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Sex differences in acute ischaemic stroke patients: clinical presentation, causes and outcomes

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Background and purpose: The aim was to investigate sex differences in the causes, clinical presentation, outcome and stroke recurrences in a large cohort of consecutive acute ischaemic stroke patients.

Methods: Patients from the Acute Stroke Registry and Analysis of Lausanne were included from March 2003 to April 2016. Multivariate analysis of clinical, pathophysiological and biological variables was conducted. The 12-month functional outcome using modified Rankin Scale shift analysis, 12-month mortality and cerebrovascular recurrences were compared after adjustment for potential confounders.

Results: From 3993 patients, 44% were female, were older and had more pre-stroke handicap than male patients. In the multivariate analysis, higher frequencies of several comorbidities were observed in women (migraine, hypothyroidism, depression/psychotic disorders) and of risk factors in men (more past cerebrovascular events, coronary artery disease, low cardiac ejection fraction, alcohol abuse and active cancer). Women had a lower body mass index and more pretreatment with antihypertensive drugs but less with antidiabetic/lipid-lowering or antiplatelet drugs. Stroke severity was higher in women, but men had more cerebellar signs. Stroke due to atherosclerosis, small vessel disease or multiple origins was less frequent in women. In the adjusted 12-month modified Rankin Scale shift analysis, female sex was associated with less favourable functional outcome (odds ratio 1.19, 95% confidence interval 1.04–1.35), whilst 12-month mortality (hazard ratio 1.01, 95% confidence interval 0.86–1.19) and cerebrovascular recurrences (hazard ratio 1.14, 95% confidence interval 0.9–1.45) were similar.

Conclusions: In this retrospective analysis of consecutive acute ischaemic stroke patients, women had higher age, more pre-stroke handicap and less atherosclerotic, lacunar or multiple stroke mechanisms. Female sex was associated with higher levels of long-term disability than men, but mortality and cerebrovascular recurrences were not significantly different.

Introduction

Epidemiological data have led to a better recognition of sex differences in stroke, including in acute ischaemic stroke (AIS) [1–4]. The overall age-related higher incidence of stroke due to longer life expectancy for women together with the poorer outcomes in terms of disability and quality of life underline the social and public health importance of stroke in women [1,2,5,6]. Furthermore, sex-specific stroke mortality rates are strongly related to age: women have a higher risk at older age (>85 years) whilst men have a higher risk at middle age (45–74 years) [2].

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However, besides the insufficiently understood higher age-specific stroke rates in men, little is known concerning the influences of sex on pathophysiological, clinical and radiological aspects of AIS. Furthermore, data investigating specifically sex disparities in acute stroke treatment are sparse. The aim was to investigate sex differences in demographics, clinical presentation, causes and adjusted long-term outcomes in a large cohort of consecutive AIS patients in a single comprehensive stroke centre.

Methods

Patients and data collection

All patients from March 2003 to April 2016 from the prospectively constructed Acute Stroke Registry and Analysis of Lausanne (ASTRAL) were retrospectively reviewed [7]. ASTRAL collects all AISs admitted to the stroke unit and/or intensive care unit of Lausanne University Hospital within 24 h of last known well-time. Our centre's patient population consists of about two-thirds local and one-third distant referrals from community practices or community hospitals, mainly addressed for revascularization treatment.

