AHA/ASA Guideline

Guidelines for the Prevention of Stroke in Women

A Statement for Healthcare Professionals from the American Heart
Association/American Stroke Association Council on Stroke
The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists





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Guideline Purpose

The aim of this statement is to summarize data on stroke risk factors that are unique to, and more common in women than men, and to expand upon the data provided in prior stroke guidelines and cardiovascular prevention guidelines for women.



Guideline Experts

- This guideline is composed of experts in women's health:
 - Neurology
 - Neuroscience research
 - Internal Medicine
 - Obstetrics/gynecology
 - Cardiology
 - Pharmacy Nursing epidemiology
 - Public policy



Guideline Goals

- Review risk factors unique to women
- Provide recent primary and secondary prevention recommendations
- Empower women and their families to understand their risk factors
- Determine a need for stroke risk score for women



Sex-Specific Risk Factors

Risk Factor	Sex-specific Risk	Stronger prevalence in women	Similar prevalence in men and women
Pregnancy	Х		
Pre-eclampsia	X		
Gestational diabetes	X		
Oral contraceptive use	Х		
Postmenopausal hormone use	X		
Changes in hormonal status	X		
Migraine with aura		X	
Atrial fibrillation		X	
Diabetes		X	



Sex-Specific Risk Factors- continued

Risk Factor	Sex-specific Risk	Stronger prevalence in women	Similar prevalence in men and women
Hypertension		X	
Physical inactivity			X
Age			X
Prior cardiovascular disease			X
Obesity			X
Diet			X
Smoking			X
Metabolic syndrome			X
Depression		X	
Psychosocial stress		X	



Epidemiology of Stroke in Women

Women are disproportionally affected:

- Women have a higher lifetime risk
- 3.8 million women vs. 3 million in men
- 5th leading cause of death for men, the 3rd for women
- 53.5% of the estimated 795,000 new or recurrent strokes occur in women annually



Mortality

 In the US approximately 60% of stroke related deaths in woman occurred in 2010 (77,109 of 129,476 deaths)

 Age specific stroke mortality is higher for men than women for >85 years



Stroke Awareness Sex Differences

Women:

- Have longer pre-hospital delay than men
- Have higher awareness of stroke signs and symptoms
- Are more likely to know about tPA therapy
- Are less likely to be aware of 3 hour window
- Have overall poor knowledge about CV disease and stroke



Epidemiology Gap Summary

- Ischemic (IS) and hemorrhagic stroke in women
 - Studies report primarily IS
 - Additional research is needed in intracerebral hemorrhage (ICH)
 - Data is limited in terms of sex, race, age specific rates of stroke incidence, mortality and case-fatility



Vascular Stroke Risk

- Hypertension (HTN):
 - Is the most modifiable RF in both men and women
 - Is the major RF for women and first stroke
 - Is higher in post-menopausal years or >55
 years of age
 - Is prevalent in about 78% of women (diagnosed and undiagnosed)
 - Is present in about 75% of women over the age of 60



HTN Prevention Challenges

- No sex specific studies regarding responses to anti-HTN meds
- Variation in prescribed anti-HTN medications
- BP control in elderly women is poor (goal 140/90)
- Women >55 years old on BP treatment would achieve 38% risk reduction of fatal and nonfatal CV events (one meta-analysis of predominantly white women)



HTN Summary and Gaps

Further study needed regarding hormone related BP management

- BP management guidelines should be followed
 - AHA/ASA Guidelines for the Primary Prevention of Stroke, the ESH/ESC Guidelines and JNC-7



HTN Summary and Gaps-continued

 Women should adhere to treatments prescribed by the MD

- Women should follow non-pharmacological interventions for BP management
 - Dietary modification
 - Lifestyle behaviors



Pregnancy and Stroke

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

Due to:

venous stasis

edema

hypercoagulable states

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



Hypertensive Disorders of Pregnancy

Preeclampsia

- Multisystem disorder that includes: hemolysis, elevated liver enzymes, low platelets, DIC, acute renal failure, myocardial infarction, pulmonary edema and stroke may occur
- Increasing BP and proteinuria of >300mg (24 hour urine specimen)

Eclamspia

Is preeclampsia that progresses to seizures



Hypertensive Disorders of Pregnancycontinued

Pregnancy-induced HTN

- Also known as gestational HTN
- Elevation of BP, usually near term
- May or may not progress to preecalmpsia
- Usually resolves by 12 weeks postpartum



Risk Factors of Pregnancy-Induced HTN

- Obesity
- Age (>40 years)
- Chronic HTN
- Personal or family history of preeclampsia
- Gestational HTN
- Nulliparity (first time pregnancy)

- Multiple pregnancy
- Pre-existing vascular disease
- Collagen (connective tissue) vascular disease
- Diabetes
- Renal disease



