Guidelines for the Prevention of Stroke in Women

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Despite the importance of stroke in women, there has never previously been an American Heart Association (AHA/American Stroke Association) guideline dedicated to stroke risk and prevention in women.
Guidelines for the Prevention of Stroke in Women
A Statement for Healthcare Professionals From the American Heart Association/
American Stroke Association

Objectives

• Be able to summarize data on stroke risk factors that are unique to
women and more common in women than men

• Expand on the data provided in prior stroke guidelines and
cardiovascular prevention guidelines for women

• To more accurately reflect the risk of stroke in women across the lifespan
OVERVIEW

• Stroke burden
• Stroke subtypes (ischemic and hemorrhagic)
• Stroke risk factors (gender-neutral, gender-specific) and their management
• Discussion of primary and secondary stroke prevention (including hormone replacement therapy, migraines, stress and atrial fibrillation)
Multiple Disciplines Were Represented

Neurology, neuroscience research, internal medicine, obstetrics/gynecology, cardiology, pharmacology, nursing, epidemiology and public policy

• The panel reviewed relevant articles on adults using computerized searches of the medical literature through May 15 2013.

• The evidence is organized within the context of the AHA framework and is classified according to the joint AHA/American College of Cardiology and supplementary AHA Stroke Council methods of classifying the level of certainty and the class and level of evidence.

• Each topic was assigned a primary author and a secondary reviewer.

• Topics that were not covered in detail include management of diabetes mellitus and cholesterol because there are no recommendation for these risks factors specific to women.
All Strokes Are Not the Same

There is increasing recognition of gender difference in stroke

• Female population carries a higher stroke burden

• Reasons:
  (1) females have a longer life expectancy
  (2) most stroke deaths occur in women

• Example: Among stroke survivors, women tend to have worse outcomes than men

• Evidence: Disability in women is more severe
  Likelihood of institutionalization in women is increased
An estimated 6.8 million (2.8%) of people are living after having had a stroke, 3.8 million are women and 3 million are men.

Stroke is the 5th leading cause of death for men and the 3rd leading cause of death in women.

Women are more likely to be living alone and widowed before stroke, and are more often institutionalized after stroke and have poorer recovery from stroke than men.

These demographics suggest an anticipated increase of the burden of stroke in women.

Annual stroke care cost is over $33 billion (CDC 2016)
Strokes in Women

• Women ages 45-54 are at higher risk of stroke than men in the same age group

• Hypothesis - common stroke risk factors HTN, HLD, BMI may not be as closely observed and controlled in this subset of women

• Risk of ischemic stroke is more likely to be inherited by women than men

• Male to female ratio = 1:2-3 (family history+)

• Women over age 35 who smoke + take high-estrogen oral contraceptives (i.e., > 35 mcg estrogen) have a stroke risk 22 times higher than average
Stroke Awareness - Not Uniform

Sex Difference in Stroke Awareness (Delay, Warning Signs, Risk Factors)

• Delayed hospital arrival is the single most important reason for the failure to administer thrombolytic treatment within the eligible time window of 3 or 4.5 hours. Several of the studies found women have longer pre-hospital delay than men.

• Several population-based studies have shown that knowledge and awareness of stroke warning signs and symptoms are somewhat higher in women than men.

• One study reported that although women were more likely than men to have heard of tissue-type plasminogen activator therapy for stroke, they were less likely to know it must be administered within 3 hours.

• Population-based surveys of women conducted by the AHA, have identified an overall poor level of knowledge of CVS and stroke, particularly in minority women.
Vascular Difference in Stroke Risk: Sex and Hypertension

Hypertension is the most common modifiable risk factor for stroke in both men and women and has the highest population attributable risk.

- Studies have shown that women are more likely to have hypertension than men.
- Women have a higher risk of first stroke with hypertension.
- One study showed that women with self-reported blood pressures of 160/90 mmHg, had a higher risk of stroke than men.
- Older women (mean average age of 63 years) with prehypertension had a 93% increased risk of stroke compared with normotensive women in the Women’s Health Initiative (WHI) cohort, which implies that early and sustained treatment of hypertension is critical.
Efficacy of Hypertension Treatment and Reduction of Stroke in Women

No studies have specifically examined a differential effect of pharmacological BP treatment in men and women on stroke events.

- The effects of pharmacological intervention to lower BP and thereby reduce the risk of stroke on cardiovascular outcomes and strategic cardiovascular endpoints have been studied extensively, and women have been well represented in large clinical trials of antihypertensive therapy. However, no trials have specifically examined a differential effect of pharmacological BP treatment in men and women on stroke events.

