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Stroke Prevention in Women: Challenges and Opportunities

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Abstract

Women have a 20% lifetime risk of stroke. In addition, the majority of stroke-related deaths occur in women. Reducing the burden of stroke in women through prevention would positively affect public health. Unfortunately, most of the data used to develop specific evidence-based guidelines for stroke prevention in women were derived from coronary heart disease studies. Stroke was a secondary and less common outcome, if it was included at all. In addition, women have traditionally been underrepresented in stroke prevention trial cohorts. Stroke prevention in women offers many challenges, not only related to data extrapolated from clinical trials primarily composed of men, but also because physicians may underestimate cardiovascular risk in women, and therefore prevention strategies may not be appropriately undertaken. The opportunities to improve stroke prevention in women include increasing patient and physician awareness of risk and optimizing management of key modifiable risk factors (eg, hypertension, hyperlipidemia, physical inactivity, obesity, and diabetes).

Introduction

Stroke is a devastating and disabling disease, impacting about 780,000 people in the United States annually [1]. Stroke is also preventable; therefore, developing prevention strategies requires an in-depth examination of the population at risk. Women make up about half the population at age 50, but the ratio of women to men increases with each decade to a ratio of 2.70 at age 90 [2]. As a result of the larger number of women in older age groups, an excess of stroke deaths occur in women, a statistic that will increase as the population ages. The prevalence of stroke is lower in women than men until the ages of 75 [3] to 85 [4], depending on where the data were collected. However, recent studies suggest that there is a midlife surge in stroke among women at higher rates than men [5]. The reasons for this surge are not understood, but may be related to increasing blood pressure, cholesterol, and blood glucose at higher rates in women during ages 35 to 54 compared with men of the same age [5]. In addition to this potential increase during midlife, other risk factors are unique to women and can impact prevention. The purpose of this review is to discuss risk prevention in terms of the challenges and opportunities (summarized in Table 1) to reduce the burden of stroke in women.

Challenges in Stroke Prevention for Women

Gender disparities in prevention management

Women traditionally have been screened and treated for cardiovascular disease (CVD) less aggressively than men [6]. A study of physician awareness and application of evidence-based cardiovascular guidelines provided some insight into why this occurs. Questionnaires with patient scenarios were completed by primary care physicians, cardiologists, and ob/gyns.

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Participating physicians were less aware of the CVD guidelines for women (64%) than they were for the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) (86%) and National Cholesterol Education Program/Adult Treatment Panel (NCEP ATP III) (89%) recommendations [7]. Physicians older than 50 years were more likely to be aware of these guidelines than those younger than 50 years [7]. Some gender disparities were obvious, but the most important related to risk assignment. Specifically, intermediate-risk women were more often incorrectly assigned to a low-risk category and this lower risk assignment was associated with less aggressive recommendations for lifestyle and prevention treatment [8•]. In addition, fewer than one in five physicians were aware that more women than men die from CVD each year [8•].

Consistent with these physicians' perceptions, a recent national study evaluating several cardiovascular quality indicators in the ambulatory setting showed that women with a history of CVD and diabetes were less likely to have met low-density lipoprotein (LDL) cholesterol target levels (< 100 mg/dL) although women achieved target blood pressures more often than men [6]. Therefore, many challenges in improving prevention quality of care for women may be associated with physician and patient awareness of risk factors and preventive strategies. Almost no studies have been done examining gender disparities in secondary prevention in stroke patients. In this article, the remaining prevention challenges are presented in the context of individual risk factors.

Hypertension

High blood pressure is one of the most important modifiable risk factors for stroke. From a secondary prevention perspective, awareness and treatment of hypertension is important because women with a history of stroke are more likely than men to have hypertension [9–13]. The major challenge is that 30% of patients do not know they have hypertension, 40% are not treated, and more than 60% do not have adequate blood pressure control [14]. In addition, ob/gyns (who frequently function as primary providers for women) are significantly less aware of the most recent JNC-7 blood pressure management guidelines, and are less likely than primary care providers or cardiologists to recommend blood pressure therapy in addition to β -blockers when blood pressure is 140/95 mm Hg [8]. In general, primary care physicians, cardiologists, and ob/gyns are all less likely to follow the JNC-7 guideline for the use of diuretics as first-line treatment for hypertension [8]. Other studies of ambulatory blood pressure management reported that of those with hypertension, women aged 65 to 80 were 38% less likely than men to have adequate blood pressure control (OR 0.62; 95% CI, 0.45–0.85), and 40% less likely to receive β -blockers (OR 0.60; 95% CI, 0.36–0.99) [15].

