

Stroke Prevention in Women: Synopsis of the 2014 American Heart Association/American Stroke Association Guideline

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Description: In February 2014, the American Heart Association/American Stroke Association released their first guideline focused on stroke prevention in women. This new guideline highlights unique risk factors for stroke in women, including oral contraception and hormone therapy, and pregnancy-associated disorders, such as pre-eclampsia, that may have long-lasting consequences on a woman's health. It also addresses hypertension; atrial fibrillation; migraine headache with aura; and the epidemiology of types of stroke, such as aneurysmal subarachnoid hemorrhage and cerebral vein thrombosis, that are predominant in women.

Methods: Members of a multidisciplinary expert panel searched, reviewed, and critiqued relevant English-language literature pub-

lished between 1990 and May 2013. The panel devised evidence tables and developed recommendations using American Heart Association guideline procedures and levels of evidence.

Recommendations: This synopsis of the guideline summarizes the evidence about risk factors for stroke in women and suggests prevention strategies. It also describes the new recommendations relevant to identifying and treating hypertensive disorders in pregnancy that increase risk for stroke.

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Sex differences are increasingly recognized in many areas of medicine, and stroke is no exception. An estimated 6.8 million persons in the United States have had a stroke, most of whom are women (3.8 million) (1). At the time of stroke, women are older and more likely to be living alone and have worse premorbid status than men. After stroke, they also are more likely to be institutionalized and have a poorer recovery and worse quality of life than men (2–6).

There are many unique risk factors for stroke in women, such as pregnancy and pregnancy complications, hormonal contraception, and hormone therapy for menopause symptoms. Several other risk factors are more common in women than in men, including hypertension, atrial fibrillation, migraine headache with aura, and depression and psychosocial stress (Table). With these issues in mind, we developed a sex-specific guideline that consolidates recommendations specific to stroke prevention in women from primary and secondary prevention guidelines (7, 8) and emphasizes stroke-specific issues in more detail than previously published cardiovascular prevention guidelines (9).

GUIDELINE DEVELOPMENT PROCESS

The American Heart Association Manuscript Oversight Committee and the Scientific Statement Oversight Committee of the Stroke Council approved the topic areas for the guideline and the expert panel that developed and wrote the guideline. Panel members had expertise on stroke in women and stroke prevention. They represented many disciplines, including neurology, neurosurgery, neurocritical care, neuroscience and research on sex differences, internal medicine, obstetrics and gynecology, cardiology, pharmacology, nursing, epidemiology, and public policy.

We assigned topic areas to 1 primary reviewer and 1 or 2 secondary reviewers selected from the panel. These reviewers developed search terms to identify literature relevant to their topic area. Members of the writing group then searched PubMed, MEDLINE, the Cochrane Library, CardioSource, and EMBASE for English-language literature published between 1990 and 15 May 2013.

The reviewers scanned the search results, selected papers relevant to their topic, and abstracted data from selected studies to create evidence tables. All members of the panel then reviewed evidence tables and developed recommendations using the American Heart Association's ratings for class of recommendation and level of evidence (10). The Stroke Council leadership committee and the Scientific Statements Oversight Committee coordinated extensive peer review of the guideline, and the Science Advisory and Coordinating Committee approved the final draft.

RECOMMENDATIONS

Risk Factors for Stroke

Hypertension in Nonpregnant Women

Hypertension, the most modifiable risk factor for stroke, is more prevalent in women than men (11). Hypertension is more often poorly controlled in older women; only 23% of women versus 38% of men older than 80 years have a blood pressure less than 140/90 mm Hg (12). There is currently no evidence that antihypertensive treatments differentially affect blood pressure response or stroke