- Similarly, post hoc analysis and meta-analysis of clinical trial data have not reported sex differences in response to treatment or stroke events. In a recent meta-analysis of 31 large randomized BP trials, treatment of hypertension in women aged > 55 years was associated with a 38% reduction in fatal and nonfatal cerebrovascular events.
Sex, BP, Antihypertensive Treatment, and Achieving BP Goals

Analysis of women in different ethnic and age groups suggests benefits of BP reduction in both younger and black women

• The prevalence of hypertension in adults < 45 years of age is lower in women than men but hypertension becomes increasingly prevalent and is higher in postmenopausal women after the age of 55 which suggests an important role of sex hormones in the regulation of BP.

• Currently, there is no compelling evidence that there are differences in response to BP medications between the sexes. In large-scale reviews that examined the efficacy of β-blockers, angiotensin-converting enzyme inhibitors, angiotensin, receptor blockers and diuretics; there is no mention that sex-specific efficacy end points were evaluated or even considered. The possibility of differences in efficacy of BP medications therefore exists.
Pregnancy and Stroke

- Pregnancy is a condition unique to women. Although stroke is uncommon in pregnancy (34 strokes per 100,000 deliveries) the risk for stroke is higher in pregnant than non-pregnant young women. The highest risk occurring in the third trimester and post partum.

- Hypertensive disorders of pregnancy and other complications (preterm birth, small size for gestational age, and first-trimester bleeding) are associated with increased risk of stroke during pregnancy, immediately after delivery, and years after delivery.

- Research suggests that clinicians are not aware of the association between adverse pregnancy outcomes and CVD and stroke, which suggests a need for better clinician and patient education.
Preeclampsia and Pregnancy Outcomes – Recommendations:

• Prevention of Preeclampsia: Women with chronic primary or secondary hypertension or previous pregnancy-related hypertension should take low-dose aspirin from the 12th week of gestation until delivery. Calcium supplementation should be considered for women with low dietary intake of calcium to prevent preeclampsia.

• Treatment of Hypertension in Pregnancy and Post Partum: Severe hypertension in pregnancy should be treated with safe and effective antihypertensive medications such as methyldopa, labetalol, and nifedipine, with consideration of maternal and fetal side effects. Atenolol, angiotensin receptor blockers, and direct renin inhibitors are contraindicated in pregnancy and should not be used. After giving birth, women with hypertension should be continued on their antihypertensive regimen with dose adjustments as indicated.
Screening for Potential Pro-thrombotic Conditions

• Conditions that predispose a person to CVT (use of contraceptives, underlying inflammatory disease, infectious process).

• Protein C, protein S or anti-thrombin deficiency: antiphospholipid syndrome; prothrombin G20210A mutation; and factor V Leiden can be beneficial. Testing should be performed 2 to 4 weeks after anticoagulation.

• For women with a history of CVT, prophylaxis with LMWH during future pregnancies and the post partum period is reasonable.
Oral Contraceptives – Recommendations:

• Oral contraceptives may be harmful in women with additional risk factors (e.g., cigarette smoking, prior thromboembolic events)

• Among OC users, aggressive therapy of stroke risk factors may be reasonable.

• Routine screening for pro-thrombotic mutations before initiation of hormonal contraception is not useful.

• Measurement of BP before initiation of hormonal contraception is recommended
Postmenopausal HT – Recommendations:

• HT should not be used for primary or secondary prevention of stroke in postmenopausal women.

• Selective estrogen receptor modulators, such as raloxifene, tamoxifen or tibolone should not be used for primary prevention of stroke.
Risks Factors More Common in Women than Men

Migraine with Aura - Recommendations:

• Because there is an association between higher migraine frequency and stroke risk, treatment to reduce migraine frequency might be reasonable, although evidence is lacking that this treatment reduces the risk of first stroke.

• Because of the increased stroke risk seen in women with migraine headaches with aura who also smoke, it is reasonable to strongly recommend smoking cessation in this group.
Risk Factors More Common in Women than Men

Obesity, Metabolic Syndrome, and Lifestyle Factors

Recommendations:

• A healthy lifestyle consisting of regular physical activity; moderate alcohol consumption (< 1 drink/day for non-pregnant women); abstention from cigarette smoking; and a diet rich in fruits, vegetables, grains, nuts, olive oil, and low in saturated fat (such as the DASH (Dietary Approaches to Stop Hypertension) is recommended for primary stroke prevention in women with cardiovascular risk factors.

