See related article, pages 2055–2062.

Stroke affects both women and men, but it is the leading cause of mortality in women. Although many aspects of the disease are similar in women and men, there is a growing body of evidence to support sex (a biologic status determined by sex chromosomes and sex hormones) and gender (sex determined by social, cultural, and educational context) differences in the epidemiology of stroke. Numerous reports have demonstrated sex-specific differences in the prevalence, clinical presentation, management, recanalization rate of intracranial artery stenosis after intravenous or intraarterial thrombolysis in acute ischemic stroke, and clinical outcomes of stroke of all subtypes. The results are, however, often conflicting and there is a paucity of randomized controlled trial support regarding sex-related stroke care delivery. The recent gender-specific analysis from the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) study provided very important evidence that women with symptomatic intracranial arterial stenosis have considerable increased risk for stroke and vascular death than men. These data contrast a common perception that men have greater risk of recurrent stroke than women. The WASID study had a good representation of women (38%), similar to the NINDS Stroke TPA study (42%), and the recent SPARCL study (40%), but in comparison to these studies showed a considerable gender-specific difference in stroke outcome. Women in the WASID study had more comorbidities (except coronary artery disease), higher body mass index and total cholesterol, were more sedentary but consumed less alcohol and cigarettes, had positive family history of stroke, and had different sociodemographic characteristics. In addition, women were more likely to have intracranial stenosis of the middle cerebral artery, but the proportion of severe intracranial artery stenosis was not different in men. Women had a considerable greater risk of stroke or vascular death. The 2-year rates of fatal and nonfatal stroke or related vascular death was 16.6% for men. After accounting for the traditional vascular risk factors associated with atherosclerosis and stroke severity, women had almost a 2-fold increased risk of ischemic stroke than men (HR, 1.85; 95% CI, 1.14 to 2.35), and a 1.6-fold increased risk of combined outcome: stroke or vascular death (HR, 1.58; 95% CI, 1.01 to 2.48). These results suggest that increased risk of ischemic stroke and related vascular death among women cannot be contributed to the differences in traditional vascular risk factors between men and women, or to the difference in stroke severity or to time from qualifying event.

What can the increase risk of stroke and related death among women in the WASID be contributed to? There is no easy answer to this question. Many contributing factors can influence a poor outcome after stroke in women. Gender stands for many factors associated with comorbidities and outcomes, including a combination of vascular risk factors and a complex interaction between risk factors, genetic determinants, gene–environment interaction, and sociodemographics. Although the traditional vascular risk factors were included in the WASID study, they were analyzed as independent contributors, and their combination within an individual was not considered. The vascular risk factors have sex-specific attributable risk to stroke, and they appear to be attributable to a combination of biologic (sex) and behavioral (gender) factors. The Framingham Heart Study established the sex-specific and independent impact of cigarette smoking, elevated blood pressure, elevated total cholesterol and low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, diabetes, and advancing age on the development of cardiovascular disease and stroke. These vascular risk factors in combination within an individual are associated with sex-specific risk of vascular outcomes. Although treatment targets for blood pressure and lipid levels are developed according the Framingham Risk Score and now dictated by global recommendations, the translation of these recommendations into the clinical practice is a major challenge in men as well as in women. There is evidence, however, that women are less likely to be able to afford essential medications. This inability to obtain evidence-based therapy is associated with a 50% increase in the incidence of angina, nonfatal acute myocardial infarction, and nonfatal stroke among women in the US. In addition, gender may also be a proxy for low socioeconomic characteristics including social isolation, which may be associated with poor outcomes. Whether and how these baseline environmental characteristics including the information on the effectiveness of primary prevention treatments contribute to sex-specific outcomes after stroke, or in particular after stroke caused by intracranial atherosclerosis, is not clear and this area is undergoing intense investigations.

Besides traditional vascular risk factors, new emerging factors associated with atherosclerosis are becoming more important in sex-specific risk stratification and various treat-
ments of stroke and cardiovascular disease. A number of studies have reported sex-specific differences in inflammatory markers, specifically in C-reactive protein. Higher adjusted baseline C-reactive protein values are reported for women than for men.15,16,17 C-reactive protein concentrations on average are ≈30% higher in women in comparison to men. Furthermore, an age–sex interaction has been demonstrated, whereby C-reactive protein was predictive of death or acute myocardial infarction in women and men younger than 55 years of age, but only for men older than the age of 55 years.16 Recently, carotid artery plaques obtained from women were shown to be more stable and with less inflammatory phenotype compared with men, independent of clinical presentation and cardiovascular risk profile.18 These findings could explain why women benefit less from carotid endarterectomy compared with men as reported in randomized trials.19

Female sex hormones and their receptors may also be implicated in vascular outcomes.20 Compared with their male counterparts, premenopausal women tend to have more favorable vascular risk profiles. However, this “sex protection” is much attenuated with age among postmenopausal women. There is a possibility that the evolution of sex differences in risk profiles is at least partly attributable to sex hormones or their receptors. In terms of health behavior, women tend to be more sedentary and obese than men, but smoking rates are higher among men than women. Although lower levels of activity and higher rates of obesity may be offset by better overall cardiovascular risk profiles before menopause, they may contribute to a marked deterioration in risk profile after menopause, increased risk of vascular events, and poor outcome.

Finally, genetic determinants may be considered contributors in outcome after stroke. Sex is a biologic status, determined by sex chromosomes and their interactions with autosomes, X chromosome inactivation, sex hormones, and related determinants. It was only recently realized that genes show variation in expression and action in men and women.20 Sex-specific transcriptional regulation could be attributable to different growth hormone and sex hormone profiles in men and women, which can affect the expression of numerous genes, and these genes in turn affect the transcriptome of many tissues. We are just entering a new exciting era of genetic discoveries, and because many questions remain regarding molecular contributions to sex-specific differences, and their effect on complex traits such as stroke, the answers are easier foreseen.

The gender-specific analysis from the WASID study is well done and results are elegantly presented. However, can these results be generalized? The WASID study was a randomized clinical trial and, as such, had firm inclusion/exclusion criteria regarding which patients were selected. A selection bias often seen in the secondary analyses of the clinical trials is also the main limitation of the WASID. Enrollment in the WASID was not stratified by sex. Women enrolled in the WASID had more strokes, less TIs, and their qualifying event was more often caused by middle cerebral artery stenosis in comparison to men. Therefore, men enrolled in this study were more likely to have better outcome than women, even more so if they had a high case fatality before enrollment (the time window from a qualifying event to enrollment in the WASID was 90 days). Therefore, the conclusion that women had worse outcome than men must be taken with caution and cannot be generalized outside the scope of the clinical trial. The replication of these results is needed in population-based studies. These studies must be sufficiently powered to allow statistical inferences and identification of sex-specific outcomes. Understanding how sex and gender differences translate into stroke pathophysiology will help improve the health of women and men.

Generally, the power to detect sex-specific differences in clinical trials is limited because of under-representation of women. There is a lack of sex-specific information in published studies. Although most studies now enroll women, few provide sex-specific outcomes or test for interactions to determine whether sex differences exist. We need to develop a better understanding of sex differences at stroke presentation, stroke progression and outcome, development of effective treatments, and the dissemination of evidence-based practices specifically targeting those areas neglected for women.

**Disclosures**

None.

**References**


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