In summary, demographic data, vascular risk factors (arterial hypertension, smoking, valve replacements, atrial fibrillation, dyslipidaemia, diabetes mellitus and coronary artery disease, either already known or newly diagnosed), multiple other comorbidities and previous cerebrovascular events were recorded. Depression and psychosis were defined according to the Elixhauser comorbidity index which uses specific International Classification of Diseases, 10th revision (ICD-10) codes for each of this comorbidity group [8]. Pre-stroke modified Rankin Scale (mRS) score and medications at the time of stroke were collected. On arrival, the National Institutes of Health Stroke Scale (NIHSS) was performed or supervised by NIHSS-certified personnel. Similarly, metabolic variables (serum glucose, creatinine, cholesterol, full blood count) and vital signs (skin temperature, systolic and diastolic blood pressure) were recorded on arrival. At least one arterial study of cervical and cerebral arteries was obtained within 24 h of stroke onset, mainly computed tomography (CT) angiography or alternatively magnetic resonance angiography, Doppler (including transcranial Doppler) or digital subtraction angiography in patients considered for acute endovascular revascularization. The arterial occlusion site in the ischaemic territory was recorded and the following definitions were utilized: any intracranial arterial occlusion equals any occlusion in the ischaemic territory; proximal intracranial artery occlusion equals carotid siphon, M1 and basilar artery occlusion; distal intracranial artery occlusion equals M2, M3–4, any anterior cerebral artery/posterior cerebral artery and V4 occlusion; any extracranial artery occlusion equals extracranial internal carotid artery and V1–3 occlusion. Perfusion CT was performed in most patients arriving ≤24 h with a suspicion of supratentorial stroke. Images were reviewed with neuro-radiologists for acute and chronic ischaemic changes, arterial pathology and other findings. The stroke mechanism was classified according to TOAST [9], with dissection and multiple causes added as additional mechanisms. The rest of the acute stroke management and secondary prevention followed current European Stroke Organization guidelines [10]. Rankin-certified personnel assessed mRS at 7 days and 3 months in the outpatient clinic. At 12 months and for patients not able to attend the 3-month outpatient clinic, Rankin-certified personnel assessed the mRS in a structured telephone interview. The destination at discharge was recorded in patients who left the hospital alive and was analysed according to the degree of handicap (mRS 0–2 vs. mRS 3–5) on day 7 after the index stroke.

The STROBE method (Strengthening the Reporting of Observational Studies in Epidemiology) was applied [11].

Standard protocol approval

The ethics commission for research on humans of the Canton of Vaud (ECCV) approved the scientific use of ASTRAL.

Data availability statement

An anonymized copy of the data used for the current project can be obtained by writing to the last author. Data will be provided based on a reasonable request describing the reasons, methods of planned analysis, and type and authorship of a potential publication, if applicable.

Statistical analyses

The included patients were divided into two groups according to sex as shown in Fig. 1. All demographic, clinical, biological and radiological variables from the acute phase of stroke (<24 h) that were collected in ASTRAL were analysed. Continuous variables were expressed as median with interquartile range and categorical variables were presented as percentages and numbers. All variables had fewer than 5% missing values except mRS at 12 months (missing in 6.29%),

body mass index (BMI) (missing in 19.1%), pre-stroke NIHSS (missing in 26.6%), NIHSS at 24 h (missing in 5.7%), further cerebrovascular events (missing in 5.9%), acute temperature (missing in 10.1%), subacute temperature (missing in 11.6%), death at 12 months (missing in 6.2%) and occlusion site (missing in 16%).

First a univariate comparison was performed according to sex and the unadjusted odds ratios (ORs) were calculated. Then a multivariate regression analysis of selected variables was conducted in order to identify independent associations with sex.

Functional 12-month outcome was assessed by mRS shift analysis. The selection of variables used for adjustment was based on the significant differences identified in the preceding multivariate analysis and on variables influencing outcome in previous studies by ourselves [12,13] and others.

The following variables were used to adjust when comparing the 12-month functional outcome, death and recurrence rates between the two sexes: age, pre-stroke handicap, previous cerebrovascular events, NIHSS at admission, onset-to-door time, cerebellar signs, stroke mechanism (TOAST), prior treatment with antiplatelet, lipid-lowering, antidiabetic or antihypertensive medications, low cardiac ejection fraction (<35%), BMI, migraine, alcohol abuse, coronary artery disease, hypothyroidism, depression, psychosis, active cancer and acute temperature. On top of these, decreased level of consciousness and glucose level at admission were used in the 12-month functional outcome and death rate analyses and hypertension, smoking and diabetes were used in the recurrence rate analysis. The 12-month mortality and recurrences were presented as Kaplan–Meier survival curves and then assessed by Cox regression analysis. Missing data were imputed using multivariate imputation by chained equations. Statistical analyses were conducted using R statistical software version 3.4.2 (R Core Team 2017) [14].

