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Decrease in the Stroke Case Fatality Rates in a French Population-Based Twenty-Year Study

A Comparison between Men and Women

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Key Words
Stroke · Case fatality rates · Epidemiology · Registry · Cerebrovascular disease

Abstract
Background: The aim of the study was to estimate trends in stroke case fatality in a French population-based study over the last 20 years, and to compare trends in men and women. ***Methods:*** We prospectively ascertained first-ever strokes in a well-defined population-based study, from 1985 to 2004, in Dijon (France) (150,000 inhabitants). The study was both specific and exhaustive. The follow-up made it possible to analyze case fatality, according to stroke subtypes and sex. ***Results:*** From the ascertainment of 3,691 strokes divided in 1,920 cerebral infarcts from large artery atheroma, 725 cerebral infarcts from small perforating artery atheroma, 497 cardioembolic infarcts, 134 cerebral infarcts from undetermined mechanism, 341 primary cerebral hemorrhages and 74 subarachnoïd hemorrhages, we observed a significant decrease in 28-day case fatality rates of almost 25% ($p = 0.03$). Case fatality rates decreased in men aged >75 years ($p = 0.01$) and in women aged >75 years ($p = 0.02$) and >65 years ($p = 0.03$). The magnitude of the decrease was smaller in women but not significantly so. According to stroke subtypes, case fatality rates significantly decreased for small perforating artery infarct ($p = 0.04$) and for primary cerebral hemorrhage ($p = 0.03$). In multivariate regression analyses, hemorrhagic stroke, the first period of the study (1985–1989), blood hypertension, previous myocardial infarction and age <85 years had a negative effect. ***Conclusion:*** This is the first population-based study using continuous ascertainment over a period of 20 years that has demonstrated a significant reduction in case fatality rates. We did not observe any significant differences between men and women.

The burden of stroke may increase over the coming years because of the rapid rise in the elderly population [1]. Yet, stroke medicine is one of the fastest progressing branches of medicine with regard to primary and secondary prevention and acute care [1].

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It is important to evaluate reliable population-based studies to determine if such active processes are associated with any change in mortality from stroke, similar to that observed with the declining mortality rates in cardiovascular disease [1]. For stroke, the results are not so clear [1]. In the 1980s, trends in stroke data were conflicting with either falling case fatality and mortality rates [2–5] or rising mortality rates [6].

In Dijon, we have managed an ongoing population-based stroke registry that was launched in 1985 to monitor first-ever stroke occurrence in the population of the city of Dijon [7].

The aim of the present study was to analyze case fatality trends, according to stroke subtypes, in both men and women, from 1985 through 2004.

Materials and Methods

We used the same methodology throughout the 20-year period [7].

Study Area and Population

According to the censuses of 1982, 1990 and 1999, the population of Dijon grew from 145,325 inhabitants in 1985 to 150,138 in 2004. Over the same period the proportion of people ≥75 years increased by 17%, whereas the proportion of those ≥85 years increased by 51%.

Case Ascertainment

The major advantage of the Dijon Stroke Registry was the continuing ascertainment, irrespective of age, which had been continued without interruption since 1985.

A detailed description of the Stroke Registry of Dijon, using 5 sources of ascertainment, has already been published [7]. (1) Numerous investigators from various departments of the University Hospital (85% of the cases), the 3 private hospitals (15% of the cases), the 3 private radiological centers (42% of the cases), the public and private specialists (91% of the cases) and general practitioners (12% of the cases) have collaborated in the creation and maintenance of the registry. (2) Stroke was defined according to WHO recommendations [8]. The ischemic or hemorrhagic mechanism had been identified by CT scan in >90% of cases since 1985, and in 98% of cases since 1990, and with magnetic resonance imaging (MRI) in 22% of cases since 2000. (3) All of the public and private hospital admission and discharge diagnoses, as well as cerebrovascular deaths, were routinely checked as source data, and were entered and validated for stroke classification according to the International Classification of Disease [9] (98% of the cases). (4) If the subject was alive 28 days from the stroke onset, the stroke was considered nonfatal. (5) We also consulted the Regional Causes of Death Register every month, to collect the death certificates of the subjects who had died of stroke outside hospital or at home before a CT scan (4% of the case).