Even very high-risk women (ie, those who have had a stroke) may have poor blood pressure control. A secondary analysis of the Women Estrogen Stroke Trial (WEST), a trial of 17 β -estradiol versus placebo in women with stroke or transient ischemic attack [16], showed that about 1 month after stroke, only 44% of women had blood pressure values within national guidelines (JNC 6 when this analysis was published) [17]. Of those outside the guideline measurements, 55% were still beyond the guideline at follow-up. The clinical predictors of severely elevated blood pressure (systolic blood pressure > 160 mm Hg or diastolic blood pressure > 100 mm Hg) included a history of hypertension and education less than college, whereas impaired mental status protected against elevated blood pressures [17]. This analysis demonstrated that even women participating in a secondary stroke prevention trial had poorly controlled blood pressure, in part because hypertension was undiagnosed.

In summary, the challenges for hypertension management are as follows: patients with hypertension, but especially women, are not achieving adequate blood pressure control in the ambulatory setting; women who primarily receive their general medical care from ob/gyns may not receive the guideline-recommended antihypertensive therapy; and women who have

already had a stroke and are at the highest risk for recurrence are poorly managed, in part because of under-recognition of the diagnosis.

Cholesterol management

Lowering cholesterol is important because high levels have been associated with mortality in women. As shown in the Cholesterol Pooling Project, the highest quintile of cholesterol levels was associated with an increased risk of death from nonhemorrhagic stroke in women under age 55 years, particularly black women [18]. Because the majority of subjects in clinical trials with statins for secondary prevention have been men, it has also been unclear whether women benefited from statins as much as men did. However, the first prospective randomized controlled trial of statins in patients without coronary disease specifically designed as a secondary prevention for stroke, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, found no difference in the benefit from atorvastatin in stroke prevention in men and women [19].

Given an equal benefit from statins for preventing stroke and heart disease, achieving cholesterol targets is as important for high-risk women as it is for high-risk men. Unfortunately, in real-world practice, women at high risk may not be adequately treated. An analysis of women with a history of CVD, diabetes, or chronic kidney disease followed in managed care practices showed that only 32% received lipid-modifying medication during the duration of the study, and only 35% of the women with LDL > 100 mg/dL received lipid-modifying therapy [20•]. Overall, only 7% obtained optimal control of LDL, high-density lipoprotein (HDL) cholesterol, and triglycerides (as defined by American Heart Association [AHA] guidelines) [21] at baseline, increasing to only 12% with optimal control after 36 months [20•]. Therefore, very few of the highest risk women achieve the guideline-recommended lipid profile targets, suggesting significant opportunities to reinforce the guidelines.

Diabetes

Diabetes is a very important risk factor for stroke and heart disease, especially in women. Diabetic women have a higher risk for ischemic heart disease mortality than men [22]. In addition, the Women's Pooling Project reported that women with diabetes but without CVD had stroke mortality similar to nondiabetic women with a prior history of stroke. Therefore, diabetes is considered to be a stroke risk equivalent, justifying more aggressive prevention strategies in women with this condition [23]. In addition, diabetes was independently associated with poor outcomes in women with ischemic stroke [24]. This evidence further reinforces the need for prevention in these high-risk women. Because the stroke prevention guidelines recommend lower blood pressures and LDL levels for diabetic than nondiabetic patients, this further increases the challenge for treating physicians, especially when women may be treated less aggressively [25•,26•]. Given the evidence that many women do not reach the optimal targets for LDL and blood pressure, strategies to improve risk factor management in diabetic women are clearly needed.

Obesity and physical inactivity

Both obesity and physical inactivity are risk factors for stroke in women, although the association with body mass index (BMI) is most likely mediated by diabetes, hypertension, and hyperlipidemia [27–29]. It is important for providers to counsel their female patients that increasing physical activity, even more than weight loss, may protect against CVD. For example, the Women's Ischemia Syndrome Evaluation (WISE) study showed that low functional capacity (approximately 7 metabolic equivalents [METs]) was more strongly associated with the likelihood of obstructive coronary artery disease and cardiovascular risk factors than BMI [30]. Therefore, even if women are overweight or obese, improving physical fitness may mitigate the risk of CVD [30].

Atrial fibrillation

A disease of aging, atrial fibrillation will become more prevalent as life expectancy increases. In a registry of first-ever ischemic stroke patients, women made up the majority with atrial fibrillation [31]. The evidence for the benefit from adjusted dose warfarin (target International Normalized Ratio [INR] 2.0 to 3.0) for stroke prevention in this high-risk group is robust, meeting the criteria for class I recommendation in the stroke prevention guidelines [25•, 26•]. Some [12,32] but not all studies [10,13] have found that women may be less likely than men to be appropriately discharged on warfarin after stroke.