Results

A total of 3993 patients fulfilled the inclusion criteria and were retrospectively analysed (Fig. 1). Of these, 44% were female with 3% of non-Caucasian ethnicity and a median age of 73.4 years. The proportion of women in the referral population was 39% and lower than in the primary catchment area (46%) (demographic, clinical characteristics and outcome parameters for the entire population and dichotomized for sex are described in Table 1, with more details in Table S1).

Unadjusted comparisons showed higher age in women, higher pre-stroke handicap (mRS) and admission NIHSS scores and longer onset-to-door and onset-to-CT times (Table 1). Regarding stroke referral, female patients were less often admitted from other emergency departments but more frequently sent by the emergency medical system. Clinically, paresis, sensory and visual deficits, eye deviation, aphasia or neglect were more often encountered in women at initial presentation whereas oculomotor brainstem symptoms and cerebellar or vestibular symptoms were less present compared to men. The anterior circulation was more frequently affected in women and bilateral strokes more often in men. Intracranial arterial occlusions in the acute phase were more prevalent in females (mainly proximally), whereas extracranial arterial occlusions were more frequent in males.

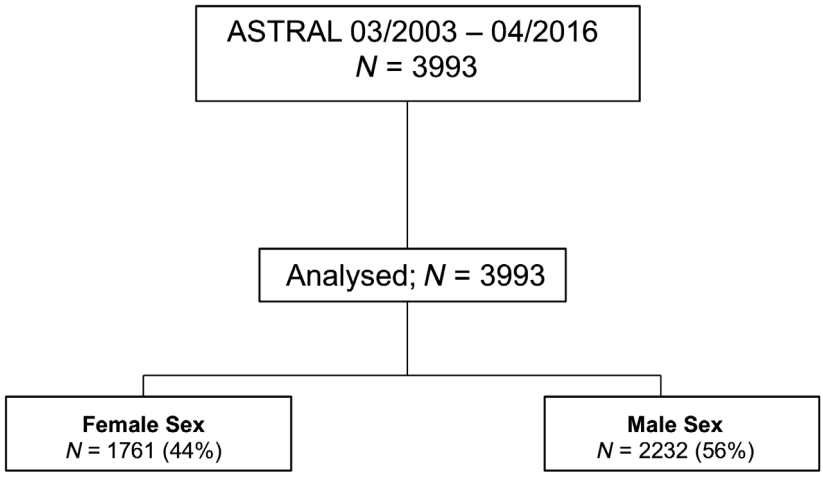

Figure 1 Study flow diagram.

Table 1 Overall and sex-specific demographics and clinical characteristics of the analysed population, non-adjusted

