Sex differences in the use of therapeutic resources and stroke outcomes in 5 randomized trials

Luciano A. Sposato, MD, MBA, FRCPC, and Devin L. Brown, MD, MS

Correspondence
Dr. Sposato
Luciano.Sposato@
LHSC.on.ca

Despite their lower age-adjusted incidence of stroke, women have worse functional and patient-reported outcomes, including more activity limitations, worse health-related quality of life, and more poststroke depression than men.[1] Women's higher age, greater stroke severity, and poorer health at the time of stroke partially explain these disparities.[1] However, a substantial knowledge gap remains regarding sex differences in stroke care and outcomes. The complex interaction of sex-based factors such as genetics, epidemiology, frailty, clinical presentation, access to preventive care, diagnostic testing and treatment, response to therapy, and social support make this a challenging field of study.[2,3]

In this issue of *Neurology*®, Carcel et al.[4] report the results of a pooled analysis of 5 international, multicenter, randomized controlled trials investigating differences in prestroke and poststroke treatment and outcomes. This analysis included data from 19,652 patients enrolled in the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage trials (INTERACT-1 and INTERACT-2),[5,6] the Enhanced Control of Hypertension and Thrombolysis Stroke study (ENCHANTED),[7] the Head Position in Acute Stroke Trial (HeadPoST),[8] and the Scandinavian Candesartan Acute Stroke Trial (SCAST).[9]

Carcel et al.[4] first performed logistic regression analyses for each of the 5 clinical trial cohorts, stratified by ischemic stroke, hemorrhagic events, and both types of stroke combined. Main outcomes were the use of medications on admission, in-hospital poststroke management, death, disability, quality of life, and secondary stroke prevention. Second, they combined study-specific association estimates in random-effects meta-analyses to assess the same outcomes. In adjusted analyses (figure), women were more likely to receive antihypertensive medications than men before stroke, but less prone to receive lipid- and glucose-lowering and antiplatelet agents. After stroke, women were more likely to be admitted to a stroke unit but less prone to be admitted to an intensive care unit, treated for fever, intubated, or applied a nasogastric tube. Women had higher odds of surviving than men after ischemic and hemorrhagic stroke combined, and lived with greater disability after ischemic stroke, although there were no differences in disability after hemorrhagic stroke or both types combined. Likewise, women had poorer health-related quality of life after ischemic stroke. There were no differences in the use of secondary prevention medications.

The study by Carcel et al.[4] has several strengths: a large international study cohort with data available at the individual patient level, participants from a wide variety of world regions, statistical analyses adjusted for a large number of relevant variables, and carefully adjudicated endpoints. The authors appropriately acknowledged most limitations, including the observational nature of data, post hoc results, lack of adjustment for variables known to be related to sex differences (e.g., marital status), potential residual confounding, inability to adjust all analyses for the same potential confounders, lack of information about treatment indication, and the limited generalizability of the results because the study was based on a highly selected population of patients enrolled in randomized controlled trials.

