

STROKE

Comparable care, worse outcomes for women with stroke

Louise D. McCullough and Judith H. Lichtman

Sex differences are increasingly recognized in many areas of medicine, and stroke is no exception. Women tend to be more adversely affected by stroke than are men and, as a new study illustrates, this discrepancy cannot be attributed solely to sex-related differences in acute stroke care.

McCullough, L. D. & Lichtman, J. H. *Nat. Rev. Neurol.* 10, 367–368 (2014); published online 17 June 2014; doi:10.1038/nrneuro.2014.103

In the USA, stroke is the third leading cause of death in women—elderly women being at particularly high risk—but has dropped to fifth place among the leading causes of death in men.^{1,2} Even more concerning is the growing incidence of stroke in women in low-income and middle-income countries, leading to an impending public health crisis for women worldwide. Studies have shown that compared with men, women are more likely to be institutionalized and have poor functional recovery after stroke.^{3–5} Early work suggested that the inferior outcomes in women could be attributed to a myriad of prehospital and hospital factors, such as delayed presentation, atypical symptoms, less efficient or timely work-up, delays in treatment with thrombolytics, and/or lower rates of receipt of recommended treatments.^{5–7} Over the past few years, however, it has become apparent that the gaps in acute care experienced by women are narrowing.

This narrowing of the treatment gap is exemplified by new findings presented by Gatttringer *et al.*, who examined sex-related differences in acute stroke care in Austria.⁸ In this analysis of data collected from stroke units from 2005–2012, over 47,000 patients were identified. Although some differences in prehospital factors were observed between men and women, there were no marked disparities in the care received once the patients were in the hospital. This is good news for women, as equal access to treatment, appropriate work-up and secondary prevention strategies enhances the chances of recovery. However, despite comparable care in the hospital and equal access to rehabilitation, women had poorer

functional outcomes than men (modified Rankin Scale score 3–5: OR 1.26, 95% CI 1.17–1.36) and required more nursing care and assistance. The median age of women at the time of stroke was 7.6 years higher than that of men, but the differences in outcomes held after controlling for age.

“...despite comparable care ... and equal access to rehabilitation, women had poorer functional outcomes...”

Several factors in the Gatttringer *et al.* study should be considered when trying to understand these sex differences. First, women had higher levels of pre-existing disability than did men. Second, women tended to have more-severe strokes on admission, with higher NIH Stroke Scale (NIHSS) scores. Rates of hypertension were equivalent between the sexes, but diabetes, hypercholesterolaemia, alcohol use, smoking, myocardial infarction and peripheral arterial disease were more prevalent in men. By contrast, atrial fibrillation was more frequent in women (32.3% prevalence, compared with 22.7% in men). Not surprisingly, therefore, cardiac embolism was more likely to be the identified aetiology of stroke in women, whereas macroangiopathy was more common in men. Embolic stroke led to a higher number of anterior circulation events in women, perhaps explaining the higher NIHSS scores.

No differences in acute treatment were seen: 14.5% of men and women received thrombolysis well within the 60 min ‘golden

hour’ (median 49 min for women versus 48 min for men). Perhaps most importantly, no sex difference was observed in the use of oral anticoagulants, despite the higher prevalence of atrial fibrillation in women. This finding raises concerns, as it suggests that women are undertreated for the most important risk factor contributing to their strokes: cardiac embolism.

One limitation of this study is that 3-month outcomes were available for less than 40% of patients, although women and men were equally represented (38.4% in women versus 39.5% in men), so this is unlikely to be a source of bias. Generalizability to other health-care systems (outside Austria) and non-stroke-unit settings might be limited, but emerging data from several US studies also suggest that sex disparities in acute stroke care are narrowing.

What can be done to address these alarming statistics? Clearly, focusing on improving acute stroke care and access to rehabilitation for women may not be the answer, and we may be missing opportunities for secondary prevention in at-risk patients. Age-adjusted rates of transient ischaemic attack were higher for women than for men, highlighting the prospect of identifying and treating these patients to avoid more-serious stroke events. One strategy would be to improve access to medications that have been shown to reduce the rates of large disabling strokes, most notably oral anticoagulants. This strategy might be effective in higher-income countries, but may be of more limited use in lower-income countries, especially in rural areas where access to appropriate medications and monitoring is restricted.

How does this new paper contribute to the bigger picture of stroke in women? If we consider the demographic profile of ageing in the USA, elderly women will increasingly outnumber men in terms of stroke events and stroke-related deficits.³ From a more global perspective, as noted in a recent paper from *The Lancet* that included 119 studies from 21 regions of the world (Figure 1), despite the decrease in age-standardized mortality rates for stroke over the past two decades, the absolute number of strokes is increasing annually, as are the numbers of stroke-related deaths and disability-adjusted life

years lost, particularly in low-income and middle-income countries.