Variable	Overall	Female sex	Male sex	OR	CI
Demographics and admission information					
Age	73.4 (20.7)	77 (18.1)	69.9 (20.4)	1.02*	1.02–1.03
mRS pre-stroke	0 (1)	1 (2)	0 (1)	1.27*	1.2–1.35
Previous ischaemic event (stroke, TIA, retinal event)	1108 (28)	434 (24.9)	674 (30.4)	0.76*	0.66–0.88
NIHSS on admission	6 (11)	7 (13)	6 (10)	1.02*	1.01–1.03
Onset-to-door time (per 60 min strata)	3.25 (8.9)	3.52 (9.9)	3.07 (8.2)	1.01*	1–1.02
Acute treatment					
IVT (with or without EVT)	873 (21.9)	379 (21.5)	494 (22.1)	0.96	0.83–1.12
EVT including bridging < 6 h	248 (6.2)	103 (5.8)	145 (6)	0.89	0.69–1.16
Stroke mechanism					
Atherosclerotic	546 (13.7)	156 (8.9)	390 (17.5)	0.46*	0.38–0.56
Cardioembolic	1341 (33.6)	661 (37.6)	680 (30.5)	1.37*	1.2–1.56
Microangiopathic (lacunar)	473 (11.9)	193 (11)	280 (12.6)	0.86	0.71–1.04
Unknown	1048 (26.3)	519 (29.5)	529 (23.7)	1.34*	1.17–1.55
Multiple or coexisting causes	226 (5.7)	82 (4.7)	144 (6.5)	0.71*	0.54–0.93
Stroke localization					
Anterior circulation stroke	2646 (67.3)	1229 (70.6)	1417 (64.7)	1.31*	1.14–1.5
Posterior circulation stroke	1009 (25.7)	386 (22.2)	623 (28.4)	0.72*	0.62–0.83
Bilateral	373 (9.4)	135 (7.7)	238 (10.8)	0.69*	0.55–0.86
Arterial occlusion site in ischaemic territory					
Any intracranial occlusion	1525 (38)	695 (39)	830 (37.2)	1.24*	1.08–1.42
Proximal intracranial occlusion	893 (22.3)	431 (24.4)	462 (20.7)	1.36*	1.17–1.59
Distal intracranial occlusion	559 (13.9)	248 (14.1)	311 (13.9)	1.08	0.9–1.3
Any extracranial occlusion	637 (16)	223 (12.7)	414 (18.5)	0.67*	0.56–0.8
Medications prior to stroke onset					
Antiplatelets	1514 (38.4)	626 (35.9)	888 (40.3)	0.83*	0.73–0.94
Antihypertensive treatment	2337 (59.4)	1093 (63)	1244 (56.6)	1.3*	1.15–1.48
Lipid-lowering drugs	1121 (28.3)	418 (24)	703 (31.8)	0.68*	0.59–0.78
Antidiabetic treatment	493 (12.5)	168 (9.7)	325 (14.8)	0.62*	0.51–0.75
Cardiovascular risk factors and comorbidities					
Hypertension	2852 (71.6)	1271 (72.4)	1581 (71)	1.07	0.93–1.23
Diabetes	742 (18.6)	269 (15.3)	473 (21.3)	0.67*	0.57–0.79
Hyperlipidaemia	2910 (73.6)	1237 (71)	1673 (76)	0.79*	0.68–0.91
Smoking (current or stopped < 2 years)	919 (23.5)	315 (18.3)	604 (27.6)	0.59*	0.5–0.69
Atrial fibrillation	1157 (29.1)	591 (33.7)	566 (25.5)	1.49*	1.3–1.71
Coronary artery disease	732 (18.5)	233 (13.3)	499 (22.6)	0.53*	0.45–0.63
Ejection fraction < 35%	212 (5.4)	64 (3.7)	148 (6.7)	0.53*	0.39–0.71
PFO (if searched)	362 (36.9)	143 (37.8)	219 (36.3)	1.07	0.82–1.4
Peripheral artery disease	256 (6.5)	86 (5)	170 (7.7)	0.63*	0.48–0.82
Active cancer	205 (5.2)	75 (4.3)	130 (5.9)	0.72*	0.53–0.96
Migraine with or without aura	161 (4.1)	102 (5.9)	59 (2.7)	2.25*	1.62–3.12
Alcohol dependence	398 (10.1)	98 (5.6)	300 (13.6)	0.38*	0.3–0.48
Hypothyroidism	283 (7.2)	199 (11.4)	84 (3.8)	3.25*	2.5–4.23
BMI (kg/m^2)	25 (5)	24 (7)	26 (5)	0.93*	0.92–0.95
Obesity	1751 (44.6)	653 (37.7)	1098 (50)	0.61*	0.53–0.69
Alcohol abuse	418 (10.7)	104 (6)	314 (14.4)	0.38*	0.3–0.48
Depression	191 (4.9)	102 (5.9)	89 (4.1)	1.47*	1.1–1.97
Psychosis	337 (8.5)	191 (11)	146 (6.6)	1.74*	1.38–2.17
Outcome parameters					
Mortality at 12 months	781 (21)	781 (24.9)	409 (17.7)	1.53*	1.31–1.8
Further cerebrovascular events over 12 months	348 (10)	147 (9.7)	201 (10.3)	0.92*	0.75–1.17
Discharge destination in patients with mRS 0–2 at 7 days					
Home	1364 (64.4)	529 (63.4)	835 (65.1)	0.93	0.77–1.11
Rehabilitation	469 (22.1)	202 (24.2)	267 (20.8)	1.21	0.99–1.49
Long-term institution (including palliative care centre)	24 (1.1)	19 (2.3)	5 (0.4)	5.95*	2.21–15.9
Other acute care hospital	260 (12.3)	85 (10.2)	175 (13.6)	0.72*	0.54–0.94

