Remarkable Decline in Ischemic Stroke Mortality Is not Matched by Changes in Incidence

Ilonca Vaartjes, PhD; Martin O’Flaherty, PhD, MD; Simon Capewell, PhD, MD; Jaap Kappelle, PhD, MD; Michiel Bots, PhD, MD

Background and Purpose—In Western Europe, mortality from ischemic stroke (IS) has declined over several decades. Age–sex-specific IS mortality, IS incidence, 30-day case fatality, and 1-year mortality after hospital admission are essential for explaining recent trends in IS mortality in the new millennium.

Methods—Data for all IS deaths (1980–2010) in the Netherlands were grouped by year, sex, and age. A joinpoint regression was fitted to detect points in time at which significant changes in the trends occur. By linking nationwide registers, a cohort of patients first admitted for IS between 1997 and 2005 was constructed and age–sex-specific 30-day case fatality and 1-year mortality were computed. IS incidence (admitted IS patients and out-of-hospital IS deaths) was computed by age and sex. Mann–Kendall tests were used for trend evaluation.

Results—IS mortality declined continuously between 1980 and 2000 with an attenuation of decline in the 1990s in some of the age–sex groups. A remarkable decline in IS mortality after 2000 was observed in all age–sex groups, except for young men. An improved decline in 30-day case fatality and in 1-year mortality was also observed in almost all age–sex groups. In contrast, IS incidence remained stable between 1997 and 2005 or even increased slightly.

Conclusions—The recent remarkable decline in IS mortality was not matched by a decline in the number of incident nonfatal IS events. This is worrying, because IS is already a leading cause of adult disability, claiming a heavy human and economic burden. Prevention of IS is therefore now of the greatest importance. (Stroke. 2013;44:000-000.)

Key Words: epidemiology ■ incidence ■ ischemic stroke ■ mortality ■ prevention ■ trend

Stroke is a leading cause of adult disability and remains an important cause of death. Recent analyses showed that in Western Europe mortality from stroke declined until the most recent years of observation. This decline was even greater in the new millennium in the Netherlands. However, whether these mortality trends mainly reflect favorable changes in risk factors or improvement of acute treatment and secondary prevention is unclear.

The World Health Organization Monica study of people aged 35 to 64 years reported that the decline in stroke mortality probably was caused by changes in the case fatality of stroke rather than changes in event rate. It is uncertain whether this estimate is also representative for elderly people. It is also unknown whether stroke incidence decreases over time. Some studies suggest that stroke incidence may have stabilized or increased since the late 1980s, whereas others suggest that the incidence of stroke continues to decline.

In the present study, we assess age–sex–specific ischemic stroke (IS) mortality rates from 1980 to 2010. Because treatment and (magnitude of) risk factors for IS and hemorrhagic stroke differ, we restricted our analysis to IS. To investigate whether IS incidence, 30-day case fatality, and 1-year mortality after hospital admission contributed to the accelerated decline in IS mortality in the Netherlands in the new millennium, we determined nationwide age–sex–specific incidence rates, case fatality, and 1-year mortality after hospital admission from 1997 to 2005.

Methods

IS Mortality Rate

Data on all deaths from both first and recurrent IS (International Classification of Diseases [ICD]-10 codes I63, I64) in the Netherlands from 1980 to 2010 were provided by Statistics Netherlands by year, sex, age at death, along with population estimates for each year–age–sex group.

