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A focus on stroke in women

In this issue of *Women's Health* different authors have comprehensively reviewed the most important aspects of stroke medicine for women. At present, there are no recommendations regarding primary and secondary stroke prevention in women. However, in cardiology medicine, the 'Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women' were published for the first time in 2004 [1] and updated in 2007 [2]. The 2004 guidelines were the first to challenge both the conventional wisdom that women should be treated in the same manner as men and was the first to highlight the fact that women were under-represented in clinical trials for cardiovascular disease. Following this, more women have participated in cardiovascular research studies and more sex-specific analyses have been published. Consequently, in January 2011, the latest recommendations on sex-specific prevention treatment in cardiovascular disease for women were published [3].

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Nonetheless, the overwhelming majority of recommendations regarding cardiovascular prevention are similar for women and men [3]. However, pregnancy, menopause and longer life-expectancy are three obvious conditions that support sex-specific cardiovascular research [3]. This issue will not be able to offer evidenced-based recommendations for sex-specific stroke medicine, with the exception of HRT-treatment and pregnancy, which are already part of current stroke guidelines [4].

Furthermore, atrial fibrillation (AF), which is one of the most important risk factors for women [5], will be extensively discussed. The Anticoagulation and Risk factors in Atrial Fibrillation (ATRIA) study found that AF is more common in men than in women (1.1 vs 0.8%; $p < 0.001$); however the sex analysis demonstrated that nonanticoagulated women had a significantly greater annual rate of thromboembolic events than men (3.5 vs 1.8%; adjusted rate ratio: 1.6; 95% CI: 1.3–1.9), even after

correction for other stroke risk factors, such as age and diabetes, among others [6]. For this difference, a new risk factor-based approach recognizes that being of female sex is an additional risk factor in patients with AF compared with the more commonly used congestive heart failure, hypertension, age, diabetes, stroke (doubled; CHADS₂) stroke risk stratification scheme [7]. This new risk factor-based approach for patients with nonvalvular AF is expressed as: congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes, stroke (doubled), vascular disease, age 65–74 years, and female-sex (CHA₂DS₂-VASc) [8]. However, female patients with AF tend to receive oral anticoagulant therapy less often than men [9] because women are older and without caregivers at the time of stroke. Hopefully, the latest anticoagulation drugs, the thrombin inhibitors, will result in there being safe and effective alternative treatments to warfarin that reduce embolic complications in women with AF.

Not only are stroke risk factors and the epidemiology of stroke different in women and men, but studies also reveal differences in the effects of treatment when those studies include adequate numbers of women to look for such differences. Sex effects in the primary prevention of cardiovascular events, including stroke, have been sought in a randomized study comparing aspirin to placebo that included only women [10]. This trial, the Women's Health Study, demonstrated that while aspirin reduced the risk of stroke in women, it did not prevent myocardial infarction or death from cardiovascular causes. Conversely, trials such as the Physician's Health Study that included only men, demonstrated significant benefit for aspirin in the primary prevention of myocardial infarction, but not for stroke [11]. Benefits of antiplatelet agents for secondary stroke prevention in women have been less clear for agents other than aspirin, owing to the absence of sufficient women in the trials to evaluate them. Exactly how the sex effects of antiplatelet agents might be mediated is unknown. It is likely that hormonal levels have a direct contribution through regulation of estrogen receptors on platelets and effects on clot formation [12], as described in this issue.

Large trials of patients with carotid stenosis have revealed different risks of outcome events in women and men following medical treatment [13]. While both women and men with symptomatic

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high-grade carotid stenosis had significant benefit with carotid endarterectomy compared with medical therapy, women with moderate symptomatic stenosis had a less clear benefit with surgery than men did [13]. Moreover, women may have higher perioperative risks. For example, in the combined data of two large trials, 30-day perioperative risk of death was significantly higher in women than in men, and perioperative risk of stroke and death also tended to be higher in women than in men [14]. Data on the relative risks of carotid artery stenting are only now emerging. While the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) did not show an interaction with the primary end point (including periprocedural events as well as ipsilateral strokes up to 4 years) for sex, a pre-planned analysis showed that the periprocedural end point alone occurred in 6.8% of female carotid artery stenting patients versus 3.8% of female endarterectomy patients ($p = 0.047$) [15]. The rate of stroke was higher for stenting than for endarterectomy, but rates of myocardial infarction were similar in the two groups. Studies must determine whether there are factors that contribute to procedural risks in women, such as smaller vessel size, and whether those risks could be modified.

Acute stroke treatment is another area showing potential differences in men and in women. Women in placebo arms of acute stroke treatment trials have shown worse outcomes than men [16,17]. However, in a pooled analysis of intravenous tissue plasminogen activator trials and in a trial assessing intra-arterial prourokinase, the margin of benefit in women treated with thrombolytics compared with placebo was greater than in men [16,17]. A combined analysis of two mechanical embolectomy trials using the Merci Retriever did not show different outcomes in men and women when the vessel was

revascularized, suggesting that the sex effects seen in the thrombolytic trials may represent factors other than large vessel opening [18].

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In summary, this *Women's Health* special focus issue outlines the latest findings in sex differences relating to stroke. The articles in this issue show that much has been discovered about the epidemiology and mechanisms of stroke in women. They reveal that treatment differences can exist between men and women, including distinct responses to antiplatelet therapy, to carotid revascularization procedures and to acute stroke treatment with thrombolytics. Some of these findings may lead to different management decisions in women compared with men. However, this special focus issue also uncovers the broad concern that most stroke trials do not include sufficient numbers of women to evaluate treatment effects in this group. Women must be adequately represented in trials to assess the efficacy and safety of stroke treatments in both sexes.

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