(continued)

Table 1 *(Continued)*

Variable	Overall	Female sex	Male sex	OR	CI
Discharge destination in patients with mRS 3–5 at 7 days					
Home	93 (6.4)	44 (6.1)	49 (6.6)	0.92	0.6–1.4
Rehabilitation	808 (55.2)	394 (54.6)	414 (55.9)	0.95	0.77–1.17
Long-term institution (including palliative care centre)	139 (9.5)	91 (12.6)	48 (6.5)	2.08*	1.44–3
Other acute care hospital	423 (28.9)	193 (26.7)	230 (31)	0.81	0.65–1.02

Values are expressed as median and interquartile range for continuous variables, or absolute count and percentage for categorical variables unless stated otherwise. BMI, body mass index; CI, confidence interval; EVT, endovascular treatment; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PFO, patent foramen ovale; TIA, transient ischaemic attack. *Statistically significant in univariate comparisons.

The frequency of vascular risk factors and comorbidities showed multiple differences, notably a lower rate of preceding cerebrovascular events, smoking, diabetes, obesity, coronary artery disease and alcohol abuse in women, and more atrial fibrillation, migraine, depression/psychotic disorders compared to men. Stroke mechanism also varied on several accounts.

In the multivariate analysis of differences between women and men (Table 2), several comorbidities and risk factors were noted as being more frequent in women, in particular migraine, hypothyroidism and depression/psychotic disorders. Other risk factors were more prevalent in men, i.e. past cerebrovascular events, coronary artery disease, low cardiac ejection fraction, alcohol abuse and active cancer. Furthermore, women were older, had lower BMI, more pretreatment with antihypertensive agents and less with antiplatelet, antidiabetic and lipid-lowering drugs. Stroke severity at admission and onset-to-door time were higher in women, and men had more cerebellar symptoms and elevated temperature at admission. Stroke due to large-artery atherosclerosis, small vessel disease or multiple causes was found less often in women. The discharge destination was more often a long-term care facility for women in univariate comparison, independently of the disability level (Table 1). On the other hand, women with lower disability in the subacute phase were less often transferred to other acute care hospitals.

Functional outcome measured by the mRS at 12 months was worse in women in the unadjusted shift analysis [OR 1.54 for shift towards a higher mRS, 95% confidence interval (CI) 1.38–1.72] (Table 3). In the adjusted mRS shift analysis, this result was very similar and still significant (OR 1.19, 95% CI 1.04–1.35) (Tables 3 and S2). Multiple other factors were independently associated with functional 12-month outcome and are listed in Table S2.

The unadjusted mortality at 12 months was higher in women than men, as depicted in the non-adjusted Kaplan–Meier curves (hazard ratio 1.53, 95% CI 1.31–1.80) (Table 3, Fig. 2). In the adjusted Cox regression analysis, however, sex was no longer associated with mortality (OR 1.01, 95% CI 0.86–1.19) (Table 3, Fig. S1). Regarding cerebrovascular recurrences at 12 months, a statistically significant difference between the sexes was not observed in the unadjusted or the adjusted analysis (Table 3, Figs 3 and S2).