Vascular Risk Factors

We collected prestroke vascular risk factors at stroke onset [7]: hypertension (HT) if ≥160/90 mm Hg, diabetes mellitus if fasting plasma glucose level ≥7.8 mmol/l (patients who had been treated with insulin or oral hypoglycemic agents were also defined as diabetics), hypercholesterolemia if total cholesterol level ≥6.0 mmol/l, smoking (>1 cigarette per day, current or former habit), history of TIA, previous myocardial infarction, angina and peripheral vascular disease. These definitions remained the same throughout the study and were collected for all of the patients whatever the period.

Atrial fibrillation (AF) was diagnosed on electrocardiogram (EKG) performed in all cases or Holter recordings in 30, 28, 29 and 31% of cases in the 4 periods respectively. Two-dimensional echocardiography was performed to detect a possible cardioembolic source in 12, 18, 21 and 23% in the 4 periods respectively. Carotid and vertebral ultrasonography was performed in almost 97% of cases, as were standard blood tests for inflammation and coagulation, and urine tests.

Diagnosis of Stroke Subtypes and Classification

The diagnosis of the subtypes of stroke was always performed on a clinical basis and with cerebral imaging. We recorded (1) ischemic stroke (IS) from atheroma of large arteries for cases presenting cortical-subcortical focal palsy lasting >24 h, with a territory infarct on cerebral, cerebellar or brain stem arteries on CT scan or MRI, associated with severe atheroma on cervical arteries (either occlusion or ≥50% stenosis of the lumen diameter) on ultrasound scan or on magnetic resonance angiography; (2) IS from atheroma of small arteries, so-called lacunar infarct (LI): for cases presenting lacunar clinical syndromes associated with a circular infarct <1.5 cm in diameter restricted to the territory of a perforation artery on CT scan or MRI; (3) IS from cardiac embolism (CE) due to either AF diagnosed on EKG or Holter EKG, or to valve disease, patent foramen ovale or spontaneous intracavitar thrombus on echocardiography; (4) primary cerebral hemorrhagic (PCH) stroke diagnosed on focal cortical-subcortical palsy and associated with a cerebral hematoma on CT scan or on MRI, and (5) subarachnoid hemorrhage, for cases presenting with spontaneous headache, meningeal syndrome associated with spontaneous hyperdensity of the subarachnoid space or bloody cerebral spinal fluid.

For IS, when it was difficult to differentiate between IS, LI and CE stroke (undetermined IS), medical staff meetings were held to classify the difficult cases into 1 of the 3 groups.

Data Processing and Statistical Methods

The raw and specific incidence rates according to age and sex with the population of Dijon as denominator and the standardized rates were calculated by the direct method according to the SEGI world population [2]. We assumed a Poisson distribution for the annual number of events to calculate 95% confidence intervals (CI) for the incidence rates [10], and to calculate relative incidence for the first (1985–1989) and the last (2000–2004) periods [10]. Exponential regression was performed to test time trends in stroke incidence after adjustment for age and sex to the population of Dijon.

Case fatality rates were based on survival at 28 days and their trends were evaluated with linear regressions. We used multivariate regression to identify the independent class variables (age, sex, stroke subtype, HT, diabetes mellitus, hypercholester-

