Ischemic Stroke in Young Adults

Cardiovascular Disease Is the Main Cause of Long-Term Excess Mortality After Ischemic Stroke in Young Adults


Abstract—Adults with stroke at a young age (18–50 years) remain at an increased risk of death for decades. It is unclear what cause underlies this long-term excess mortality and whether this is sex and time specific. Therefore, we investigated sex-specific temporal changes in cause of death after transient ischemic attack or ischemic stroke in young adults aged 18 to 50 years.

We included all 845 consecutive 30-day survivors, of a first-ever transient ischemic attack (n=261) or ischemic stroke (n=584), admitted to our hospital between 1980 and 2010. Survival status was assessed at April 1, 2013.

Observed cause-specific mortality was compared with expected mortality, derived from mortality rates in the general population with similar age, sex, and calendar-year characteristics. During a median follow-up of 9.2 years, 146 patients (17.3%) died, such that 29 years of life was lost by each individual. For all causes of death, observed mortality exceeded expected mortality. The absolute excess risk of death was for 74% attributable to a vascular cause (absolute excess risk, 2.8 per 1000 person-years [95% confidence interval, 1.8–4.1] for stroke and absolute excess risk, 4.3 per 1000 person-years [95% confidence interval, 2.9–5.9] for other vascular causes). The absolute excess risk was highest between 10 and 15 years after stroke and this peak was most pronounced in men and mainly attributable to vascular death. Long-term excess death after stroke in young adults is mainly attributable to a vascular cause and most pronounced in men.

Attempts to reduce the risk of vascular disease after stroke in young adults should extend beyond the acute phase into the long term. (Hypertension. 2015;65:670-675. DOI: 10.1161/HYPERTENSIONAHA.114.04895.)

Key Words: cardiovascular diseases • cause of death • longitudinal studies • mortality • stroke

Stroke is one of the few diseases of which the mean age of onset is decreasing, which is mainly attributable to an increased incidence of stroke in young adults (aged <50 years).1 This increased stroke incidence in young adults has been associated with a rising prevalence of some vascular risk factors such as hypertension, hyperlipidemia, and diabetes mellitus, in this age group.

Apart from the dramatic consequences for the relatives of the patients, stroke at a young age may have a substantial impact on society as a whole because of premature death. Stroke in adults aged 18 to 50 years is associated with substantial excess mortality compared with the general population, even decades after stroke.2 However, it is unclear which cause at which moment after stroke underlies this excess risk of death.

Ideally, the information on both the (excess) risk and the cause of mortality is available for the decades after stroke in young adults, as especially the long-term prognosis is important in these relatively young patients, given that they have a long-life expectancy during a demanding period of life in which they start to form families and make decisive career moves. Information on the cause of mortality is important as it may provide opportunities for treatment strategies to perhaps postpone death after stroke.

Apart from investigating the cause of death within a young stroke population, its comparison with that from the general population in a time-after-event–dependent fashion yields information on what causes underlie excess mortality at which specific moment after stroke. This is important because it may be used to optimize the right therapeutic window for secondary prevention strategies, but may also identify time periods after stroke during which patients are vulnerable to other than vascular causes of death, each with their own treatment strategy. To date, there are only few reports on cause of death after stroke in young adults and they are limited with respect to follow-up duration and number of deaths.3–7 Moreover, those studies report cause of death within their young stroke population without comparison with the general population, without taking time after event into account.

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The aim of this study was to investigate sex-specific temporal changes in cause of death and years of life lost (YLL) after first transient ischemic attack (TIA) or ischemic stroke in adults aged 18 to 50 years.

Methods

Patients and Study Design
This study is a part of the Follow-Up of Transient Ischemic Attack and Stroke Patients and Unelucidated Risk Factor Evaluation (FUTURE) study, a prospective cohort study designed to investigate the pathogenesis and consequences of a young stroke.

The medical review ethics committee region Arnhem-Nijmegen provided approval for the study and granted a waiver of consent to collect information on vital status and cause of death. The report was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

In short, the FUTURE study comprised all consecutive patients aged 18 through 50 years with a TIA or stroke admitted to the Radboud University Medical Center Nijmegen from January 1, 1980, until November 1, 2010. In the present study, we only included patients with a first-ever TIA or ischemic stroke who survived beyond the first 30 days. Patients with cerebral venous sinus thrombosis were excluded. To minimize bias resulting from changing diagnostic techniques, the World Health Organization definition for TIA and stroke was used.