A major challenge for preventing stroke in women with atrial fibrillation is weighing the risk of stroke against the risk of complications from bleeding, because these women are frequently older and frailer than their male counterparts. The risk of falls is often used as a reason not to anticoagulate; however, at least one study has suggested that even though the risk of hemorrhagic stroke increases with anticoagulation in those with a high risk of falling, the risk of ischemic stroke is still higher [33].

Aspirin use in women

Aspirin has long been the mainstay of secondary prevention of CVD. A recent analysis from the Nurses' Health Study showed that women who used aspirin long term had significantly lower mortality, especially cardiovascular mortality [34]. However, for primary prevention, there appear to be important differences between women and men, depending on whether the outcome is heart disease or stroke. A meta-analysis focused on sex-specific outcomes showed that women had a 17% reduction in overall stroke (HR 0.83; 95% CI, 0.70–0.97), a 14% reduction in ischemic stroke (HR 0.76; 95% CI, 0.63–0.93), and a small increased risk of hemorrhagic stroke (HR 1.07; 95% CI, 0.42–2.69) [35]. However, in men, there was a 13% increased risk of stroke overall (HR 1.13; 95% CI, 0.96–1.33), with no effect on ischemic stroke (HR 1.00; 95% CI, 0.72–1.41), with the primary effect related to a significant 69% increased risk of hemorrhagic stroke (HR 1.69; 95% CI, 1.04–2.73) [35]. The analysis for heart disease events by sex resulted in the opposite effects. Women had essentially no protection from myocardial infarction (HR 1.01; 95% CI, 0.84–1.21), whereas men had a substantial 32% benefit (HR 0.68; 95% CI, 0.54–0.86) [35]. The trial that was primarily represented in the effects of aspirin and outcome events in women was the Women's Health Study of 100 mg of aspirin every other day [36]. The primary result of the trial showed no overall benefit in the composite outcome of first major cardiovascular event (nonfatal myocardial infarction, nonfatal stroke, or death from CVD) [36]. Given the overlap in risk factors for heart disease and stroke, the determination of whether a woman may be at higher risk for one more than the other when considering aspirin therapy is perhaps a moot point. The guidelines for cardiovascular prevention in women currently recommend carefully weighing the benefit of protection from ischemic stroke against the potential risk of bleeding with aspirin therapy [37•].

Do the platelets of men and women respond to aspirin differently? A study addressed this question by performing platelet aggregometry before and after 14 days of low-dose aspirin treatment in men and women [38]. The investigators found that women showed the same or greater decreases in platelet reactivity after aspirin therapy compared with men, but women also retained modestly more platelet reactivity. No substantial differences were seen in women based on menopausal status or the use of exogenous hormone therapy. Both men and women had complete suppression of the cyclooxygenase-1 pathway, the most important pathway for cardioprotection, after aspirin administration [38]. Study limitations include the short-term effects of aspirin, and the lack of measurement of cardiovascular events in addition to the use of surrogate measures of platelet aggregometry. What is the mechanism behind the observed cerebrovascular protection of aspirin in women but not in men? More studies are clearly needed to answer this question.

Stroke Prevention in Women: Opportunities

The most recent AHA Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women have redefined risk categories that may guide and ultimately improve recognition and appropriate prevention strategies for women [37••]. The classification of risk includes high risk, at risk, and optimal risk (Table 2). The rationale for reclassifying women is related to their very high lifetime risk of CVD. In fact, the lifetime risk of stroke is about 20% [39], and for all CVD, lifetime risk approaches 40% [40]. In addition, not only does the traditional Framingham risk score limit the prediction to 10 years or less, but it may underestimate the future risk of CVD in women who are found to have subclinical disease, measured with coronary artery calcium or carotid intima-media thickness [37••].

The guidelines also included a useful algorithm for evaluating risk and implementing various prevention strategies. All women, regardless of risk, should be counseled on class I lifestyle recommendations (smoking cessation, heart-healthy eating patterns, regular physical activity, and weight management). High-risk women who have not had a recent cardiovascular event and do not meet requirements for rehabilitation should have class I recommendations for blood pressure control, LDL goal < 100 mg/dL, aspirin/antiplatelet agents, glycemic control in diabetic women, and aldosterone blocker in selected women. Selected at-risk women (those with more than one major risk factor for CVD, evidence of subclinical vascular disease, metabolic syndrome, or poor exercise capacity on treadmill test and/or abnormal heart rate recovery after stopping exercise) should have blood pressure control and LDL therapy. Other class II recommendations to consider include LDL less than 70 mg/dL, HDL/non-HDL therapy, omega-3 fatty acids, and depression referral and treatment [37••].

