Editorial
Statins and stroke prevention: focus on women

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Stroke is the third leading cause of death in women and is a major cause of disability in the United States[1]. Prevention of stroke and cardiovascular disease with estrogens alone or combined with progesterone has been rigorously studied in randomized controlled trials such as the Heart Estrogen-progestin Replacement Study (HERS)[2,3], Women Estrogen Stroke Trial (WEST)[4], and the Women's Health Initiative (WHI)[5]. These large trials definitively showed no benefit and the WHI showed an increased risk of cardiovascular disease and stroke. Since there is no role for hormone replacement therapy in cardiovascular disease protection, the focus for prevention is to identify risk factors and prescribe medications that effectively modify these risks. Dyslipidemia is a risk factor that can be modified with the use of cholesterol-lowering drugs, namely statins. The focus of this editorial is to summarize the current evidence for stroke prevention with statins in general and to specifically highlight their role in women.

Although elevated cholesterol has not been associated with a substantial risk of stroke in most cohort studies, statins have been shown to reduce risk of stroke in patients with heart disease by 25-30%[6-10]. Recently, the Heart Protection Study (HPS) results related to stroke outcomes were published[6]. This included an analysis of outcomes stratified by gender. Similar to other statin trials, HPS found an overall 28% reduction in first strokes, but there was only a trend toward a benefit in women (4.4% stroke rate in simvastatin-treated vs 5.2% in placebo-treated women, relative risk 0.86, 95% confidence interval [CI] 0.7-1.1)[6]. The most likely explanation for this result was a lack of statistical power because of fewer strokes in women compared with men.

One way of addressing the problem of inadequate sample sizes is through secondary analyses of large trials focused on women, such as the HERS. These analyses present an opportunity to explore observational research questions targeting women at risk for cardiovascular disease. In addition, these analyses are valuable because of the prospective collection of outcomes of interest, risk factors, and use of concomitant medications for an extended follow-up period. Two secondary analyses of baseline statin use have been performed using the HERS data, one for coronary events and one for stroke. Interestingly, women who were randomized to combination hormone therapy (HT) but were not using statins at baseline had a 75% increased risk of coronary heart disease (CHD) events (relative hazard [RH] 1.75, 95% CI 1.02-3.03, p = 0.04) after the first year of follow-up, whereas baseline statin users randomized to combination HT had a lesser risk (RH 1.34, 95% CI 0.63-2.86, p = 0.45). However, the formal test for interaction between HT and statin use was not significant for CHD events at 1 year, and there was no overall difference in event rates for these groups for the 4-year follow-up period[11].

An analysis of stroke events in the HERS revealed no overall difference in either all strokes or non-fatal strokes between baseline statin users and non-users[12]. However, subgroup analyses suggested a large, but non-significant reduction in all fatal strokes (RH 0.52, 95% CI 0.23-1.18, p = 0.12), fatal ischemic stroke (RH 0.51, 95% CI 0.18-1.45, p = 0.21), and fatal hemor-

rhagic strokes (RH 0.18, 95% CI 0.02-1.46, p = 0.11)[12]. The reason CHD events were significantly reduced in statin users in this cohort, whereas strokes were not, was possibly because stroke was a secondary outcome and the event rates were low in these women.

As reflected in the analyses of stroke in women, inadequate sample sizes and low event rates limit definitive conclusions. In other words, the statin trials enrolled too few women, and the trials focused on women with heart disease had too few strokes. Fortunately, an ongoing study of statins for stroke prevention[13] (with stroke as the primary outcome) will provide the best evidence to date that may confirm the benefit of statins in women. But until the data are available, there is no reason to suspect a difference in responses to statins between men and women.

In addition to dyslipidemia, there are several risk factors that significantly increase stroke risk in women, including metabolic syndrome and diabetes. Metabolic syndrome occurs in both men and women and is associated with lipid abnormalities that include hypertriglyceridemia and low HDL. However, in women metabolic syndrome may occur around menopause specifically because of changes resulting from estrogen depletion, including weight gain, increased total cholesterol and triglycerides, reduced HDL-cholesterol, increased insulin resistance, and endothelial dysfunction[14]. Metabolic syndrome is significantly associated with risk of stroke or transient ischemic attack as shown in a recent analysis of the Framingham Offspring cohort. There was a greater impact on stroke risk for women (population attributable risk 38%) than men (population attributable risk 18%) in this cohort[15]. Diabetes also significantly increases the risk for stroke and heart disease, and disproportionately affects women.

In the Women's Atorvastatin Trial on Cholesterol (WATCH) study, statins lowered total cholesterol and triglycerides by 20% in women with and without heart disease risk factors[16,17]. Therefore, statins may reduce stroke risk in women by modifying unfavorable dyslipidemic profiles in high-risk conditions such as metabolic syndrome and diabetes. A subgroup analysis from the HPS revealed a 24% lower stroke risk in subjects with diabetes treated with simvastatin compared with placebo[18]. However, not all large statin trials showed the same result[7].

To address the question of whether statins reduce the risk of first or recurrent stroke in women, several future studies could be planned or are already in progress. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study is the first randomized controlled trial to investigate stroke prevention in patients with prior stroke but no cardiac disease[13]. It is hoped this trial will be enrolling a sufficient number of women to determine whether there are any gender differences in outcomes. Other randomized or observational studies of stroke in women could be analyzed to determine the impact of statins on stroke recurrence, such as WEST or the WHI.

A special concern for women with a history of heart disease or stroke is the risk of vascular events in women using HT for debilitating vasomotor symptoms. HT use leads to an increase in C-reactive protein (CRP)[19], a marker of inflammation and an independent predictor of stroke[20]. However, an analysis of the WHI observational study showed that HT use or non-use had no effect on the risk of heart disease beyond the baseline CRP level[21]. Statins have anti-inflammatory effects, and lower CRP independently of lipid-lowering[22]. Based on the attenuated risk of heart disease in women taking statins and combination HT early after initiation in the HERS[11], a prospective placebo-controlled crossover study was performed in women specifically to measure CRP levels at baseline and after treatment with various combinations of HT and simvastatin. The investigators found that HT alone increased CRP levels from baseline after 8 weeks, but that women taking a combination of both simvastatin and HT had no significant increase in CRP[23]. Larger outcome-based studies are necessary to determine whether women with vasomotor symptoms requiring HT in the setting of dyslipidemia and other risks for stroke and heart disease can add a statin to their prevention regimens to minimize the risk of first or recurrent events. Another option is the use of the transdermal estrogen and/or progesterone formulation, as this does not lead to a significant elevation of CRP when compared with oral formulations[24].

In conclusion, it is clear that larger studies with adequate samples of women at high risk of stroke are necessary to confirm the benefit of statins in stroke prevention, although there is no evidence to date suggesting that substantial gender differences exist. Additional large prospective studies are necessary to determine whether statins attenuate the risk of stroke in women taking HT for vasomotor symptoms. Dedicated research in this area will lead to a better understanding of how to reduce the risk of this devastating disease in women.

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