• Lifestyle interventions, focusing on diet, and exercise are recommended as primary prevention among individuals at high risk for stroke.
MODIFIABLE RISK FACTORS

- HTN, CAD/Carotid disease/PVD, Atrial fibrillation, Diabetes, Weight, High cholesterol/Diet, Lack of exercise, Obstructive sleep apnea, Smoking, Psychological/Emotional stress, ETOH/drug abuse (cocaine, heroin, stimulants)

CAN MODIFIED BY MEDICAL INTERVENTION:
Coagulopathy, Cancer, Sickle cell anemia, Patent Foramen Ovale (PFO)
NON-MODIFIABLE STROKE RISK FACTORS

• Age > 55 years
• Gender
• Prior history of TIA and/or stroke
• Race: African Americans have twice the risk of death and disability
  Asians have 1.4 times the risk of death and disability
• Family history of stroke
RISK FACTORS UNIQUE TO WOMEN

• Hypertension
• Diabetes mellitus
• Hormonal contraception
• Pregnancy
• Pre-eclampsia/eclampsia/gestational diabetes
• Cerebral venous sinus thrombosis (CVT)
• Using Hormone replacement therapy
• Migraine headaches with aura
• Depression and psychosocial stress
• Atrial fibrillation
Atrial Fibrillation – Recommendations:

- Risk stratification tools in AF that account for age and sex-specific differences in the incidence of stroke are recommended.

- Considering the increased prevalence of AF with age and the higher risk of stroke in elderly women with AF, activating screening in women > 75 years in primary care settings using pulse taking followed by an ECG as appropriate is recommended.

- Oral anticoagulation in women <65 years with AF alone is not recommended with CHAD scores 1 or 0. Antiplatelet therapy is a reasonable option for selected low-risk women.

- New oral anticoagulants are a useful alternative to warfarin for the prevention of stroke in women with paroxysmal or permanent AF and prespecified risk factors to CHAD who to not have prosthetic heart valve or hemodynamically significant valve disease or renal disease.
HORMONAL CONTRACEPTION

• Two-fold increase in risk with combined OCP use
• NO risk with progesterone-only method
• Absolute risk of stroke low in young women but still present
  Non-OCP user: 10/100,000 person-years
  OCP user: 20/100,000 person-years
• Incidence-
  Stroke occurs in 34/100,000 pregnancies
  Stroke in non-pregnancy aggregate 21/100,000
PREGNANCY AND STROKE

• Incidence -
  Stroke occurs in 34/100,000 deliveries
  Stroke in non-pregnant aggregate 21/100,000

• Increased risk during pregnancy (especially 3rd trimester) and postpartum period

• Reasons: Venous stasis, Edema, Hypercoagulable states
STROKE MANAGEMENT AND PREGNANCY

• t-PA is a relative contraindication

• successful maternal and fetal outcomes have been reported in several cases of t-PA administration in pregnant patients

• Special consideration for cerebral venous sinus thrombosis
HTN AND PREGNANCY

• Complications during pregnancy (preeclampsia, gestation diabetes and pregnancy induced HTN) create a higher risk for future CV disease
• ACC/AHA GUIDELINE:
  Treat severe HTN in pregnancy with safe and effective antihypertensives.  Rx: methyldopa, labetalol and/or nifedipine
• Keep maternal and fetal side effects in mind
HRT: ENDOCRINE SOCIETY’S 2015 CLINICAL PRACTICE PRACTICE GUIDELINE

• Indication - to manage menopausal symptoms; NOT to prevent CVD, osteoporosis, or dementia

• Before initiating HRT: Calculate cardiovascular and breast cancer risks (recommend non-hormonal therapies for symptomatic women at high risk [10% 10-yr risk] for CVD)
MIGRAINE WITH AURA

• 3 times more prevalent in women than men
• Women who have h/o migraines with aura are at 2-fold higher risk of stroke than those without
• Absolute risk increase (migraine with aura): 4 additional ischemic strokes per 10,000 women
• OCPs and smoking further increase risk of stroke for these women
Strategies for Prevention of Stroke in Women –
Recommendations:

• Women with asymptomatic carotid stenosis should be screened for other treatable risk factors for stroke and appropriate lifestyle changes and medical therapies should be instituted

• Aspirin therapy 75-325 mg/d is reasonable in women with diabetes mellitus unless contraindicated

• If a high-risk woman has an indication for aspirin but is intolerant of aspirin therapy, clopidogrel should be substituted

• Aspirin therapy can be useful in women > 65 yrs of age (81 mg/d or 100 mg every other day) if BP is controlled and the benefit of MI prevention out weighs the risk of GI bleeding
In Conclusion

• Prevention efforts for women would be enhanced if future epidemiological studies provided more detail on stroke subtypes, especially hemorrhagic stroke, in addition to accounting for age and sex.

• Similarly, it is important to improve stroke awareness and provide more rigorous education to women at younger ages. This is important because of a woman’s risk of stroke associated with pregnancy, gestational hypertension, and hormonal contraception; and the onset of stroke with risk factors such as obesity, hypertension and diabetes mellitus, which occur at younger ages.

• Future research focused on risk profile development is urgently needed to appropriately tailor prevention strategies for women.
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On behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Council for High Blood Pressure Research

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