30-Day Case Fatality and 1-Year Mortality After Hospital Admission

To determine 30-day case fatality and 1-year mortality after hospital admission, a cohort of incident hospitalized IS patients for the period 1997–2005 was constructed. This period was selected because good quality data were available for these years and include surrounding
years of the millennium. Information from the national hospital discharge registry, the Dutch population registry, and the national cause of death registry were linked. Data sources and procedures have been detailed earlier. In brief, all hospital admissions with principal diagnosis for IS (ICD-9-CM code 434 and 436) between January 1, 1997 and December 31, 2005 were selected from the hospital discharge registry. Through merger with the population registry, a combination of partial identifying variables (date of birth, sex, and numeric part of postal code) can be used to identify different admissions from the same person provided that this combination is unique in the population. Then the first admission for an individual of all subsequent admissions of a person occurring between 1997 and 2005 was selected. Subsequently, information was collected on hospital admissions that may have occurred previously (data earlier than 1995 not available because linkage with population registry is only possible from 1995) for the same condition. Those with a previous admission for IS were excluded. This resulted in a cohort of 118,058 patients with first hospitalization for IS between 1997 and 2005 in the Netherlands. Information on mortality of the patients was obtained by linkage of the cohort with the cause of death register. Patients were censored if they migrated out of the Netherlands, or if their linkage key was no longer unique at any time during follow-up.

**IS Incidence**

The incidence of IS was defined as the sum of patients with first hospitalization for IS and patients who died from IS before hospitalization. The number of patients with an incident hospitalization for IS between 1997 and 2007 was determined by constructing a cohort as was described above. The risk of IS does not depend on whether a unique combination of linking variables is present or not. Therefore we increased the observed number of IS in the constructed cohort using the age-sex-specific uniqueness percentage (% of uniqueness ranges from 79.3% in age group 35–44 years to 99.8% in age group >95 years) allowing us to calculate an absolute number of first IS events in the Netherlands. To construct a cohort of patients who died from an incident IS before hospitalization, information from the cause of death register, the population registry, and hospital discharge registry were linked. All out-of-hospital deaths attributable to IS (ICD-10 code I63 and I64) between January 1, 1997 and December 31, 2005 were selected from the cause of death register. Information was subsequently collected on hospital admissions that may have occurred previously for the same condition. Those with a previous admission for IS were excluded. In total, there were 166,249 first IS events between 1997 and 2005 in the Netherlands (127,943 patients with an incident hospitalization for IS and 38,306 patients who died from an incident IS before hospitalization).

**Data Analysis**

**IS Mortality Rate**

To identify points where a significant change of the age- and sex-specific trend in mortality happened, we performed joinpoint regression analysis with the software (joinpoint version 3.4.3) provided by the Surveillance Research Program of the US National Cancer Institute (2010). For every period, we tabulated the linear slope of the trend and probability value of the final model of the joinpoint regression analysis, the minimum and maximum observed number of deaths and the minimum and maximum observed IS mortality rates per 100,000. Furthermore, we calculated the change in observed IS mortality rate per 100,000 per period ((IS mortality rate last year of period–IS mortality rate first year of period)/IS mortality rate first year of period). Finally, we present 4 age–sex-specific graphs showing the observed and modeled IS mortality rates per 100,000 from 1980 to 2010; age groups were 35 to 64 years, 65 to 74 years, 75 to 84 years, and 85 to 94 years. The dots in the age–sex-specific graphs represent the observed number of deaths per 100,000 from 1980 to 2010. The line in each age–sex-specific graphs represents the final model from the joinpoint regression analysis.

**Thirty-Day Case Fatality and 1-Year Mortality After Hospital Admission**

Survival time was calculated as the time from the initial admission date for IS to the date of death for any cause or to the date that a patient was censored, whichever came first. Thirty-day case fatality and 1-year mortality (defined as mortality between 31 and 365 days) were both computed by age and sex according to the actuarial life table method and expressed as percentages. To investigate whether 30-day case fatality and 1-year mortality changed significantly between 1997 and 2005, we performed Mann–Kendall trend tests by age and sex group. Furthermore, we calculated the change in observed IS 30-day/1-year mortality for the period between 1997 and 2005 that were previously defined with joinpoint. Data were analyzed with SPSS software, version 14.0 (SPSS Inc, Chicago, IL) and Microsoft Office Excel 2003.