Table 2 Multivariate analysis of sex-specific demographic and clinical characteristics of the analysed population (reference male)

	OR (95% CI)	*P* value
Demographics and admission information		
Age	1.02 (1.02–1.03)	0.000
Onset-to-door time per 60 min strata	1.01 (1.00–1.02)	0.035
mRS pre-stroke	1.13 (1.05–1.21)	0.001
NIHSS on admission	1.02 (1.01–1.03)	0.000
Previous cerebrovascular events	0.77 (0.65–1.70)	0.001
Initial cerebellar signs	0.82 (0.7–0.96)	0.014
Acute temperature	1.23 (1.10–1.38)	0.000
Vascular risk factors		
Migraine	2.76 (1.93–3.94)	0.000
Active cancer	0.67 (0.49–0.93)	0.015
BMI	0.95 (0.93–0.96)	0.000
Obesity	0.78 (0.61–0.99)	0.039
Alcohol abuse	0.41 (0.32–0.52)	0.000
Comorbidities		
Coronary artery disease	0.49 (0.40–0.61)	0.000
Ejection fraction < 35%	0.52 (0.37–0.73)	0.000
Hypothyroidism	2.85 (2.14–3.79)	0.000
Depression	1.61 (1.16–2.21)	0.004
Psychosis	1.71 (1.33–2.20)	0.027
Stroke mechanism		
Atherosclerotic	0.42 (0.34–0.53)	0.000
Lacunar	0.79 (0.63–0.99)	0.038
Multiple/coexisting stroke causes	0.58 (0.43–0.79)	0.001
Pretreatment		
Antiplatelets	0.84 (0.71–1.00)	0.049
Antihypertensive treatment	1.51 (1.28–1.78)	0.000
Lipid lowering treatment	0.81 (0.68–0.96)	0.017
Antidiabetic treatment	0.68 (0.55–0.86)	0.001

BMI, body mass index; CI, confidence interval; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

Table 3 Functional outcome, mortality and recurrences during follow-up (reference male)

Variable	Unadjusted result	Unadjusted CI	Adjusted result	Adjusted CI
Shift of the mRS spectrum towards a higher mRS	OR 1.54	1.38–1.72	OR 1.19	1.04–1.35
Mortality at 12 months	HR 1.53	1.31–1.80	HR 1.01	0.86–1.19
Recurrence at 12 months	HR 0.95	0.76–1.18	HR 1.14	0.90–1.45

CI, confidence interval; HR, hazard ratio; mRS, modified Rankin Scale; OR, odds ratio.

Discussion

In this retrospective study of 3993 consecutive AIS patients admitted to a comprehensive stroke centre, the multivariate regression analysis found that female patients were older and more often had pre-stroke handicap. Despite their higher initial stroke severity, delay to hospital arrival was longer. Differences in risk factors and comorbidities resembled known patterns in elderly vascular patients, i.e. female patients less often had coronary artery disease, low cardiac ejection fraction, alcohol abuse disorder and active oncological disease, but more often had a history of migraine or thyroid, depressive or psychotic disorders. Pretreatment with vascular secondary preventive drugs was less prevalent in women, except for antihypertensive treatment which was more frequent.

Somewhat unexpectedly, BMI was lower in women than in men in our cohort (median 26 kg/m^2 in men vs. 24 kg/m^2 in women), which is in contrast to most other data derived from stroke populations [15]. The reasons for this finding remain speculative.