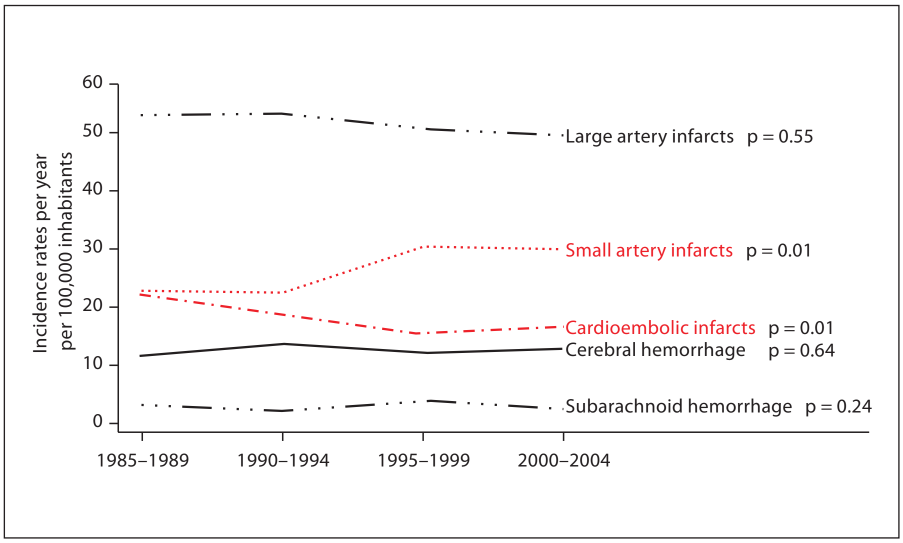

Fig. 1. Trends of standardized incidence rates for 20 years according to stroke subtypes.

olemia, previous TIA, AF, previous myocardial infarction, peripheral vascular disease, time periods) that may influence the 28-day death (dependent variable). $p < 0.05$ was considered significant.

Results

Stroke Subtypes among the 3,691 Stroke Patients

We recorded 1,920 IS, 725 LI, 497 CE strokes, 134 undetermined IS, 341 PCH and 74 subarachnoid hemorrhages. There was no variation in the proportion of fatal and nonfatal cases among the undetermined IS.

Distribution of Risk Factors

Among risk factors, over the 20-year period, the prevalence of patients with hypercholesterolemia significantly rose from 11.7 to 28.7% ($p < 0.01$). This was also true for diabetes, whose prevalence rose from 10.4 to 17.5% ($p < 0.01$).

The prevalence of diastolic HT at stroke onset ≥90 mm Hg significantly decreased from 53.7 to 36.4% ($p < 0.01$). We noted a significant decrease in smoking from 37.8 to 25.2% ($p < 0.01$) and a significant decrease in the proportion of patients with previous myocardial infarction from 22.2 to 17.9% ($p = 0.01$).

Prevalence of HT history [607 cases (65.3%) to 734 (64.1%); $p = 0.57$], previous TIA [234 cases (25.2%) to 255 (22.3%); $p = 0.12$], AF [213 cases (22.9%) to 265 (23.1%); $p = 0.91$] and peripheral vascular disease [112 cases (12.1%) to 117 (10.2%); $p = 0.17$] did not change.

These changes were observed in men and women but without any significant differences and without any well-defined intervention during follow-up.

Trends of Standardized Incidence Rates according to Stroke Subtypes

In figure 1 we report the trends of the standardized incidence rates according to stroke subtypes.

Whereas the rise in IS incidence was not significant ($p = 0.09$), that of LI was ($p = 0.05$), and the incidence of CE stroke significantly decreased ($p = 0.02$). There was no change for the incidence of PCH, subarachnoid hemorrhage and all strokes.

Distribution of 28-Day Case Fatality Rates by 5-Year Periods Adjusted for Age and Sex

Table 1 shows that the decrease in case fatality rates was significant for overall stroke during the 20 years ($p = 0.03$).

In particular, the decrease in case fatality rates for the men was not significant ($p = 0.09$) but significant in men <75 years ($p = 0.01$). Similarly, the decrease of case fatality rates for the women was not significant ($p = 0.16$) but significant in women aged <75 years ($p = 0.02$) and in those <65 years ($p = 0.03$). With regard to stroke subtypes, case fatality rates significantly decreased for LI ($p = 0.04$) and for PCH ($p = 0.03$).