The definition of TIA included a rapidly evolving focal neurological deficit, without positive phenomena such as twitches, jerks, or myoclonus, with vascular cause only and persisting for a period of <24 hours. Stroke was defined as focal neurological deficit persisting for ≥24 hours. Stroke was divided into ischemic and hemorrhagic categories on the basis of radiological findings.

Patients were identified through a prospective registry of all consecutive young patients with stroke that has been maintained at the Department of Neurology, Radboud University Medical Center, beginning in 1978 with a standardized collection of baseline and clinical characteristics (including demographics, stroke subtype, and vascular risk factors; see online-only Data Supplement).

We assessed both stroke pathogenesis (modified Trial of ORG 10172 in Acute Stroke Treatment classification) and severity (National Institutes of Health Stroke Scale; see online-only Data Supplement).

Cause-Specific Mortality
The primary outcome was cause-specific mortality. Information on the vital status was retrieved from the Dutch Municipal Personal Records database. Patients underwent follow-up until death or April 1, 2013, whichever occurred first. Information on cause of death was obtained from the general practitioner or other treating physicians and medical records and subsequently classified according to the rules and guidelines for mortality coding, described in the International Classification of Diseases-Tenth Revision (ICD-10).

The causes of death were classified as ischemic stroke, intracerebral hemorrhage, other vascular, malignancies, and miscellaneous. Other vascular deaths were those that were not clearly nonvascular and did not meet the criteria for fatal stroke. Cause of death was missing for 7 patients (4.8%).

Statistical Analysis
Cause-specific cumulative mortality and 95% confidence intervals (CIs) were estimated using Gray’s method (see online-only Data Supplement).

Person-years at risk were calculated for each patient from date of the index stroke until death or date of end of follow-up. Patients who did not reach the end point were censored.

For 30 (3.6%) patients follow-up was not complete. In our analyses, we took these patients into account until the last known recording of their survival status. Theoretically, the follow-up of these 30 patients could have contributed to a maximum of 451 person-years. But on their last known survival status they contributed 205 person-years.

This means that a maximum of 246 person-years of, in total, 10,380 person-years of follow-up are missing, resulting in a follow-up rate of 98%.

An explorative analysis was performed to assess whether type of index event (TIA or ischemic stroke) influenced our results.

Cause-specific mortality of the reference population was obtained from mortality data of the whole population of the Netherlands, stratified by 5-year age categories, sex, and calendar-year at risk, matched to the study population on these factors. The reliability of cause of death coding in The Netherlands has shown to be high for major causes of death such as cancers, myocardial infarction, and stroke (intercoder agreement >90% on ICD chapter level [eg, circulatory system]; one level below: 82% for acute ischemic heart disease, 79% for cerebrovascular diseases).

Standardized mortality ratios (SMRs) were calculated to compare risk of cause-specific death in our population with that in the general population. The SMR was derived as the ratio of observed to expected deaths during the duration of the follow-up, and the exact 95% CI was calculated according to the Poisson distribution.

The absolute excess risk (AER) was calculated as the difference between observed and expected deaths, divided by the number of person-years at risk and expressed per 1000 person-years. Furthermore, we calculated the cause-specific AER as a proportion of the total AER (AER%).

To assess the AER over time for vascular and nonvascular death, we plotted these numbers for 0 to 5, 6 to 10, 11 to 15, 15 to 20, and 20 to 30 years of follow-up.

Cause-specific YLL were calculated by estimating the difference between the actual age at death of a subject who died of young stroke and the expected age at death according to life tables of the whole population of the Netherlands, stratified by 1-year age categories, sex, and calendar-year.

Two-sided P values of <0.05 were considered to indicate statistical significance. Statistical analysis were done using IBM SPSS Statistics version 20 and R version 2.15 (http://www.R-project.org) software packages.

Results
Between January 1, 1980, and November 1, 2010, 845 30-day survivors of a first-ever ischemic stroke or TIA were included. There were 261 patients (30.9%) with a TIA and 584 patients (69.1%) with an ischemic stroke. The baseline characteristics of the study population are shown in Table 1. Frequencies of rare causes of the index event are shown in Table S1 in the Online Supplement.