In the multivariate regression analysis, stroke mechanisms in women were less frequently atherosclerotic, lacunar or multiple/coexisting types, partially in keeping with more vascular risk factors (or treatment of vascular risk factors) in men. A higher proportion of cardioembolic strokes in the literature [16,17] could not be confirmed in female patients in our adjusted analysis. In our analysis, the only independent difference in clinical presentation of stroke, other than higher stroke severity, was the lower frequency of cerebellar signs in women. Other authors found that women tend to present with less specific symptoms such as disorientation, generalized weakness, fatigue and mental status change than men [18], but our register does not capture such symptoms. Given the absence of important differences in clinical symptoms in our study and given the higher stroke severity in women, their longer delay to hospital presentation could be explained either by symptoms being taken less seriously or more likely by the fact that women more often live alone at this age [19] and thus potentially have more difficulties accessing emergency medical services, a factor that unfortunately was not collected in our registry. These longer prehospital

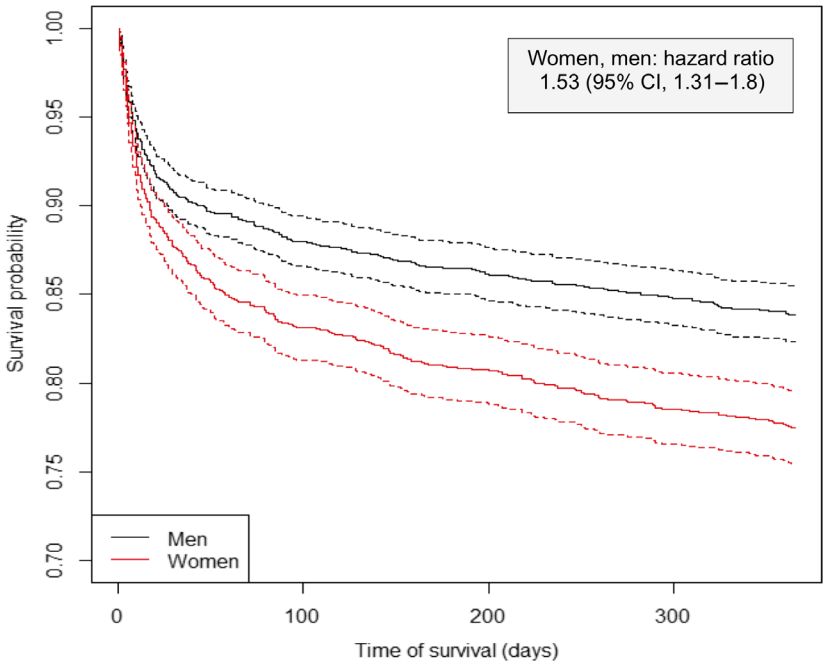

Figure 2 Unadjusted one-year survival rates by sex.

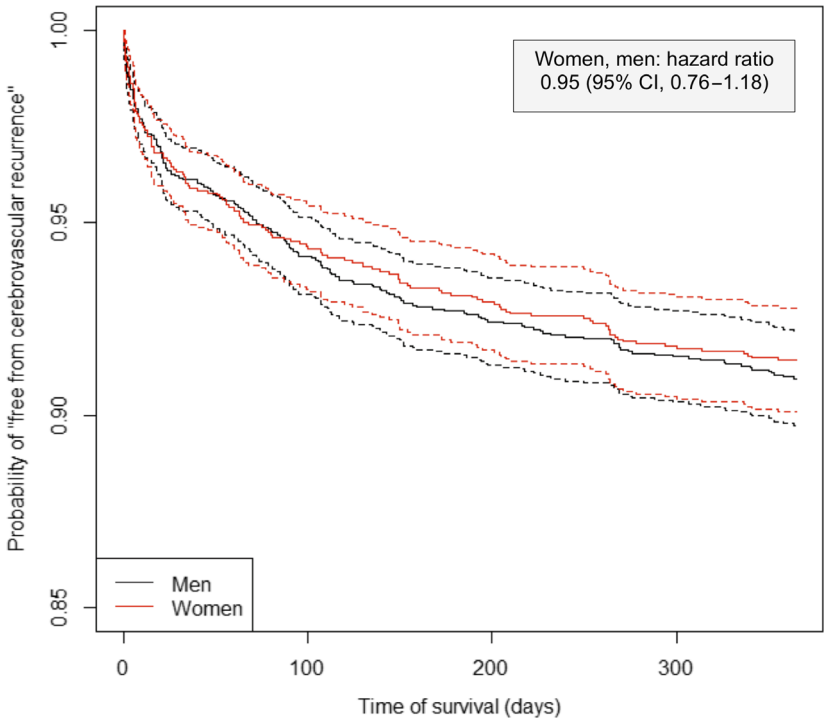

Figure 3 One-year cerebrovascular recurrence rates by sex, unadjusted.