In multivariate regression analyses (table 2), hemorrhagic stroke, the first period (1985–1989), HT, previous myocardial infarction and age >85 years were associated with bad case fatality rates at 28 days. Sex, hyper-

Table 1. Distribution of 28-day case fatality rates by 5-year periods adjusted by age and sex

	1985–1989			1990–1994			1995–1999			2000–2004			p value
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	
Sex													
Men	80	17.8	14.6–21.7	66	12.5	9.7–15.9	63	13.0	10.1–16.5	54	9.7	7.3–12.8	0.09
<65 years	10	8.4	4.9–14.4	7	3.4	1.3–8.8	7	7.0	3.4–14.1	6	3.7	1.6–8.7	0.45
<75 years	30	13.1	9.5–17.9	28	8.8	5.9–12.9	22	7.4	4.7–11.5	7	3.1	1.5–6.4	0.01
>75 years	50	24.4	18.8–31.2	38	17.2	12.6–23.3	41	19.7	14.8–26.0	47	16.6	12.4–22.2	0.24
Women	83	17.7	14.5–21.6	115	20.3	17.1–24.1	81	14.8	11.9–18.4	57	10.3	7.9–13.3	0.16
<65 years	9	13.7	7.4–24.8	4	9.5	4.4–20.0	6	6.8	2.9–5.6	3	3.4	1.1–10.2	0.03
<75 years	24	17.0	11.8–24.1	17	9.8	6.2–15.3	13	7.8	4.5–13.3	6	2.4	0.9–6.4	0.02
>75 years	59	18.0	14.1–22.9	98	25.7	21.3–30.7	68	18.2	14.4–22.9	51	13.9	10.6–18.0	0.48
Overall	163	17.8	15.4–20.5	181	16.6	14.4–19.1	144	13.9	11.8–16.3	111	10.0	8.3–12.1	0.03
Stroke subtypes													
Ischemic stroke													
Atheroma of large artery	77	11.9	9.2–15.2	90	11.6	9.1–14.6	61	12.4	9.7–15.8	46	7.6	5.6–10.3	0.30
Atheroma of small artery	10	6.9	3.8–12.4	5	4.1	1.9–9.0	9	3.4	1.6–6.9	7	2.4	1.0–5.8	0.04
Cardioembolic	39	25.8	19.5–33.7	47	32.4	25.1–41.1	35	23.1	16.8–31.4	29	19.6	13.7–27.5	0.33
Primary intracerebral													
Hemorrhage	33	42.6	32.1–54.8	37	39.4	30.1–50.4	33	34.0	24.7–45.6	25	24.5	17.0–34.6	0.03
Subarachnoid hemorrhage	4	23.0	9.3–50.3	2	7.7	1.1–43.4	6	23.3	10.3–47.9	4	26.1	10.6–55.5	0.61

cholesterolemia, history of TIA, AF and peripheral artery disease did not have any effect on 28-day case fatality.

Discussion

Our major result highlights the decrease of stroke case fatality rates, as reported in other studies [1, 2–5, 11, 12]. According to the literature, the lowest case fatality rates were observed in LI [13] and the highest in PCH [14]. The distributions of stroke subtypes and vascular risk factors found in our study were similar to those observed in other developed countries [3–5].

Several factors observed in Dijon may account for the fall in case fatality rates: the rise in the incidence of LI, the decrease in the incidence of severe CE strokes, and in case fatality rates for LI and PCH. Case fatality rates also declined in Dijon in old men and in younger women as reported in other populations [3, 4, 9, 12]. The role of primary prevention and improvement of acute care for stroke may explain in part the decrease in the case fatality rates. The improvement of the general health status of the population, the quality of life in the city, and the easy access to prevention and care for the population at risk is another partial explanation. This reduction may also be a cohort effect [3, 10] because life expectancy in the background population was also improving.

The main question concerns the problem of higher case fatality rates in women and the small decrease in mortality rates in women, even though not significant.

Some differences between men and women were reported in the literature [2, 15–18]. These differences may reflect differences in competing causes of death, socioeconomic status and other factors influencing death rates, such as lack of health insurance and lack of knowledge about the early warning signs of stroke.