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Table. Risk Factors for Stroke

| Risk Factor | Sex-Specific Risk Factors | Risk Factors That Are Stronger or More Prevalent in Women | Risk Factors That Are Similar in Men and Women |
|--|---------------------------|---|--|
| Pregnancy, preeclampsia, or gestational diabetes | X | | |
| Oral contraceptive or postmenopausal hormone use | X | | |
| Migraine headache with aura | | X | |
| Atrial fibrillation | | X | |
| Diabetes | | X | |
| Hypertension | | X | |
| Physical inactivity, obesity, or unhealthy | | | X |
| Age | | | X |
| Prior cardiovascular disease | | | X |
| Smoking | | | X |
| The metabolic syndrome | | | X |
| Depression | | X | |
| Psychosocial stress | | X | |

prevention by sex, but many trials of antihypertensive agents do not report sex-specific analysis for efficacy or adverse effect profiles. Moreover, there are major evidence gaps about appropriate drug choices, treatment resistance, adherence, and hormone-dependent and -independent approaches to blood pressure treatment by sex (13).

Atrial Fibrillation

Sex differences in atrial fibrillation include a higher prevalence and a higher associated risk for thromboembolic events in women (14). The effect of this epidemiology has translated into the development of risk scores for patients with atrial fibrillation, with an additional point given for female sex in the CHA₂DS₂-VASc (congestive heart failure/left ventricular dysfunction, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack/thromboembolism, vascular disease, age 65 to 74 years, sex category) score (15). Therefore, we recommend use of risk stratification tools that account for age- and sex-specific differences in the incidence of stroke. Women, particularly those older than 75 years, should be actively screened for atrial fibrillation with pulse rate measurement and electrocardiography as appropriate (class I; level of evidence B). We also suggest antiplatelet therapy for women with lone atrial fibrillation who are aged 65 years or younger (13).

Migraine Headache With Aura

Women are 4 times more likely than men to have migraine headache (16). Although the absolute risk for stroke associated with migraine headache is low, the association between migraine headache with aura and stroke seems strongest in women younger than 55 years (17, 18). The frequency of migraine headache may also be associated with stroke (19).

We therefore suggest reducing the frequency of migraine headache as a possible strategy to reduce the risk for stroke, although there is no evidence that specific treatment strategies (for example, calcium-channel blockers, β-blockers, and antiepileptic drugs) reduce the risk for stroke (13). Given a synergistic relationship between smoking and migraine headache with aura, we recommend smoking cessation treatments and counseling for persons who smoke and have migraine headache. Finally, we encourage clinicians to caution women with migraine headache about the use of oral contraceptives (13).

Hormonal Contraception

The use of oral contraceptives is a risk factor for stroke in young women, increasing the risk from 1.4- to 2.0-fold compared with that of women who do not use these agents (13). The absolute risk is low—approximately 2 events per 10 000 women per year with the use of the lowest-dose formulation, according to a recent study from Denmark (20). The risk for stroke among women using oral contraceptives increases exponentially from 3.4 per 100 000 women aged 15 to 19 years to 64.4 per 100 000 women aged 45 to 49 years (20). Factors that could further increase risk for stroke include prior thromboembolic events, hypertension, cigarette smoking, hyperlipidemia, diabetes, and obesity. Accordingly, we recommend identifying women with such risk factors and increasing efforts to manage modifiable risk factors in women who use oral contraceptives.

The guideline also addresses prothrombotic mutations and biomarkers that increase the risk for stroke in a synergistic manner. Studies show that markers of endothelial dysfunction, such as von Willebrand factor and ADAMTS13 (a disintegrin and metalloproteinase with the thrombospondin type 1 repeat 13), increase the risk for stroke more than 10-fold in women who use oral contraceptives compared with those who do not (21). Although many prothrombotic mutations increase the risk for stroke in women using oral contraceptives, we do not recommend screening for these mutations before starting oral contraceptive therapy because of their low prevalence in otherwise healthy women, especially in the absence of a positive family history (13).

Additional research is needed to better characterize the risk for hemorrhagic stroke with oral contraceptive use, focusing on older women who may use these agents until menopause, members of underrepresented minority groups, genetic makeup, and parity. The study of clinically available biomarkers, such as von Willebrand factor, is warranted in broader populations of women.

Menopause and Hormone Replacement

Menopause, particularly younger age at menopause, and risk for stroke may be related, but evidence defining such a relationship is inconsistent. Whether natural versus

surgical menopause is associated with risk for stroke is also unclear. However, the use of hormone therapy in postmenopausal women is a unique risk factor for stroke in women.