The guideline recommendations for weight maintenance/reduction for women is to work to a goal BMI of 18.5 to 24.9 kg/m² and a waist circumference less than 35 inches through a balance of physical activity, lower caloric intake, and formal behavioral programs when indicated [37••]. Recommended diets are those rich in fruits and vegetables, whole-grain, high-fiber foods, fish (especially oily fish) at least twice a week, and very limited proportions of saturated fats and trans-fatty acids. Physical activity recommendations for women include an accumulated total of at least 30 minutes of moderate-intensity physical exercise (eg, brisk walking) on most days of the week. Women who are working to lose weight or sustain weight should increase to 60 to 90 minutes of moderate-intensity activity on most, if not all, days of the week [37••].

Measuring exercise capacity is an opportunity to improve cardiovascular prevention because of its association with cardiac death in women [41]. Women with and without coronary disease symptoms underwent symptom-limited treadmill tests and were followed for cardiac outcomes. The percent of predicted exercise capacity was measured with exercise nomograms developed for women who were active and those who were sedentary [41]. Regardless of the presence of symptoms, those women whose exercise capacity was less than 85% of the age-appropriate predicted value had a twofold increased risk of death from any cause and a 2.4-fold risk of cardiac death [41]. Although not specifically developed for stroke, this type of exercise nomogram is important for general cardiovascular prevention screening and helps identify women who may benefit from exercise programs. Increasing physical fitness would ultimately decrease stroke risk in these women.

Specific recommendations for physical activity for stroke survivors have also been published [42]. Not only do these guidelines encompass stroke rehabilitation, but physical activity is also an important component of the lifestyle changes recommended for secondary prevention of stroke [26••]. Patients who have disability from ischemic stroke may be considered for a supervised exercise regimen. These guidelines provide recommendations for aerobic, strength

training, flexibility, and neuromuscular aspects of potential exercise programs, depending on the goals and needs of the stroke survivor [42].

Important opportunities are highlighted in the newest guidelines for prevention in women, along with a growing recognition of the acceleration of risk factors in women during midlife. An analysis of the National Health and Nutrition Examination Survey (NHANES) cohort focusing on midlife trends in blood pressure and cholesterol among men and women presented interesting insights [5]. For instance, systolic blood pressure (SBP) increased with each decade from 35 to 44 years (average SBP 113.9 mm Hg), 45 to 54 years (average SBP 123.5 mm Hg), and 55 to 64 years (average SBP 132.0 mm Hg) at a higher rate in women than in men. Although men initially had a higher SBP between ages 35 and 44 (average SBP 120.0 mm Hg), women surpassed men between the ages of 55 and 64 (average SBP 128.6 mm Hg). In addition, women had a substantial increase in total cholesterol, triglycerides, waist circumference, homocysteine, and glycosylated hemoglobin and a lowering of the ankle brachial pulsatility index between the ages of 45 and 54, and 55 and 64 [5]. These data suggest that an acceleration of multiple risk parameters occurs in women a decade or more before the ages when cardiovascular and stroke events traditionally occur. In addition, these data showed a surge of self-reported stroke prevalence that was higher in women than men [5], despite the epidemiologic dogma that women have a lower incidence of stroke in this age group. Assuming these data are valid, there is a significant opportunity to increase efforts to recognize risk factors in women during midlife and improve prevention strategies.

Although the menopausal status of women in the NHANES cohort was unknown, the surge in risk factors and stroke prevalence in these age groups may reflect changes that are occurring in women as they move through menopause. Multiple studies have examined the effects of menopause on risk factor development in women. For example, the Healthy Women Study showed that HDL decreased, and LDL and triglycerides increased the most during perimenopause, whereas blood pressure and fasting glucose levels were greater during postmenopause. More importantly, premenopausal systolic and pulse pressure, LDL, HDL, triglycerides, and BMI predicted carotid intima-media thickness and plaque, measures of subclinical atherosclerosis [43]. Recognizing the changes in blood pressure (including pulse pressure), fasting glucose, BMI, and lipid profiles in women as they move through menopause represents an opportunity to improve management of these risk factors and reduce the risk of stroke.