The higher prevalence of risk factors such as HT, AF, obesity, diabetes, inactivity or poor nutrition are well known in women [15–17] but we observed no significant differences between men and women. We cannot argue that changes in risk factor prevalence may explain the decrease in case fatality rates because these changes did not involve the incidence rates. The rise in case fatality rates observed in women but not in men for 1990–1994 (table 1) was due to a rise for women >75 years. We have no clear explanations because the incidence rates in women, the stroke subtype prevalence, the vascular risk factor prevalence according to age and the medical practice did not change. In the literature, the increased delay times for arrival at the emergency room, and lower use of antiplatelets before stroke, of carotid endarterectomies and angiograms in women [15–17] could explain in part the small progress in case fatality in women [15, 18]. A proportion of deaths might be due to do-not-resuscitate orders, in which advanced age could take a part [17]. Another ex-

Table 2. Multivariate regression analysis of factors of case fatality rates at 28 days

Variable	OR	95% CI	p value
Cerebral infarction from atheroma from small arteries		1	
Cerebral infarction from atheroma from large arteries	2.22	1.65–2.99	<0.001
Cardioembolic cerebral infarction	3.16	2.29–4.36	<0.001
Hemorrhage	7.10	5.04–10.01	<0.001
Period 1985–1989		1	
Period 1990–1994	0.86	0.66–1.13	0.275
Period 1995–1999	0.58	0.44–0.77	<0.001
Period 2000–2004	0.44	0.33–0.59	<0.001
Systolic blood pressure <160 mm Hg		1	
Systolic blood pressure ≥160 mm Hg	1.48	1.15–1.92	0.003
Diastolic blood pressure <90 mm Hg		1	
Diastolic blood pressure ≥90 mm Hg	1.32	1.02–1.71	0.039
No history of myocardial infarction		1	
History of myocardial infarction	1.28	1.01–1.61	0.040
Age			
<65 years		1	
65–75 years	1.84	1.26–2.68	0.002
75–85 years	2.56	1.82–3.62	<0.001
>85 years	5.98	4.19–8.53	<0.001

planation could be due to an age effect (women older than men).

It is estimated that 16% of women will die from stroke, whereas 4% of them will eventually die from breast carcinoma, but only 8% of men will die from stroke [18]. This highlights the fact that the severity of stroke is greater in women than in men, although recent issues demonstrate that these differences are small [17].

Our study may have some limitations. It is possible that there were some biases around the ascertainment of the cases in our study. However, there were no changes either in the racial mix or the economic status of the population of Dijon or in the organization of the health care system during the 20-year study. The strength of our population-based register is that uniform registration and diagnostic criteria established by the WHO [8] were applied strictly over the study period to ensure that secular trends in the incidence of stroke were not affected by changes in diagnostic practices or incomplete ascertainment of cases.

Another interest of our study was the long-term involvement by the same investigators and the same research team during the 20-year period. The excellent Oxford study [3] ran from 1982 through 1985 and from 2002 through 2004, with a long stop between 1985 and 2002. The same remarks may be made for the Söderham study [10], which was discontinuous: active ascertainment occurred between 1975 and 1977, 1983 and 1986, and between 1987 and 1990.

The fact that our results come from a well-defined population study, without any limit of age, is also of great importance. In comparison, the Finstroke study [2], which also evaluated the incidence and mortality trends over a long period (15 years), limited the population study to patients from 25 to 74 years of age, erasing trends in the young and even more so in the elderly and excluding a lot of strokes.

In Dijon, we think that the ascertainment was exhaustive and specific because consistency and reliability were also ensured by a high percentage of diagnostic investigations performed on each patient. CT and MRI were performed in almost 98% of the patients in Dijon. In contrast, only 56% of the stroke patients in Oxford [3] were hospitalized and it is not clear when neuroimaging verification of stroke subtypes was done after the onset of stroke.

Then, certain ischemic and hemorrhagic strokes may have been misdiagnosed because of the lack of exhaustive ascertainment from general practitioners. Nevertheless, some progress is observed every year.

Conclusion

This is the first population-based study, investigating case fatality rates on the basis of continuous ascertainment over 20 years, during which every stroke subtype was identified thanks to almost 98% of verification by neuroimaging. Our study provides evidence that acute care does reduce case fatality rates in stroke.

With regard to stroke trends, we did not observe any significant differences between men and women.

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