.4 (97.3-99.6)	94.0 (91.8-96.3)	75.9 (71.3-80.9)
Women	453	97.1 (95.5-98.7)	93.0 (90.6-95.4)	71.8 (67.1-76.9)
UND	1245	86.2 (84.3-88.1)	77.7 (75.4-80.1)	50.3 (47.2-53.7)
Men	554	90.8 (88.4-93.3)	81.8 (78.6-85.1)	54.3 (49.7-59.4)
Women	691	82.5 (79.7-85.4)	74.5 (71.2-77.8)	47.2 (43.1-51.7)

Table 2. Hazard ratio for year of event for risk of death adjusted for age by Cox regression and stratified according to TOAST classification and sex.

TOAST categories	Hazard Ratio (95%-CI) for year of event					
	All*	p-value	Men	p-value	Women	p-value
All	0.98 (0.97–0.99)	<0.001	0.97 (0.96–0.99)	<0.001	0.98 (0.97–0.99)	<0.001
LAA	1.00 (0.97–1.03)	0.816	1.00 (0.96–1.05)	0.914	0.99 (0.94–1.04)	0.579
CE	0.98 (0.96–0.99)	0.010	0.97 (0.94–1.00)	0.020	0.98 (0.96–1.00)	0.106
SAO	0.97 (0.95–1.00)	0.022	0.98 (0.95–1.02)	0.367	0.96 (0.93–0.99)	0.015
UND	0.98 (0.97–1.00)	0.018	0.97 (0.94–0.99)	0.006	0.99 (0.97–1.01)	0.402

*Adjusted for age and sex **. p-values are for each HR of the continuous variable year of event.**

Table 3. Cumulative risk of recurrent stroke (1 - Kaplan Meier estimator) stratified according to TOAST classification and sex

TOAST categories	Number at risk	Stroke recurrence rates % (95%-CI)		
		3 months	1 year	5 years
All	3346	3.1 (2.5-3.7)	7.5 (6.5-8.4)	20.1 (18.3-21.9)
Men	1563	3.2 (2.3-4.1)	7.5 (6.1-8.9)	20.1 (17.5-22.7)
Women	1780	3.0 (2.1-3.8)	7.5 (6.1-8.8)	20.1 (17.5-22.6)
LAA	272	6.2 (3.1-9.2)	7.7 (4.2–11.0)	17.7 (11.4-23.6)
Men	159	7.7 (3.2-12)	8.6 (3.8-13.1)	16.6 (8.7-23.9)
Women	113	4.0 (0.1-7.8)	6.4 (1.3-11.2)	19.3 (8.6-28.8)
CE	742	3.1 (1.8-4.5)	8.0 (5.7-10.2)	21.1 (16.9-25.1)
Men	321	2.4 (0.6-4.2)	6.5 (3.5-9.5)	19.6 (13.7-25.1)
Women	421	3.7 (1.7-5.6)	9.2 (5.9-12.4)	22.3 (16.2–28.0)
SAO	904	1.8 (0.9-2.7)	5.6 (4.0-7.2)	17.2 (14.1-20.2)
Men	451	2.1 (0.7-3.4)	6.1 (3.7-8.4)	18.4 (13.8-22.8)
Women	453	1.6 (0.4-2.8)	5.2 (3.0-7.3)	16.0 (11.7-20.1)
UND	1245	3.3 (2.3-4.3)	8.2 (6.5-9.9)	21.9 (18.7–25.0)
Men	554	3.5 (1.9-5.1)	8.2 (5.7-10.7)	21.4 (16.7-25.9)
Women	691	3.1 (1.7-4.5)	8.3 (5.9-10.6)	22.3 (17.8-26.6)

Table 4. Hazard Ratios for year of event for risk of stroke recurrence adjusted for age by Cox regression and stratified according to TOAST classification and sex

TOAST categories	Hazard Ratio (95%-Confidence Interval) for year of event[#]					
	All*	p-value	Men	p-value	Women	p-value
All	0.99 (0.97–1.00)	0.160	1.00 (0.97–1.02)	0.837	0.98 (0.96–1.00)	0.073
LAA	1.00 (0.93–1.06)	0.890	1.00 (0.92–1.08)	0.934	0.99 (0.88-1.10)	0.803
CE	0.98 (0.94–1.02)	0.239	0.96 (0.91-1.02)	0.217	0.99 (0.94–1.04)	0.566
SAO	1.00 (0.97-1.03)	0.856	1.02 (0.97-1.06)	0.608	0.98 (0.94–1.03)	0.406
UND	0.99 (0.96–1.01)	0.339	1.00 (0.96-1.04)	0.972	0.98 (0.94–1.01)	0.191

*Adjusted for age and sex, and interaction between age and sex

year of event was included as continuous factor

+Adjusted for age and sex