Mean follow-up was 12.0 (SD 8.6) years (median, 9.2 [interquartile range, 4.9–18.3] years). During follow-up, 146 30-day survivors (17.3%) had died. Mean age at time of death was 52.6 (SD 10.3) years.

Cause-specific observed 20-year cumulative mortality was 5.3% (95% CI, 3.2%–7.5%) for stroke, 9.6% (95% CI, 6.8%–12.5%) for other vascular disease, 6.4% (95% CI, 4.1%–8.7%) for malignancies, and 4.4% (95% CI, 2.5%–6.3%) for miscellaneous causes.

The SMR was significantly increased for all causes of death (Table 2). A substantial excess risk (SMR ≥5) was apparent for death because of stroke (SMR, 15.8 [95% CI, 10.9–22.3]) and other vascular causes (SMR, 6.0 [95% CI, 4.5–7.8]). The absolute excess risk of dying was highest because of stroke (AER, 2.8 per 1000 person-years [95% CI, 1.8–4.1]) or other vascular diseases (AER, 4.2 per 1000 person-years [95% CI, 2.9–5.9]).

The SMR of death because of vascular causes was 6.2 (4.6–8.2) in men and 12.1 (8.5–16.7) in women. The SMR of death because of nonvascular causes was 1.6 (1.1–2.2) in men and 2.1 (1.4–3.0) in women. The proportion of all excess...
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deaths attributed to a vascular cause was 78% in men and 69% in women.

The absolute excess risk of all cause death was highest at 10 to 15 years after the index event (AER, 15.3 [95% CI, 9.0–23.5]; Figure 1) and was mainly attributable to a vascular cause (84% of total AER at 10–15 years) and most pronounced in men (AER, 18.6 [95% CI, 9.8–31.4]).

The mean YLL for each patient who died was 26.1 years (95% CI, 24.4–27.8) for men and 32.1 years (95% CI, 29.6–34.7) for women. Cause-specific mean YLL is shown in Figure 2.

Figure 3 shows the contribution to the total YLL by cause of death. Total YLL in men was 2038 years and this was for 60% attributable to a vascular cause. In women, total YLL

Table 1. Baseline Characteristics Stratified by Stroke Subtype

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Total</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (% of total)</td>
<td>845</td>
<td>388 (45.9)</td>
<td>457 (54.1)</td>
</tr>
<tr>
<td>Mean age at event, y (SD)</td>
<td>40.3 (7.9)</td>
<td>41.8 (7.2)</td>
<td>39.0 (8.2)</td>
</tr>
<tr>
<td>Median follow-up, y (IQR)</td>
<td>9.2 (4.9–18.3)</td>
<td>9.8 (5.1–18.3)</td>
<td>8.9 (4.7–18.1)</td>
</tr>
<tr>
<td>&gt;15 y FUP, n (%)</td>
<td>279 (33.0)</td>
<td>131 (33.8)</td>
<td>148 (32.4)</td>
</tr>
<tr>
<td>&gt;20 y FUP, n (%)</td>
<td>174 (20.6)</td>
<td>79 (20.4)</td>
<td>95 (20.8)</td>
</tr>
<tr>
<td>TOAST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atherothrombotic stroke</td>
<td>84 (9.9)</td>
<td>55 (14.9)</td>
<td>29 (6.3)</td>
</tr>
<tr>
<td>Likely atherothrombotic stroke</td>
<td>127 (15.0)</td>
<td>59 (15.2)</td>
<td>68 (14.9)</td>
</tr>
<tr>
<td>Cardioembolic stroke</td>
<td>105 (12.4)</td>
<td>46 (11.9)</td>
<td>59 (12.9)</td>
</tr>
<tr>
<td>Lacunar stroke</td>
<td>92 (10.9)</td>
<td>44 (11.3)</td>
<td>48 (10.5)</td>
</tr>
<tr>
<td>Rare causes</td>
<td>129 (15.3)</td>
<td>52 (13.4)</td>
<td>77 (16.8)</td>
</tr>
<tr>
<td>Coexisting cause</td>
<td>20 (2.4)</td>
<td>7 (1.8)</td>
<td>13 (2.8)</td>
</tr>
<tr>
<td>Unknown cause</td>
<td>288 (34.1)</td>
<td>125 (32.2)</td>
<td>163 (35.7)</td>
</tr>
<tr>
<td>Median NIHSS at admission (IQR)*</td>
<td>3 (1–7)</td>
<td>3 (1–7)</td>
<td>2 (0–6)</td>
</tr>
<tr>
<td>History of cardiovascular risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>46 (5.4)</td>
<td>25 (6.4)</td>
<td>21 (4.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>231 (27.3)</td>
<td>106 (27.3)</td>
<td>125 (27.4)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>206 (31.5)</td>
<td>100 (32.4)</td>
<td>106 (30.6)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>14 (1.7)</td>
<td>7 (1.8)</td>
<td>7 (1.5)</td>
</tr>
<tr>
<td>Smoking†</td>
<td>434 (53.2)</td>
<td>209 (55.9)</td>
<td>225 (50.9)</td>
</tr>
<tr>
<td>Excess alcohol consumption‡</td>
<td>62 (7.3)</td>
<td>56 (14.4)</td>
<td>6 (1.3)</td>
</tr>
<tr>
<td>Any vascular risk factor</td>
<td>491 (78.4)</td>
<td>245 (83.3)</td>
<td>246 (74.1)</td>
</tr>
</tbody>
</table>