**IS Incidence**

The incidence per 100,000 was computed by age and sex. To investigate whether incidence changed significantly over time we performed Mann–Kendall trend tests by age and sex group. Furthermore, we calculated the change in observed IS incidence for the period between 1997 and 2005 that were previously defined with joinpoint. Data were analyzed with SPSS software, version 14.0 (SPSS Inc, Chicago, IL) and Microsoft Office Excel 2003.

Because of small numbers, patients <35 years and >94 years old were excluded from all the analyses. All analyses were performed in accordance with privacy legislation in the Netherlands.

**Results**

**Age- and Sex-Specific IS Mortality: Overall Trends**

IS mortality declined continuously between 1980 and 2000 with some attenuation of this decline during the 1990s in some age–sex groups (Figure 1). Mortality rapidly declined in the new millennium in both men and women (Tables 1 and 2). For example, we observed a decline in mortality in men aged 65 to 74 years (change in IS mortality rate during the period 1996–2002: −0.14 and during the period 2002–2010: −0.52), and in women aged 65 to 74 years (change in IS mortality rate during the period 1988–2000: 0.02 and during the period 2000–2008: −0.57).


**Mortality Rate per 100,000**

In all age–sex groups, mortality rate per 100,000 declined significantly between 1997 and 2005, and a remarkable acceleration of decline was observed in the new millennium (Tables 3 and 4).

**30-Day Case Fatality**

In all age–sex groups, 30-day case fatality significantly declined between 1997 and 2005 (Tables 3 and 4). The decline in the new millennium was also observed in 30-day case fatality in men and women of all ages, except for women aged 75 to 85 years. The decline was most pronounced in men aged 65 to 84 years and in women aged 35 to 74 years.

**One-Year Mortality**

The decline in mortality in the new millennium was also observed in 1-year mortality (31–365 days) in men and women of all ages, except for men aged 85 to 94 years. The decline was most pronounced in men aged 65 to 84 years and in women aged 35 to 84 years.
In contrast to the decline in IS mortality, IS incidence remained stable over time or even slightly increased (Table 3 and 4). In total, there were 161,393 stroke events among patients aged 35 to 94 years. The number of IS events increased from 16,223 in 1997 to 19,356 in 2005.

**Discussion**

**Summary of the Key Findings**

IS mortality declined continuously between 1980 and 2000 with some attenuation of this decline during the 1990s in some of the age–sex groups. In the new millennium, a remarkable acceleration of the decline was observed in all age–sex groups, except for young men. A corresponding decline was observed in 30-day case fatality and 1-year mortality (31–365 days) after admission for IS between 1997 and 2005 in most age–sex groups. In contrast, IS incidence remained stable between 1997 and 2005 or even increased slightly.

**Possible Explanations**

Attenuation of the decline in IS mortality rate in the 1990s was also observed in the Scandinavian countries, United States, and Canada. In addition, a similar attenuation has been observed...
Stroke January 2013

in the decline of coronary heart disease mortality rate in the Netherlands as well in other Western countries. Both are atherosclerotic manifestations, responsive to similar risk factors, and suggesting risk factor changes as underlying mechanism. Obesity and diabetes mellitus both increased during the 1990s in the Netherlands, and compounded by persistent smoking, both may have powerfully contributed to the observed attenuation of decline in mortality rate of both IS and coronary heart disease.

The accelerated decline in IS mortality that was observed in the new millennium is remarkable and to our knowledge not yet reported for other countries. In the Netherlands, a similar decline in the mortality in the new millennium was also observed for diabetes mellitus-related causes of death, deaths attributable to vascular dementia, and pneumonia. In the new millennium, nationwide health care use, the number of cardiovascular procedures, medication use, and the number of surgical procedures all rapidly increased. This may be an important explanation for the observed declines in mortality rate accompanied by the dramatic increase in life expectancy observed in the Netherlands since 2002.