From the Stroke Program, Division of Neurology, Department of Clinical Neurological Sciences, Schulich School of Medicine and Dentistry (L.A.S.), Heart & Brain Laboratory (L.A.S.), Department of Epidemiology & Biostatistics (L.A.S.), Department of Anatomy & Cell Biology (L.A.S.), and Robarts Research Institute (L.A.S.), Western University; Lawson Research Institute (L.A.S.), London, Canada; Stroke Program, Department of Neurology (D.L.B.), University of Michigan; and Cardiovascular Center (D.L.B.), University of Michigan Medical School, Ann Arbor.
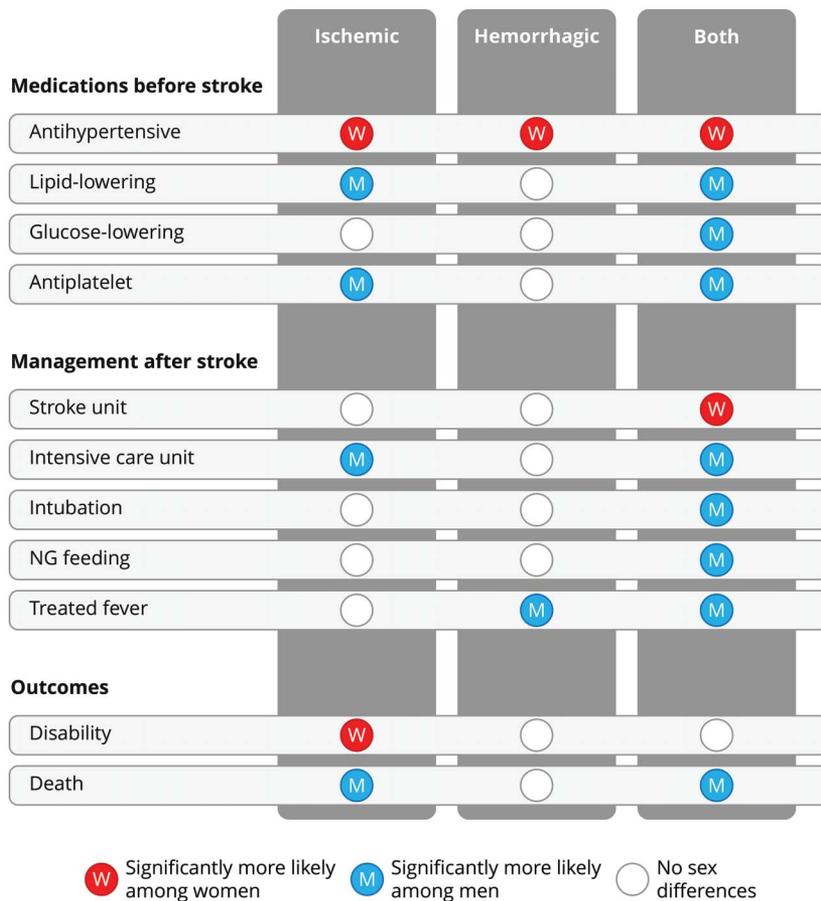
Figure Mapping of significant differences in stroke management and outcomes in the study by Carcel et al.[4]

The figure shows outcomes with significant results in random-effects meta-analyses combining the summary estimates of logistic regression analyses performed in each of the 5 randomized controlled trials included in the study, stratified for ischemic stroke, hemorrhagic stroke, or both types of stroke combined. Outcomes for quality of life are not shown, regardless of their level of significance. Outcomes with nonsignificant results are not shown and include anticoagulant treatment before the stroke, antihypertensive drugs and antiplatelet agents at 90 days after stroke, use of compression stockings, use of subcutaneous heparin, neurosurgery, rehabilitation, withdrawal of active care during hospital stay; and poststroke myocardial infarction and stroke recurrence. NG = nasogastric.

Women received preventive medications before stroke and in-hospital resources after stroke less often than men. Prior studies have shown results in the same direction, with women receiving less frequent diagnostic imaging and longer door to imaging times.[3] Health provider biases towards patients' sex, delays in seeking medical attention, and different attitudes towards acute neurologic illnesses may explain these findings. Importantly, this study evaluated the use of stroke therapies, but not their prescription. Conceivably, men received these treatments because they needed them more frequently than women and not because of bias in their prescription. Therefore, strictly, the results of this study reflect the use of therapeutic resources rather than quality or access to care.

Stroke severity does not likely explain the more intense use of life support measures and elevated risk of death among men given the greater severity of strokes among women and the adjustment of all analyses for stroke severity. Alternatively, the increased prevalence of coronary artery disease, diabetes mellitus, and smoking among men might explain these findings. Indeed, although the authors adjusted the analyses for myocardial infarction in 3 of the 5 cohorts (ENCHANTED and INTERACT-1 and INTERACT-2),

they did not consider overall coronary artery disease—with or without prior myocardial infarction—in any of them. Furthermore, they only used diabetes and smoking as covariates for a limited number of outcomes in HeadPoST, and smoking just in ENCHANTED.

Regarding the greater disability among women, it is less likely explained by baseline stroke severity because, as mentioned, the authors adjusted all analyses for this variable. Rather, it may reflect a survivor bias effect.

The study by Carcel et al.[4] shows important sex-related differences in the utilization of preventive and acute stroke therapies and outcomes, and thus leaves a number of relevant questions to be addressed. Research on sex differences in stroke should be prioritized globally to better understand these disparities and their causes.

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Disclosure

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