FUP indicates follow-up; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; and TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

*Scores range from 0 to 42 with higher scores on the scale indicating worse stroke severity. 0.5% of NIHSS was missing.

†Defined as smoking ≥1 cigarette/d in the year before the event; 3.4% of the data were missing.

‡Defined as consuming >200 g of pure alcohol per week.

Table 2. Cause-Specific Mortality After Transient Ischemic Attack or Ischemic Stroke in Young Adults Compared With Mortality in the General Population

<table>
<thead>
<tr>
<th>Causes of Death</th>
<th>Observed, n (%)*</th>
<th>Expected</th>
<th>SMR (95% CI)</th>
<th>AER (95% CI)†</th>
<th>%AER</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause</td>
<td>139 (100)</td>
<td>42.9</td>
<td>3.2 (2.7–3.8)</td>
<td>9.6 (7.4–12.1)</td>
<td>100</td>
</tr>
<tr>
<td>Vascular</td>
<td>81 (58.3)</td>
<td>10.3</td>
<td>7.9 (6.3–9.7)</td>
<td>7.1 (5.4–9.0)</td>
<td>74</td>
</tr>
<tr>
<td>Stroke</td>
<td>30 (21.6)</td>
<td>1.9</td>
<td>15.8 (10.9–22.3)</td>
<td>2.8 (1.8–4.1)</td>
<td>29</td>
</tr>
<tr>
<td>Other vascular</td>
<td>51 (36.7)</td>
<td>8.5</td>
<td>6.0 (4.5–7.8)</td>
<td>4.3 (2.9–5.9)</td>
<td>45</td>
</tr>
<tr>
<td>Nonvascular</td>
<td>58 (41.7)</td>
<td>32.6</td>
<td>1.8 (1.4–2.3)</td>
<td>2.5 (1.1–4.2)</td>
<td>26</td>
</tr>
<tr>
<td>Malignancies</td>
<td>35 (25.2)</td>
<td>19.7</td>
<td>1.8 (1.3–2.4)</td>
<td>1.5 (0.5–2.9)</td>
<td>16</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>23 (16.5)</td>
<td>12.9</td>
<td>1.8 (1.2–2.6)</td>
<td>1.0 (0.2–2.2)</td>
<td>10</td>
</tr>
</tbody>
</table>

%AER indicates cause-specific AER as proportion of AER of all cause death; AER, absolute excess risk; CI, confidence interval; and SMR, standardized mortality ratio.

*Cause of death was missing in 7 (4.8%) patients.

†Per 1000 person-year.
was 1960 years of which 53% was attributable to a vascular cause. There were no indications that type of index event influenced our results. Both the AER and the mean YLL of vascular and nonvascular death did not significantly differ between TIA and stroke.

**Discussion**

During a mean follow-up of 12 years, \( \approx 17\% \) of the 30-day survivors of a first-ever ischemic stroke or TIA had died and the corresponding excess risk of death persisted for decades after stroke. The AER was for 74% attributable to vascular death and the highest risk was between 10 and 15 years after the index event, which was most pronounced in men. Death occurred prematurely and led to 29 YLL, with the largest number of YLL in men.

Strengths of our study include the long follow-up period, one of the largest study populations in the field of young stroke with a high follow-up rate of 98% and the comparison with nationwide age- and sex-matched cause-specific mortality rates. Moreover, collecting data all in 1 site allowed us to collect baseline and follow-up information according to identical procedures in all patients, thereby reducing the risk of information bias.