With regard to health care for IS patients in the Netherlands, stroke units were introduced in the late 1990s and became

<p>| Table 2. Ischemic Stroke Mortality Trends by Age in the Netherlands, 1980–2010 for Women Aged &gt;35 Years |</p>
<table>
<thead>
<tr>
<th>Age Group</th>
<th>Identified Periods</th>
<th>Linear Slope</th>
<th>Number of Deaths (min-max)</th>
<th>Stroke Mortality Rates (min-max)</th>
<th>Change in Stroke Mortality Rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>35–64</td>
<td>1980–1988</td>
<td>−0.062</td>
<td>131–214</td>
<td>5.0–9.5</td>
<td>−0.47</td>
</tr>
<tr>
<td></td>
<td>1988–2000</td>
<td>0.002</td>
<td>127–172</td>
<td>4.5–6.2</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>2000–2010</td>
<td>−0.051</td>
<td>99–186</td>
<td>2.8–5.7</td>
<td>−0.47</td>
</tr>
<tr>
<td>65–74</td>
<td>1980–1988</td>
<td>−0.051</td>
<td>520–724</td>
<td>88–130</td>
<td>−0.32</td>
</tr>
<tr>
<td></td>
<td>1988–2000</td>
<td>−0.001</td>
<td>527–582</td>
<td>83–90</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>2000–2008</td>
<td>−0.010</td>
<td>262–582</td>
<td>38–90</td>
<td>−0.57</td>
</tr>
<tr>
<td></td>
<td>2008–2010</td>
<td>0.008</td>
<td>258–294</td>
<td>37–41</td>
<td>0.07</td>
</tr>
<tr>
<td>75–84</td>
<td>1980–1983</td>
<td>−0.043</td>
<td>1825–2048</td>
<td>528–637</td>
<td>−0.17</td>
</tr>
<tr>
<td></td>
<td>1983–2002</td>
<td>−0.012</td>
<td>1825–2170</td>
<td>439–582</td>
<td>−0.15</td>
</tr>
<tr>
<td></td>
<td>2002–2008</td>
<td>−0.092</td>
<td>1264–2104</td>
<td>256–448</td>
<td>−0.43</td>
</tr>
<tr>
<td></td>
<td>2008–2010</td>
<td>−0.020</td>
<td>1203–1285</td>
<td>241–259</td>
<td>−0.06</td>
</tr>
<tr>
<td>85–94</td>
<td>1980–1991</td>
<td>−0.002</td>
<td>1234–1970</td>
<td>1572–1668</td>
<td>−0.06</td>
</tr>
<tr>
<td></td>
<td>1991–1994</td>
<td>0.020</td>
<td>1970–2335</td>
<td>1572–1724</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>1994–2002</td>
<td>−0.006</td>
<td>2335–2594</td>
<td>1620–1703</td>
<td>−0.05</td>
</tr>
<tr>
<td></td>
<td>2002–2010</td>
<td>−0.067</td>
<td>1903–2594</td>
<td>965–1620</td>
<td>−0.40</td>
</tr>
</tbody>
</table>

Periods were identified by joinpoint regression analysis.

* (rate last year of period segment−rate first year of period segment)/rate first year of period segment.

| Table 3. Trends in Ischemic Stroke Mortality and Incidence |
|------------|------|------|------|------|------|------|------|------|------|-----------------------|
| 35–64      | 9.9  | 9.0  | 8.7  | 9.3  | 9.0  | 8.8  | 7.5  | 7.3  | 6.2  | −0.37                 | 0.01                  |
| 65–74      | 12.5 | 12.3 | 9.7  | 10.9 | 11.0 | 10.4 | 8.0  | 7.8  | 6.9  | −0.45                 | <0.01                 |
| 75–84      | 19.8 | 19.0 | 19.0 | 19.2 | 17.9 | 17.2 | 16.2 | 14.7 | 11.9 | −0.40                 | <0.01                 |
| 85–94      | 22.9 | 24.1 | 22.2 | 22.0 | 23.3 | 20.3 | 19.8 | 19.4 | 17.5 | −0.24                 | <0.01                 |

Mortality rate per 100 000, 30-day case fatality, 1-year mortality (31–365 days) after admission for ischemic stroke and incidence per 100 000 by age in the Netherlands, 1997–2005 for men aged >35 years.