A second new paper, by Wang and colleagues, highlights the emerging global epidemic of stroke in women, and should raise a red flag for clinicians.⁹ The study shows that rates of first-ever stroke have increased disproportionately in women in rural China. Among 14,920 residents participating in the Tianjin Brain Study, the incidence of first-ever stroke grew by 8.0% annually in women compared with 5.8% in men, narrowing the male:female incidence ratio from 2.6 to 1.4 over a 21-year period. During this period, many known risk factors for stroke, including hypertension, obesity, alcohol consumption and diabetes mellitus, increased among women in this region.¹⁰ These findings have profound global implications for public health. More than half of the Chinese population lives in rural areas, and these data on secular

trends over two decades signal a growing stroke epidemic for women in China as a whole. As the incidence of stroke increases in women, with the potential accompanying sex-related differences in outcomes, the number of women needing assistance will continue to grow globally.

The fact that sex-related disparities in stroke care are diminishing is encouraging, but it is unsettling that women with comparable care still experience worse functional outcomes than do men. Attention to factors that disproportionately affect women, such as depression and social isolation, may lead to more appropriate and effective therapies, but additional research is needed to develop therapeutic targets based on psychosocial factors. Future research should address the factors that contribute to inferior post-stroke outcomes in women, given that stroke is likely to be a major global health burden for women in the coming years.

Department of Neuroscience, University of Connecticut Health Centre, 263 Farmington Avenue, Farmington, CT 06032, USA (L.D.M.). Yale School of Public Health, PO Box 208034, 60 College Street, New Haven, CT 06520-8034, USA (J.H.L.).

Correspondence to: L.D.M.

lmccullough@uchc.edu

Competing interests

The authors declare no competing interests.

1. Go, A. S. *et al.* Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation* **127**, e6–e245 (2013).
2. Leading causes of death and numbers of deaths, by sex, race, and Hispanic origin: United States, 1980 and 2010. *Centers for Disease Control and Prevention* [online], <http://www.cdc.gov/nchs/data/hus/2011/026.pdf> (2011).
3. Bushnell, C. *et al.* Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* **45**, 1545–1588 (2014).
4. Bushnell, C. D. *et al.* Sex differences in quality of life after ischemic stroke. *Neurology* **82**, 922–931 (2014).
5. Reeves, M. J. *et al.* Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. *Lancet Neurol.* **7**, 915–926 (2008).
6. Smith, M. A. *et al.* Gender comparisons of diagnostic evaluation for ischemic stroke patients. *Neurology* **65**, 855–858 (2005).
7. Reeves, M. J. *et al.* Quality of care in women with ischemic stroke in the GWTG program. *Stroke* **40**, 1127–1133 (2009).
8. Gattlinger, T. *et al.* Sex-related differences of acute stroke unit care: results from the Austrian Stroke Unit Registry. *Stroke* <http://dx.doi.org/10.1161/STROKEAHA.114.004897>.
9. Wang, J. *et al.* Sex differences in trends of incidence and mortality of first-ever stroke in rural Tianjin, China, from 1992 to 2012. *Stroke* <http://dx.doi.org/10.1161/STROKEAHA.113.003899>.
10. Wang, J. *et al.* Trends of hypertension prevalence, awareness, treatment and control in rural areas of northern China during 1991–2011. *J. Hum. Hypertens.* **28**, 25–31 (2014).

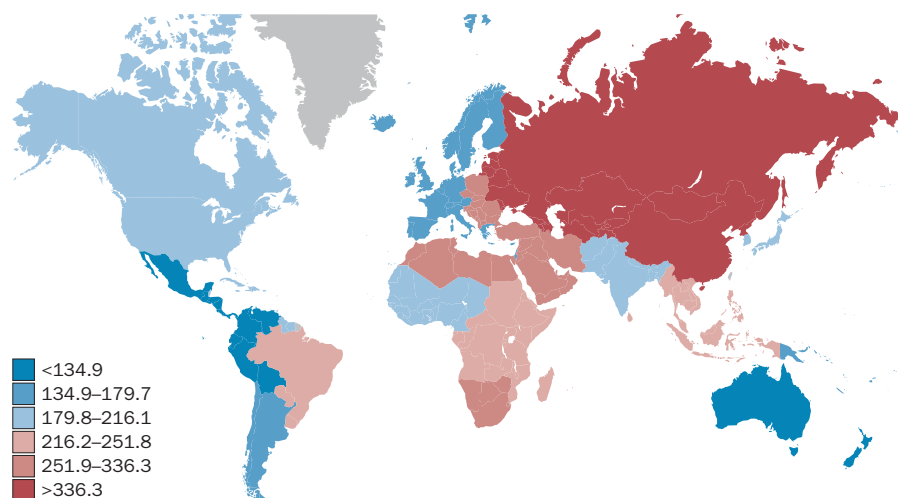


Figure 1 | Age-standardized stroke incidence per 100,000 person-years for 2010. Reprinted from *The Lancet* **383**, Feigin, V. L. *et al.*, Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010, 245–255 © (2014), with permission from Elsevier.