

## Sex Differences in Stroke Incidence in a Portuguese Community-Based Study

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**Background and Aim:** Stroke is a major health problem. Several studies reported sex differences regarding stroke. We aim to study this issue in an incidence stroke study. **Methods:** Data were retrieved from a community-based prospective register of patients that had a first ever stroke in a life time between October 2009 and September 2011. We studied sex differences regarding demographic data, vascular risk factors, stroke type, stroke severity (NIHSS), disability at 28 days (modified Rankin scale (mRS)), and case fatality at 30 and 90 days. **Results:** From 720 stroke patients, 45.3% were men. Women were older ( $75.0 \pm 13.6$  versus  $67.2 \pm 14.9$  years), had a worse premorbid mRS (39.3% versus 25.5%,  $P < .001$ ), and a higher prevalence of hypertension ( $P = .004$ ) and atrial fibrillation ( $P < .001$ ). Previous myocardial infarction was more frequent in men ( $P = .001$ ), as well as smoking habits ( $P < .001$ ). Ischemic stroke was more common in women than men (87.6% versus 81.3%,  $P = .038$ ). The 28 days' outcome was worse in women (mRS  $\geq 2$ , 77.2% versus 70.6%,  $P = .044$ ). No differences were found in initial stroke severity (median NIHSS = 4) and case fatality at 30 and 90 days, after adjusting for age and premorbid mRS. **Conclusion:** No differences were found in stroke initial severity and mortality at 30 and 90 days between men and women, despite the sex differences pertaining to the stroke profile—age, vascular risk factors, stroke type, and outcome. Our results are somewhat discrepant from those described in the literature; more research is needed to understand if this may be due to changes in stroke standard of care.

**Key Words:** Stroke—sex differences—epidemiology—stroke survival.

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Stroke is one of the leading causes of disability and death worldwide.<sup>1</sup> In Portugal, the scenario is even worse, as stroke is the first cause of death.<sup>2</sup> Although stroke mortality rates have been decreasing throughout the years,<sup>2</sup> it is still an important health concern, namely in the north of the country.<sup>3</sup>

Sex may play a role in stroke.<sup>4</sup> Although there are some inconsistencies, the literature has shown that stroke risk factors, as well etiology and type of stroke, may differ between sexes. Numerous reasons may contribute to these

findings, such as genetic differences in immunity, coagulation, and hormonal factors.<sup>1</sup> Asymmetries between sexes have been reported concerning to stroke prevention.<sup>5</sup> Also, it has been previously stated that probably women are not being offered the same acute stroke care opportunities as men.<sup>4</sup> Different stroke outcomes between sexes might reflect the promptness of diagnosis and treatment.<sup>5</sup>

The main goal of this project, based on a community registry, is to study the sex differences in stroke.

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## Methods

The information used in this study was retrieved from a database of the second population-based register undertaken in Northern Portugal (ACIN2).<sup>3</sup> It comprised all first-ever-in-a-lifetime stroke events occurring between October 2009 and September 2011 in the population registered at three health centers in Porto. Detailed information about ascertainment methods is described elsewhere.<sup>3</sup>

The population-based register was approved by the Ethics Committee of the Porto Hospital Centre, where the study was conducted, and by the National Commission for Data Protection.

The World Health Organisation defines stroke as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin.”<sup>6</sup> Stroke types were classified according to Sudlow and Warlow as ischemic stroke, primary intracerebral hemorrhage, and subarachnoid hemorrhage.<sup>7</sup>

The Bamford Oxfordshire classification<sup>8</sup> was used for ischemic stroke subtypes: total anterior circulation infarcts, partial anterior circulation infarcts, posterior circulation infarcts, and lacunar infarcts. The ischemic stroke etiology was defined according to the TOAST criteria<sup>9</sup>: large-artery atherosclerosis, cardioembolism, and small-artery occlusion — lacunes, acute stroke of other determined etiology, and stroke of undetermined etiology.