Treatment of HTN during Pregnancy

- Classification of "Severe hypertension" per the JNC VII report is:
 - BP \geq 160/110 mmHg (same for non-pregnant adults)
 - The above is associated with high risk of stroke and eclampsia
- BP goal during pregnancy:
 - systolic between 130 and 155 mmHG
 - diastolic between 80 and 105 mmHG



Pregnancy Complications and Long-Term Stroke Risk

 Research has suggested that complications during pregnancy (preeclampsia, gestational diabetes and HTN caused by pregnancy) are associated with a higher risk for future CV disease that expands beyond the childbearing years compared to women without these disorders



Long-Term Health Risks resulting from Pregnancy Complications

- Potential health risks post pregnancy complications may include:
 - Renal disease
 - chronic hypertension
 - Type 2 diabetes
 - -CVD
 - Stroke
 - Increased white matter lesions

*CVD event defined as MI, coronary bypass or angiography, stroke or carotid endarterectomy



Class I Recommendations: Prevention of Preeclampsia

Class I Recommendations	Class, (LOE)
Women with chronic primary or secondary hypertension, or previous pregnancy-related hypertension, should take low dose aspirin from the 12 th week of gestation until delivery.	Class I,LOE A
Calcium supplementation (of at least 1g/d, orally) should be considered for women with low dietary intake of calcium (<600 mg/d) to prevent preeclampsia.	Class I,LOE A



Class I Recommendations: Treatment of HTN in Pregnancy and Postpartum

Class I Recommendations	Class, (LOE)
Severe hypertension in pregnancy should be treated with safe and	Class I,
effective antihypertensive medications such as methyldopa,	LOE A
labetalol and nifedipine, with consideration of maternal and fetal	
side effects.	



Class IIa Recommendations: Treatment of HTN in Pregnancy and Postpartum

Class II a Recommendations	Class, (LOE)
Consideration may be given to treatment of moderate hypertension in pregnancy with safe and effective antihypertensive medications, given the evidence for possibly increased stroke risk at currently defined systolic and diastolic bold pressure cutoffs, as well as evidence for decreased risk for the development of severe hypertension with treatment (although maternal-fetal risk/benefit rations have not been established).	Class IIa, LOE B



Recommendations: Treatment of HTN in Pregnancy and Postpartum

Class III Recommendations	Class, (LOE)
Atenolol, ARB's and direct renin inhabitors are contraindicated in	Class III,
pregnancy and should not be used	LOE C
Prevention of Stroke in Women with a History of Preeclampsia	
Class IIa Recommendations	Class, (LOE)
Because of the increased risk of future hypertension and stroke one to	Class IIa,
30 years after delivery in women with a history of preeclampsia (Level	LOE C
of Evidence B) it is reasonable to (1) consider evaluating all women	
starting 6 months to the one year postpartum, as well as those who are	
past childbearing age, for a history of preeclampsia/eclampsia, and	
document their history of preeclampsia/eclampsia as a risk factor, and	
(2) evaluate and treat for cardiovascular risk factors including	
hypertension, obesity, smoking and dyslipidemia.	37.



Class IIa Recommendations: Treatment of HTN in Pregnancy and Postpartum

Class IIa Recommendations	Class, (LOE)
After giving birth, women with chronic hypertension should be continued on their antihypertensive regime, with dosage adjustments to reflect the decrease in volume of distribution and glomerular filtration rate that occurs following delivery, They should also be monitored carefully for the development of postpartum preeclampsia.	Class IIa, LOE C



Cerebral Venous Thrombosis (CVT)

- Stroke type caused by a thrombus formed in the venous sinuses.
 - Presents primarily with a complaint of headache
 - CVT accounts for 0.5-1% of all strokes
 - Incidence higher in women compared to men
 - Overall lower mortality and better functional outcomes than other stroke subtypes



CVT Risk Factors

- Female predominance
 - Hormonal factors
 - Contraceptives
 - Pregnancy
- Thrombophilia link
 - Antithrombin III, protein C, protein S deficiency,
 factor V Leiden



Class I Recommendations: Cerebral Venous Thrombus

Class I Recommendations	Class, (LOE)
In patients with suspected CVT, routine blood studies consisting of a complete blood count, chemistry panel, prothrombin time, and activated partial thromboplastin time should be performed.	Class I,LOE C
Screening for potential prothrombotic conditions that may predispose a person to CVT (eg, use of contraceptives, underlying inflammatory disease, infectious process) is recommended in the initial clinical assessment.	Class I,LOE C
For women with CVT during pregnancy, low molecular weight heparin (LMWH) is full anticoagulant doses should be continued throughout pregnancy, and LMWH or vitamin K antagonist with a target INR of 2.0 to 3.0 should be continued for at least 6 weeks postpartum (for a total minimum duration of therapy of 6 months).	Class I,LOE C