Previous studies provided information on cause of death within their population, but did not provide information on the excess risk of death and its underlying causes.\(^3\)\(^-\)\(^7\) Moreover, they did not quantify the possible social and economic impact in terms of YLL because of early death after stroke. In our population, about one third of life was lost by each individual who died, which will have a major social impact as these young adults are in the age that many of them will have young families. Furthermore, this population is part of the working population, thus this major number of YLL will also result in economic loss.

Both the number of excess deaths and the number of YLL because of vascular deaths were higher in men than in women. These findings suggest that men are most vulnerable to death after young stroke because of a vascular cause. One explanation could be that traditional vascular risk factors associated with vascular death are more prevalent in young men with stroke than in women.\(^19\)\(^-\)\(^20\) Conversely, the lower excess risk in women could be explained by the possible protective effect of estrogen exposure, as premenopausal women seem to have a much lower risk of vascular disease than postmenopausal women or men with similar ages.\(^21\) As the median age of menopause is \( \approx 52 \) years,\(^22\) the majority of the women in our population were still premenopausal women with the attendant low risk of vascular disease.

Excess risk of all cause death was highest between 10 and 15 years after the index event and this was mainly attributable to vascular death in men during these years. As excess risk of vascular death is the difference between observed and expected, an increase of excess risk can be caused either by an increase of observed vascular death (index population) or by a decrease of this risk in the reference population. This latter explanation is unlikely as the risk of vascular death in the reference population rises with age, thus the increase in excess risk at 10 to 15 years after stroke is fully attributable.
to an increased risk of vascular death in men at 10 to 15 years after young stroke. A possible explanation for this increased risk could be that especially these young men are more vulnerable to deleterious effects of vascular risk factors at this age that are usually more prevalent and severe than in women and perhaps because of lack of estrogen exposure. The subsequent convergence of the risk of (vascular) mortality of patients after ≈20 years after the event and the general population may be because of an increase of vascular disease in the reference population during aging.

One quarter of all excess deaths was attributable to a nonvascular cause of which malignancies contributed the most. One explanation for this is that malignancies in medical history itself were both a cause for the index stroke and also for in the increased risk of death on the long term. This is supported by the fact that the excess risk disappeared after exclusion of those who had a history of malignancies. Another explanation may be that some malignancies and stroke share risk factors including long-term excessive smoking and alcohol intake habits.

A potential limitation of our study includes the lack of detailed data on secondary preventive medication during the years after stroke. Approximately 90% of all patients used preventive medication at discharge but some patients will have stopped or (re)started medication during 30 years of follow-up, thus in the present study we cannot reliably assess its effect on the risk of vascular death. In addition, although optimal secondary prevention is likely to influence the excess risk of vascular death, the true effect of secondary prevention medication in this group can only be estimated, as young patients (<50 years) have been excluded from almost all secondary prevention trials.

Furthermore, it may be that not all cases of young stroke in our catchment area were included in our cohort because our cohort is a single-center hospital-based study, rather than community based. Only those patients who sustained a fatal stroke, who were not admitted to our hospital, would not have been included in our study. If there were any effect, this would have affected only case-fatality rate, but not mortality, during follow-up. Patients who survive usually visit a university medical center during the course of their disease. In addition, there are no restrictions to be admitted to our hospital and we included all consecutive cases admitted. Moreover, the age- and sex-standardized mortality data of our catchment area are similar to the age- and sex-standardized mortality data of the Netherlands. The same is true for the prevalence of stroke; the age- and sex-standardized prevalence of stroke in our region equals that of the age- and sex-standardized prevalence of stroke in the Netherlands. We therefore presume that our study population is a representative sample of Dutch patients with young stroke.

Another limitation may be that the distribution of TIA and ischemic stroke in our population might have influenced our results. Risk of vascular death might have been underestimated in our study, because in general prognosis after ischemic stroke is worse compared with TIA. However, previously we demonstrated that risk of recurrent vascular events was not different between patients with TIA and ischemic stroke in our population; moreover, stratification by index event did not alter our conclusions.