* (last year−first year)/first year; † Mann–Kendall trend test; n.s. indicates nonsignificant.
Table 4. Trends in Ischemic Stroke Mortality and Incidence

| Age Group | Mortality rate per 100 000 | 30-day case fatality (%) | 1-year mortality (%) | Incidence per 100 000 | 30-day case fatality (%) | 1-year mortality (%) | Incidence per 100 000 | 30-day case fatality (%) | 1-year mortality (%) | Incidence per 100 000 | 30-day case fatality (%) | 1-year mortality (%) | Incidence per 100 000 | 30-day case fatality (%) | 1-year mortality (%) | Incidence per 100 000 | 30-day case fatality (%) | 1-year mortality (%) | Incidence per 100 000 |
|-----------|---------------------------|--------------------------|----------------------|-----------------------|--------------------------|----------------------|-----------------------|--------------------------|----------------------|-----------------------|--------------------------|----------------------|-----------------------|--------------------------|----------------------|-----------------------|--------------------------|----------------------|
| 35–64     | 5.7                       | 6.4                      | 5.0                  | 39.9                  | 12.4                     | 16.7                 | 757                   | 19.9                     | 12.4                 | 1743                  | 17.0                     | 19.3                 | 1673                  | 17.0                     | 19.3                 | 1673                  | 17.0                     | 19.3                 | 1673                  |
| 65–74     | 85.6                      | 10.5                     | 12.0                 | 277                   | 19.9                     | 17.0                 | 857                   | 29.8                     | 28.9                 | 1736                  | 17.0                     | 19.3                 | 1673                  | 17.0                     | 19.3                 | 1673                  | 17.0                     | 19.3                 | 1673                  |
| 75–84     | 469                       | 17.0                     | 17.0                 | 439                   | 18.7                     | 18.5                 | 439                   | 29.8                     | 28.9                 | 1736                  | 17.0                     | 19.3                 | 1673                  | 17.0                     | 19.3                 | 1673                  | 17.0                     | 19.3                 | 1673                  |
| 85–94     | 1673                      | 17.0                     | 17.0                 | 439                   | 18.7                     | 18.5                 | 439                   | 29.8                     | 28.9                 | 1736                  | 17.0                     | 19.3                 | 1673                  | 17.0                     | 19.3                 | 1673                  | 17.0                     | 19.3                 | 1673                  |

Mortality rate per 100 000, 30-day case fatality, 1-year mortality (31–365 days) after admission for ischemic stroke and incidence per 100 000 by age in the Netherlands, 1997–2005 for women aged >35 years.

* (last year−first year)/first year; † Mann–Kendall trend test; n.s. indicates nonsignificant.

broadly implemented thereafter; thrombolytic therapy for stroke was introduced in 1995.16 Furthermore, updated guidelines with regard to secondary prevention of stroke were introduced in the Netherlands in 2000.17 Stroke unit care has a positive impact on case fatality18 and 1-year mortality.19 This may be attributable to the prevention and treatment of immobility-related complications such as venous thromboembolism, pneumonia, urinary tract infection, and decubitus ulcers.20 Our results indicate that the declining trend in IS mortality rate was matched by a declining trend in the IS 30-day case fatality and 1-year mortality. However, we did not observe a specific decline in immobility-related causes of death. The reduced 1-year mortality may be partly explained by the increased prescribing of antihypertensive, statin, and antiplatelet drugs.21

The remarkable decline in mortality in the new millennium is not simply the result of attribution bias due to the change in the versions of ICD because this ICD change actually occurred in 1996 in the Netherlands. This does not correspond with the period of the remarkable decline. Furthermore, the remarkable decline is not a result from a shift in reporting causes of death (Figure I in the online-only Data Supplement).