In general, hormone therapy is associated with an increased risk for stroke and is not recommended for primary or secondary prevention of this condition. Many gaps remain in research about the magnitude of harms and tradeoffs between benefits and risks of hormone therapy. These gaps concern treatment of subgroups of women who are at high risk for stroke after menopause; treatment of women who are early in the peri- or postmenopause period; and the optimum timing, dosage, type, and route of administration that could enhance vascular health (13).

Depression and Psychosocial Stress

Several cohort studies and a meta-analysis have identified depression and psychosocial stress as factors that increase the risk for incident stroke by 25% to 45% in women (22–24). The odds ratios across studies that included both men and women are similar to those of studies that included only men or only women, making it difficult to state conclusively that women with these conditions have a higher risk for stroke than men. More research is needed to understand the subgroups of women at risk, such as those who are treated versus not, and the method of determining depression and psychosocial stress (13).

Stroke Prevention Strategies

Healthy Lifestyle

We advise maintaining a healthy weight, eating a healthy diet, abstinence from smoking, regular physical activity, moderate alcohol intake, and activities and interventions aimed at achieving or maintaining normal blood pressure and cholesterol and blood glucose levels. The guideline highlights the risk for stroke in several high-risk conditions, including obesity, physical inactivity, and the metabolic syndrome, but found few data that suggest these conditions increase risk for stroke disproportionately in women.

However, a recent meta-analysis of studies involving more than 750 000 persons and more than 12 000 strokes found that diabetic women have a 27% greater relative risk for stroke than diabetic men (25). The mechanisms underlying this increased risk are unknown but may be related to a more adverse cardiovascular risk profile during the prediabetic phase in women than men (25). This meta-analysis provides further evidence that recognition of risk factors for stroke, especially those that may disproportionately increase risk in women, is critical to prevent stroke. Healthy lifestyle interventions, including regular physical activity, such diets as the Dietary Approaches to Stop Hypertension, abstinence from smoking, moderate alcohol consumption (13), and recognition and treatment of diabetes, are important. Until sex-specific strategies are tested, recommendations for stroke prevention in terms of healthy

lifestyle interventions remain the same for men and women.

Carotid Stenosis

Women with symptomatic carotid stenosis (recent ischemic stroke or transient ischemic attack ipsilateral to the carotid stenosis) may be less likely to receive carotid endarterectomy than men (26). Whether benefits and risks of carotid angioplasty and stenting differ between women and men is not known. Data from CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial) showed that women randomly assigned to angioplasty and stenting had a higher proportion of periprocedural events than men and a possible interaction between the treatment assignment and sex ($P = 0.064$) (27).

There are clear sex differences in carotid artery plaque (women have less inflammatory features) and a higher risk for periprocedural complications with endarterectomy for asymptomatic stenosis. However, evidence to suggest that women with symptomatic or asymptomatic carotid stenosis should be treated medically versus surgically (with endarterectomy or coronary artery stenting) or differently from men is currently lacking (13). Therefore, the guideline recommendations are the same for both sexes. There are many gaps in our understanding of the sex-specific treatment of carotid disease, so future trials are needed to determine whether surgery is superior to aggressive medical management in women with symptomatic carotid stenosis.

Aspirin for Stroke Prevention

There is no convincing evidence to suggest that a particular antiplatelet therapy or dosage of such therapy is more or less beneficial in women than men, but protection from aspirin may be specific to certain vascular diseases on the basis of sex. For example, the results of the WHS (Women's Health Study), a trial of 100 mg of aspirin every other day versus placebo, showed that aspirin did not reduce the risk for myocardial infarction or death from cardiovascular causes but did decrease stroke events (relative risk, 0.83 [95% CI, 0.69 to 0.99]), especially ischemic stroke (relative risk, 0.76 [CI, 0.63 to 0.93]) (28). A meta-analysis of aspirin and primary prevention showed that women seem to be protected from stroke, whereas men are protected from myocardial infarction (29). However, the ATT (Antithrombotic Trialists') Collaboration study reported no evidence of a sex difference in any of the vascular outcomes after adjustment for multiple comparisons (30).