Stroke severity was assessed based on the National Institute of Health Stroke Scale (NIHSS)<sup>10</sup> score at the first medical evaluation, with the exception of subarachnoid hemorrhage. Whenever the NIHSS score was unavailable, it was estimated from the patients’ clinical records,<sup>11</sup> as such retrospective evaluation has been reported to be valid.<sup>11</sup> Furthermore, the NIHSS score was categorized into mild (NIHSS  $\leq 7$ ), moderate (NIHSS 8–16), and severe (NIHSS  $\geq 17$ ).<sup>8</sup>

For the process of care of the patients the following factors were registered: time from symptom onset to emergency room (ER) admission, recombinant tissue plasminogen activator (rtPA) treatment, inpatient admission, and length of stay.

Pre- and poststroke (28 days after stroke) modified Rankin scale (mRS) scores were recorded for every patient to evaluate the functional outcome. Prestroke disability was considered whenever a patient had an mRS score greater than 1, and stroke was considered as disabling whenever the poststroke mRS score was higher than the prestroke mRS and  $>1$ .

The criteria used for prestroke risk factors was as follows: (1) history of known hypertension or antihypertensive treatment; (2) previous diagnosis/treatment of diabetes mellitus with oral antidiabetic/insulin or fasting glycemia  $>126$  mg/dl, postprandial glycemia  $\geq 200$  mg/dl, and/or  $\geq 200$  mg/dl in the 2-hour glucose

tolerance test; (3) evidence of atrial fibrillation in electrocardiogram or documented in the patient’s records; (4) previous diagnosis/treatment of hypercholesterolemia; (5) history of previous myocardial infarction episode; and (6) classification of patients as current smokers if they had smoked at any time in the preceding 12 months.

Descriptive statistics were used to summarize the socio-demographic characteristics stratified by sex. Chi-square tests, median test, and *t* tests were used to compare the baseline and clinical characteristics between sexes. The Kaplan–Meyer method was used to estimate the overall cumulative survival over 3 months after stroke; the log-rank test was used to compare survival between sexes. Cox proportional hazard models were used to evaluate independent risk factors for survival. A *P* value of .05 was considered the limit for incorrectly rejecting the null hypothesis. Data analysis was performed using SPSS Statistics v24.

## Results

From the initial sample of 721 patients, we excluded 1 patient whose final diagnosis was deep venous thrombosis. From this population, 326 were men and 394 were women.

Women were approximately 8 years older than men (mean age of  $75.0 \pm 13.6$  versus  $67.2 \pm 14.9$ ,  $P < .001$ ), accounting for 62.5% of the stroke patients aged  $>65$  years (Table 1). Also, women had a higher previous functional dependency level, showing an mRS  $\geq 2$  more frequently (39.3% versus 25.5%,  $P < .001$ ) (Table 1). Additionally, when comparing the whole mRS between sexes, we can state that women tend to have a generally higher score.

Concerning vascular risk factors, women were more likely to suffer from arterial hypertension (81.0% versus 71.8%,  $P = .004$ ) and atrial fibrillation (27.2% versus 14.1%,  $P < .001$ ). Regarding atrial fibrillation diagnosed at the time of the event (de novo), no differences were found between male and female sexes ( $P = .44$ ). Men had more frequently history of previous myocardial infarction (12.9% versus 5.8%,  $P = .001$ ) and smoking habits (67.2% versus 9.1%,  $P < .001$ ). No statistically significant differences were found between sexes for diabetes mellitus ( $P = .23$ ) and hypercholesterolemia ( $P = .22$ ; Table 1).

Clinical stroke features in both sexes are presented in Table 2. Differences were found in stroke type ( $P = .038$ ), ischemic stroke was more common in the female population (87.6% versus 81.3%), while men had a higher incidence of intracranial hemorrhage (15.6% versus 9.4%). Subarachnoid hemorrhage accounted for 3.1% of all cases, with a similar incidence in both groups (3.1% in men versus 3.0% in women).

Regarding ischemic stroke etiology, there were no statistically significant differences between men and women ( $P = .60$ ); however, there is a trend for a more frequent

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