**Perspectives**

Young stroke survivors are at substantial excess risk of death, predominantly because of a vascular cause. This excess risk of vascular death was most obvious in men, especially during the first 15 years after stroke, and was accompanied by many YLL. Given this vascular predominance as a cause of death one could argue that optimal secondary prevention might prevent, at least in part, this excess of vascular death. However, this reasoning must be done with care as young (aged <50 years) patients have been excluded from almost all secondary prevention trials. Hence, our findings can be viewed as an encouragement in the development of personalized secondary prevention (trials) in young stroke survivors.

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### Disclosures

None.

### References


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ONLINE SUPPLEMENT

CARDIOVASCULAR DISEASE IS THE MAIN CAUSE OF LONG-TERM EXCESS MORTALITY AFTER ISCHEMIC STROKE IN YOUNG ADULTS

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EXPANDED MATERIALS AND METHODS

TOAST and NIHSS

The assessment of stroke etiology (modified TOAST classification\textsuperscript{1}) and severity (National Institutes of Health Stroke Scale (NIHSS)\textsuperscript{2}) was performed retrospectively in all cases using a validated approach as previously described,\textsuperscript{3, 4} because these scales did not exist when a substantial number of our patients experienced their index event. In comparison to the original TOAST classification,\textsuperscript{5} the presently used classification has an additional category, “likely large-artery atherosclerosis”\textsuperscript{1}.

History of cardiovascular risk factors

A history of cardiovascular risk factors was defined as the presence of these risk factors, either in the patients’ medical history or when identified during admission. Cardiovascular risk factors detected during admission were defined as follows: diabetes mellitus as a random blood glucose level greater than 11.1 mmol/L or two consecutive fasting venous plasma glucose levels of 7.0 mmol/L or greater; hypertension as systolic blood pressure 135 mm Hg or greater, diastolic blood pressure 85 mm Hg or greater, or both, measured after the first week of the index event; dyslipidemia as treated with lipid-lowering medication and/or a diagnosis of dyslipidemia (total cholesterol level 5.0 mmol/L or greater, low-density lipoprotein level 3.0 mmol/L or greater, high-density lipoprotein level lower than 1.0 mmol/L); and atrial fibrillation when identified on either an electrocardiogram or during continuous electrocardiographic recording. Atrial fibrillation was diagnosed by a cardiologist. Smoking was defined as smoking at least 1 cigarette per day in the year prior to the event; 3.4% of the smoking data were missing. Excess alcohol consumption was defined as consuming more than 200 grams of pure alcohol per week. In the framework of our young stroke protocol, patients underwent imaging of intracranial and vertebral arteries, when appropriate, cardiac echography was also performed.

Gray’s method

Standard survival analytic methods such as Kaplan-Meier method make an important assumption, that censoring should be independent; this implies that patients who are censored should be representative for those patients who are still at risk.\textsuperscript{6} The Kaplan-Meier method may yield biased results when this assumption is violated, which is likely to occur in the presence of competing risks. Competing risk are observations in which one precludes the observation of the other. For example, if the cause of death of interest is cause A and a patient dies due to cause B, this patient cannot die due to cause A anymore; cause A and B are competing risks. If subsequently this patient is censored in the Kaplan-Meier method, this patient does not have the same risk to die due to cause A as the patients that are still at risk at the moment of censoring, which means that the assumption of independent censoring is violated. The Gray’s method is a survival analytic method that accounts for the presence of competing risks.\textsuperscript{7} In our analyses we used this method to estimated cause-specific cumulative mortality, whilst treating other causes of death than the one under investigation, as competing risks.
SUPPLEMENTARY REFERENCES


**SUPPLEMENTARY TABLE**

**Table S1.** Frequencies of rare causes of the index event

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>Proportion among patients with rare causes (n=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissection of cervical or intracranial artery</td>
<td>51</td>
<td>40%</td>
</tr>
<tr>
<td>Disorders of thrombosis and hemostasis</td>
<td>37</td>
<td>29%</td>
</tr>
<tr>
<td>Arteriopathy</td>
<td>18</td>
<td>14%</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>7</td>
<td>5%</td>
</tr>
<tr>
<td>Migraine</td>
<td>7</td>
<td>5%</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>3</td>
<td>2%</td>
</tr>
<tr>
<td>Mitochondrial disease</td>
<td>3</td>
<td>2%</td>
</tr>
<tr>
<td>Hypoperfusion syndrome</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>CADASIL</td>
<td>1</td>
<td>1%</td>
</tr>
</tbody>
</table>