Consistent with other published recommendations, our guideline suggests considering aspirin in women older than 65 years if blood pressure is controlled and the benefit of preventing ischemic stroke or myocardial infarction outweighs the risk for gastrointestinal bleeding and hemorrhagic stroke (13). Whether a woman younger than 65 years may benefit from aspirin could be addressed if a sex-specific risk score were available.

New Recommendations

Pregnancy and Pregnancy Complications

The risk for stroke during pregnancy is fairly low (about 34 per 100 000 deliveries) (31), but risk is highest in the postpartum period. Although the traditional definition of a postpartum time frame is 6 weeks, a recent study showed that thrombotic events may occur up to 12 weeks after birth (32). Suspicion for a postpartum stroke or vasculopathy (the posterior reversible encephalopathy syndrome or the reversible cerebral vasoconstriction syndrome) or cerebral venous thrombosis should be heightened for women who develop new-onset headache, blurred vision, or seizures or any new neurologic signs or symptoms during the postpartum period (13).

Preeclampsia and Eclampsia Preeclampsia occurs in approximately 5% of pregnancies. It is defined as high blood pressure in pregnancy associated with proteinuria (urinary protein excretion ≥ 300 mg/24 h) or thrombocytopenia, impaired liver function, progressive renal insufficiency, pulmonary edema, or new-onset cerebral or visual disturbances (33). The American Congress of Obstetricians and Gynecologists (formerly the American College of Obstetricians and Gynecologists) published an updated guideline (released after our guideline was in production) that changed the criteria for preeclampsia to include women without proteinuria if one of the other multisystem features is present (33).

Because of evidence that a history of preeclampsia is associated with a 2-fold risk for stroke and a 4-fold risk for hypertension later in life, we recommend documenting preeclampsia as a risk factor (class IIa; level of evidence C) (13). Our intent is to increase awareness that women with a history of preeclampsia would probably benefit from lifestyle change and early assessment of cardiovascular risk and interventions. Although the evidence for an association between preeclampsia and later hypertension with attendant risk for stroke is clear, the current gap in knowledge is identifying which women with preeclampsia will have these complications. More research is needed to understand biomarkers or other characteristics that might identify the women at highest risk (13).

Moderate Hypertension in Pregnancy Another new recommendation is to consider treating women with a systolic blood pressure between 150 and 159 mm Hg or a diastolic blood pressure between 100 and 109 mm Hg of new onset during pregnancy (class IIa; level of evidence B). This recommendation differs from that of the guideline of the American Congress of Obstetricians and Gynecologists, which recommends only treating patients with a blood pressure greater than 160/110 mm Hg (33). Our new recommendation is based on evidence that treatment of mild to moderately elevated blood pressure in pregnancy is associated with a 50% reduction in risk for severe hypertension (relative risk, 0.5 [CI, 0.41 to 0.61]) (34).

New studies or reanalyses of existing data using the new definition of preeclampsia would be useful to assess

the benefit of treating mild to moderately elevated blood pressure during pregnancy. Although safe and effective antihypertensive medications can be used during pregnancy, risk to the fetus must also be considered (13).

CONCLUSION

These guidelines provide recommendations for the prevention of stroke in women, emphasizing risk factors that are unique or more prevalent in women. Of note, we recognize many gaps in the literature that limit the ability to provide strong (level of evidence A), sex-specific recommendations. Some stroke-specific risk scores, such as the Framingham risk score for stroke (35), take sex into account but do not allow calculation of risk in persons younger than 54 years. Goals for our guideline included identifying unique risk factors and facilitating the development of new sex-specific tools for scoring risk for stroke.

We suggest that a more accurate assessment of risk for stroke is possible if events that occur in young adulthood known to increase this risk in later life, such as preeclampsia, are documented. In addition, risks unique to women (use of oral contraceptives and hormone therapy) and established risk factors that are more prevalent in older women (hypertension and atrial fibrillation) should be recognized. We hope that this guideline will spur additional research to determine the best approaches to stroke prevention for both men and women.

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