delays could decrease the eligibility of women for revascularization treatments; this was not found in the univariate comparison in our study, but it is planned to investigate diagnostic and therapeutic services delivered to women and men in more detail in a separate study.

It was observed that unfavourable functional outcomes at 12 months were more frequent in women after adjustment for multiple prognostic factors. This has already been described by others [5,20–23] but does not have a simple explanation. On the other hand, no difference in 12-month mortality was found between women and men, whereas others reported a lower [20,24–27], similar [2,28] or higher long-term mortality/case fatality [29,30]. It is generally considered that the above-mentioned sex-specific differences in outcome are due to the older age of women at stroke onset, higher pre-stroke handicap and presumably a result of sex-related comorbidities, in particular depression. However, our analysis was adjusted for these and multiple other covariates, making it possible that unmeasured factors such as loneliness, the absence of a caregiver at home or lifestyle factors play a role. In line with this assumption, a higher proportion of women were observed to be admitted to a long-term care facility at discharge independently of disability level, and there were lower rates of transfer to other acute care hospitals in women with minor disability in the subacute phase. Lastly, biological differences including hormones and metabolic factors are known to influence stroke outcome. Neuroprotective effects are attributed to oestradiol in, in particular, premenopausal women [31]. Regarding stroke risk, however, the Women's Health Initiative study [32] and the Nurses' Health Study [33] showed that exogenous postmenopausal oestrogen increased the stroke risk. Interestingly, a recent pooled analysis of five studies [34] found hormone replacement therapy to be associated with a longer stroke-free period when initiated within 5 years in menopausal women, underpinning the complex relationship between hormone therapy and the nervous and cardiovascular systems.

Cerebrovascular recurrences over 12 months were similar in both sexes with and without adjustment for other factors, confirming the results of the few publications on this topic [23,27,35,36]. The strengths of our work are the consecutive nature of the collected data over a long period of time, with pre-specified and standardized data collection using up-to-date scales, definitions and neurovascular imaging methods. In addition, our population is typical of a comprehensive stroke centre that includes both primary and tertiary referral populations.

The limitations of our work include the absence of measurement of certain prognostic variables as mentioned above such as educational level, nutritional

habits, physical activity, socioeconomic status and the extent of social networks. Secondly, this is not a population-based study and therefore potentially not representative of all stroke patients, calling for a confirmation of our results in other populations. Given that the proportion of women in the referral population was somewhat lower than in the primary catchment area, a possible selection bias has to be considered. Nevertheless, most patients are now cared for in stroke centres in higher income countries as in our study. Thirdly, the limitations of the mRS as a measure of functional outcome need to be acknowledged because it mixes objective and subjective items of activity, participation and impairment issues of recovery.

In conclusion, this study suggests that female ischaemic stroke patients arriving at a comprehensive stroke centre are older, more often have pre-stroke handicap and less frequently have strokes of atherosclerotic, lacunar or multiple/coexisting aetiology. Also, female sex was associated with higher handicap at 12 months, but not with long-term mortality or stroke recurrences compared to men.

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Disclosure of conflicts of interest

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Adjusted 1-year survival rates by sex

Figure S2. One-year cerebrovascular recurrence rates by sex, adjusted

Table S1. Further details of the overall and sex-specific demographics and clinical characteristics of the analysed population, non-adjusted

Table S2. Multivariate shift analysis of 12-month outcome measured by the modified Rankin Scale (only significant results are shown)

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