Not surprisingly, a healthy lifestyle has been associated with a lower risk of stroke in women. In the Women's Health Study, a healthy lifestyle profile was defined as never smoking, alcohol consumption between 4 and 10.5 drinks per week, exercise more than four times per week, BMI less than 22 kg/m², and a diet high in cereal fiber, folate, and omega-3 fatty acids, with a high ratio of polyunsaturated to saturated fat, and low in trans-fat and glycemic load [44]. Women with the highest scores on this scale had a 55% lower risk of stroke than women with the lowest scores (HR 0.45; 95% CI, 0.24–0.83) [44]. Given the benefits of healthy lifestyle, one behavioral approach to improvements in lifestyle is the use of health coaches. Such programs have shown that this aggressive approach to lifestyle changes focused on weight loss and physical activity can be used to manage risk factors without pharmacologic therapies [45].

The CVD guidelines also call attention to the fact that women with preeclampsia/eclampsia are at risk for developing hypertension, heart disease, and stroke later in life [46–48]. Women with maternal placental syndromes, which include preeclampsia, gestational hypertension, placental abruption, or placental infarction, also have an increased risk of future maternal CVD [47]. Therefore, more research is needed to determine how closely these women need to be monitored for the development of hypertension and other risk factors, and whether the

diagnosis of preeclampsia/eclampsia should be recognized as an independent risk factor. Research on the extent of subclinical disease in women with a history of preeclampsia may help to identify women at high risk of CVD and stroke.

Should Stroke Prevention Be Gender-Specific?

In addition to aspirin, gender differences in response to some of the drugs prescribed for stroke prevention have been described. For example, angiotensin-converting enzyme inhibitors were less effective in preventing cardiovascular events in women with hypertension than in men [49]. However, given the overall effectiveness of drugs for cardiovascular prevention and the limited power of gender-specific subgroup analyses, no gender-specific recommendations can be made yet. Schemes to improve the drug development process have been proposed and might significantly help direct future research efforts and medical decision making related to gender-specific treatment of CVD [50•].

Conclusions

Preventing stroke in women is challenging, primarily because there is a large population of women who are at risk for a first-ever stroke, and their awareness of the risk may be suboptimal. Therefore, significant opportunities are available to improve physician awareness and adherence to evidence-based guidelines. This awareness is the first step to improving the management of the primary modifiable risk factors—hypertension, dyslipidemia, physical inactivity, weight management, and diabetes. Other opportunities include targeting women who may have early signs of future vascular risk (ie, women with preeclampsia or maternal placental syndromes) and those transitioning from perimenopause to postmenopause. Future research should assess the effectiveness of routine screening for subclinical vascular disease to improve risk assessments for future stroke, and investigating the effectiveness of gender-specific prevention strategies, including pharmacotherapy and lifestyle changes.

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Table 1
Challenges and opportunities for stroke prevention in women

Challenges	Opportunities
Underestimation of CVD risk in women by treating physicians	Improve physician awareness and adherence of the CVD prevention guidelines for women
Women are infrequently counseled by physicians to engage in physical activity according to the guidelines	
High-risk women do not achieve target lipid profiles and blood pressures	Improve physician adherence to guidelines for stroke primary and secondary prevention—JNC 7 and NCEP-ATP III; improve patient adherence to medication recommendations
Physical inactivity is a significant risk factor for stroke in women, regardless of weight status	Exercise capacity can be assessed using a nomogram that predicts risk of cardiac and all-cause death in women
CVD risk increases as women transition through menopause; stroke prevalence may be increasing faster in women than men in this age group	More careful surveillance of CVD risk factors in women transitioning through menopause or recently postmenopause
Women with a history of preeclampsia have a higher risk of hypertension and stroke later in life	Research focused on identifying women at high risk for stroke, and careful surveillance for development of hypertension
Atrial fibrillation is more common in women with stroke, but many women may not be prescribed anticoagulation due to fall risk	Carefully assess fall risk, but risk of ischemic stroke in selected women may be even higher than risk of hemorrhagic complications of falls

CVD—cardiovascular disease; JNC 7—Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; NCEP-ATP III—National Cholesterol Education Program third Adult Treatment Panel.

Table 2
Definitions of risk categories for cardiovascular disease prevention in women

Risk status	Criteria
High risk	Established coronary heart disease Cerebrovascular disease Peripheral arterial disease Abdominal aortic aneurysm End-stage or chronic renal disease Diabetes mellitus 10-year Framingham global risk > 20%
At risk	> 1 major risk factor for CVD, including: Cigarette smoking Poor diet Physical inactivity Obesity, especially central adiposity Family history of premature CVD (CVD at age < 55 years in male relative and < 65 years in female relative) Hypertension Dyslipidemia Evidence of subclinical vascular disease (eg, coronary calcification or carotid intima-media thickness) Metabolic syndrome Poor exercise capacity on treadmill test and/or abnormal heart rate recovery after stopping exercise
Optimal risk	Framingham global risk < 10% and a healthy lifestyle with no risk factors

CVD—cardiovascular disease.