Sex Is Not a Risk Factor in Outcome When a Stroke Unit Treats the Patient

Valeria Caso, MD, PhD; Maurizio Paciaroni, MD

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There are ongoing debates on whether sex is a risk factor for stroke outcome. It is known that females tend to have worse outcomes compared with males when stroke onset is later in life. Moreover, females generally have a higher burden from atrial fibrillation translating into more thromboembolic events and more severe strokes, compared with males. Likewise, females of all ages have more hypertension, and their risk for stroke from diabetes mellitus is higher when compared with males: relative risk 2.28 (confidence interval 95% 1.93–2.69) versus 1.83 (confidence interval 95% 1.60–2.08). As well, a recent systematic meta-analysis of sex-specific risk factors for stroke reported that females could have increased stroke risk because of hypertensive disorder in pregnancy for ischemic stroke, late menopause and gestational hypertension for hemorrhagic stroke, and oophorectomy, hypertensive disorder in pregnancy, preterm delivery, and stillbirth for any stroke. However, male-specific risk factors increasing stroke risk include medical androgen deprivation therapy for ischemic stroke, and erectile dysfunction for any stroke.

Do these sex-specific risk factors and the differing burdens from stroke risk factors depending on the sex of the patient influence outcomes?

To this regard, Hametner et al analyzed data from the VISTA (Virtual International Stroke Trials Archive) aiming to investigate sex-specific differences in poststroke outcome in individual-level data pooled from randomized controlled trials. Using novel matching techniques, they approximated a randomized experiment accounting for covariates that differed between the sexes. The 2 hypotheses included investigating, first, whether the natural course of stroke was different between males and females without recombinant tissue-type plasminogen activator treatment and whether the response to recombinant tissue-type plasminogen activator treatment after adjustment for relevant prognostic factors was similar in both males and females. The authors reported that in nonthrombolysed patients, ordinal analysis of modified Rankin Scale, adjusting for stroke- and sex-related prognostic factors, suggested comparable outcomes for females and males (odds ratio 0.96, 95% confidence interval 0.85–1.06). Furthermore, females and males responded comparably to recombinant tissue-type plasminogen activator, irrespective of the outcome definition of modified Rankin Scale (ordinal: $P$ interaction =0.46, relative excess risk because of interaction =0).

The results from this elegant and sophisticated statistical model evidence that thrombolysis and stroke unit care guarantee optimal stroke outcome, regardless of sex and sex-specific risk factors.

However, the results cannot be interpreted as if they reflected the real picture throughout the world. That is, the outcomes were undoubtedly influenced by the fact that all patients received the best treatment available, and moreover, these were not limited by social conditions that could have hindered the delivery of such treatment. Where these disparities have been addressed with effective programmes, improvements in once worse outcomes for women have been turned around.

In fact, in 2009, Reeves et al found that sex disparity in the delivery of thrombolysis existed; women had a 30% lower odds of receiving recombinant tissue-type plasminogen activator treatment than men. In the meantime, the design IST 3 trial (Third International Stroke Trial) had removed an upper age limit for enrolled patients, therein achieving an inclusion rate of 52% for women. Furthermore, a recent report from the Austrian Stroke Registry showed that correcting for age, no significant sex-related differences in quality of care were identified with comparable onset-to-door times, times to and rates of neuroimaging, as well as emergency room door-to-needle times and rates of intravenous thrombolysis (14.5% for both sexes). Yet, obstacles remain regarding the home door to emergency room door because women arrive to hospital more often with private transport compared with men who more than often arrive by ambulance. The German Stroke Registry reported that intravenous thrombolysis and mechanical thrombectomy rates did not differ between males and females <80 years, but the rate of specialized stroke unit care was still lower for women than in men. According to the same authors, this lower admission could be explained by the Yentl syndrome.

In fact, women are less likely to experience typical stroke symptoms, including motor dysfunction, vertigo, and gait dysfunction, but instead complain of pain or present with reduction of consciousness, contributing to misdiagnosis, nonadmission to an available stroke unit, and consequently a worse outcome.

Regarding the results from the VISTA study, no systematic research was performed on screening logs to understand how many women could have been identified as possible candidates for the included randomized controlled trials or were excluded for nonmedical issues. Finally, most randomized controlled trials early dropouts were women.
In conclusion, this study provides a well-defined snapshot of a certain subgroup of women who had the privilege of receiving the best care in the best social environment.

However, most women worldwide lack one or even both of these privileges. For instance, Kim et al. have reported that in countries with higher sex inequality (e.g., lower rights for women compared with men), a higher stroke mortality in women has been observed. Lower access to job opportunities, lack of domestic violence legislation, and inequalities in property ownership rights were associated with higher stroke mortality rates in women. This is in line with reports that stated that women in low-income countries tend not to be admitted to hospitals. This is probably because of the absence of a universal healthcare system.

The encouraging results from this analysis should be used to formally implement stroke unit standards worldwide to improve on outcomes in both men and women.

Disclosures
None.

References

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