In contrast to the decline in IS mortality, IS incidence remained stable over time or even increased. Some other studies also suggest that incidence may have stabilized or increased since the late 1980s,1 whereas others intriguingly suggest that the incidence may have modestly declined.4,5 One Dutch cohort study noted a possible decline in incidence in both men and women in the new millennium, however these observed trends were not statistically significant.22

The access to brain CT and MRI increased and combined with improvement of diagnostic instruments.22 This could have resulted in diagnosing more patients with an incident minor IS after 2000. Because these milder patients have better prognosis, this might contribute to the observed decline in mortality risk.

The unchanged or even increased IS incidence could also partly reflect trends in risk factors. Age-sex-specific population data on changes in risk factors in the Netherlands since 2000 are limited but suggest an unfavorable increase in both blood pressure and diabetes mellitus.22 On the other hand, the prevalence of obesity seemed to stabilize and smoking prevalence decreased.22

Implications

IS is a leading cause of adult disability and cause of death.1 Clearly, the human burden of stroke is enormous, and a recent report on the costs of diseases in the Netherlands ranked stroke as one of the most expensive diseases.23 Our study suggests that annual IS death rates are declining and that decline is accelerating in the new millennium. Changes in health care for IS patients such as new guidelines, increased medication use, and stroke units have probably all successfully contributed. However, the decline in deaths from IS is not matched by a decline in the number of nonfatal IS because incidence has remained stable or even increased. Given that age is a substantiated risk factor for IS, the aging of the Dutch population implies a growing number of persons at risk. Future policy should focus on morbidity decompression rather than aiming at further lowering IS mortality risks. Prevention of IS is therefore of the greatest importance.

To inform future IS preventive strategies, a better understanding is necessary. We urgently need a more detailed analysis of recent changes in IS risk factors and treatments, including the development of an epidemiological model which might help explain the complex changes in IS mortality and morbidity rates.
Strengths and Limitations

We were able to perform mortality trend analysis over a large (30-year) time frame using joinpoint regression analysis, which is able to identify periods in an objective manner. This avoids the need to prespecify time periods (which may bias the way in which the trends are analyzed).

Randomized trials and local cohort studies often include patients that are younger and healthier than average patients seen in daily practice and therefore report lower mortality risks. Therefore, strengths of registry studies with nationwide coverage are its large size, population-based nature, and the wide range of age groups for both sexes studied. In addition, several studies have shown that the validity of the registries in the Netherlands is perfectly adequate along with a high validity of the linkages between them. Furthermore, for ICD-9 code 434 and 436, the positive predictive values have shown to be acceptable.

There are some limitations that should also be acknowledged. The hospital discharge register data do not distinguish minor and major strokes. We are therefore not able to investigate whether the percentage and absolute number of minor strokes increased over time, although we did observe a considerable increase in admissions for transient ischemic attack since 2002 indicating an increase in minor strokes (data not shown).

Furthermore, we had no information regarding previous admissions before 1995. This might have resulted in labeling some first-time IS events that were actually recurrent events. The number of recurrent events was probably the highest in the early years and decreased over time. The inclusion of recurrent events might have led to overestimation of mortality risks and the true decline in IS mortality rate might therefore be somewhat lower. However, this cannot entirely explain the remarkable decrease in IS mortality risks in the new millennium observed in this study. Finally, we had no information about the number of patients who suffered from a nonfatal, nonhospitalized IS. This clearly resulted in an underestimation of the IS incidence especially in the oldest age groups.

Conclusions

IS mortality declined continuously between 1980 and 2000. Furthermore, in the new millennium, a remarkable acceleration of the decline was observed in most age–sex groups. However, this remarkable decline in IS mortality was not matched by a decline in the number of incident nonfatal IS. This is worrying because IS is already a leading cause of adult disability, generating a heavy human and economic burden. Future policies should therefore focus on morbidity decompression as well as reducing mortality risks. Prevention of IS is therefore of the greatest importance.

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Disclosures

None.

Reference


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e-figure 1
Trends in CVA mortality in the Netherlands by ICD-10 code (I60-I69, G45) and sex, 1996 to 2010.