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Class II Recommendations: Cerebral Venous Thrombus

Class IIa Recommendations	Class, (LOE)
Testing for prothrombotic conditions, including protein C, protein S,	Class IIa,
antithrombin deficiency, antiphospholipid syndrome, prothrombin	LOE B
G20210A mutation, and factor V Leiden, can be beneficial for the	
management of patients with CVT. Testing for protein C, protein S, and	
antithrombin deficiency is generally indicated 2 to 4 weeks after	
completion of anticoagulation. There is a very limited value of testing	
in the acute setting or in patients taking warfarin.	
It is reasonable to advise women with a history of CVT that future	Class IIa,
pregnancy is not contraindicated. Further investigations regarding the	LOE B
underlying cause and a formal consultation with a hematologist and	
/or maternal fetal medicine specialist are reasonable.	



Class IIb Recommendations: Cerebral Venous Thrombus

Class III Recommendations	Class, (LOE)
In patients with provoked CVT (associated with a transient risk	Class IIb,
factor), vitamin K antagonists may be continued for 3 to 6 months, with a target INR of 2.0 to 3.0	LOE C
In patients with unprovoked CVT, vitamin K antagonists may be	Class IIb,
continued for 6 to 12 months, with a target INR of 2.0 to 3.0	LOE C
For patients with recurrent CVT, VTE, after CVT, or first CVT with	Class IIb,
severe thrombophilia (ie, homozygous prothrombin G20210A;	LOE C
homozygous factor V Leiden; deficiencies of protein C, protein S or	
antithrombin; combined thrombophilia defects; or	
antiphospholipid syndrome), indefinite anticoagulation me be	
considered, with a target INR of 2.0 to 3.0	



Class IIa Recommendations: Cerebral Venous Thrombus

Class IIa Recommendations	Class, (LOE)
It is reasonable to treat acute CVT during pregnancy with full-dose LMWH rather than UFH	Class IIa, LOE C
For women with a history of CVT, prophylaxis with LMWH during future pregnancies and the postpartum period is reasonable.	Class IIa, LOE C



Oral Contraceptives (OCs)

- Stroke risk with low dose OCs users is about
 1.4 to 2.0 times that of non-OC users
- Stroke risk is low but increases with age
- Other contraception: (need future evaluation of stroke risk)
 - Transderm patch
 - Vaginal ring
 - Intrauterine devices (IUDs)



Subgroups at Higher Risk of Stroke with Oral Contraceptives (OCs)

- -Older women
- Smoke cigarettes
- Have hypertension
- Diabetes
- Obesity
- Hypercholesterolemia
- Prothrombotic mutations



Class I Recommendations: Oral Contraceptives

Class I Recommendations	Class, (LOE)
Measurement of blood pressure prior to initiation of hormonal	Class I,
contraception is recommended.	LOE B
contraception is recommended.	LOE B



Class III Recommendations: Oral Contraceptives

Class III Recommendations	Class, (LOE)
OCs may be harmful in women with additional risk factors (e.g. cigarette smoking, prior thromboembolic events.	Class III, LOE B
Routine screening for prothrombotic mutations prior to initiation of hormonal contraception is not useful	Class III, LOE A



Class IIb Recommendations: Oral Contraceptives

Class IIb Recommendations	Class, (LOE)
Among OC users, aggressive therapy of stroke risk factors may be reasonable.	Class I, LOE C



Recommendations: Menopause and Postmenopausal Hormone Therapy

Class III Recommendations	Class, (LOE)
Hormone therapy (conjugated equine estrogen) with or without	Class III
medroxyprogesterone) should not be used for primary or secondary	LOE A
prevention of stroke in postmenopausal women.	
Selective estrogen receptor modulators, such as raloxifene,	Class III
tamoxifen, or tibolone, should not be used for primary prevention of	LOE A
stroke.	



Migraine with Aura

- Defined as a typical migraine headache with the addition of:
 - -homonymous visual disturbance
 - -unilateral paresthesia's
 - -numbness
 - -unilateral weakness
 - -aphasia or unclassified speech disturbance



Migraine with Aura

- Migraine alone:
 - aggregate prevalence about 18.5%
 - Women four times more likely over men
- Migraine plus aura:
 - Prevalence approximately 4.4%
 - results in a 2.5% increase in ischemic stroke risk
 - Stroke risk increases with oral contraceptive use



Migraine with Aura

Migraine with Aura:

- Increases stroke risk with frequency
- Is associated with risk of IS and ICH in women especially under the age of 55 years (but risk is low)
- May be included in future risk profiles
- Is linked with milder strokes and TIA's



Recommendations: Migraine with Aura

Class IIb Recommendations	Class, (LOE)
Because there is an association between higher migraine frequency	Class IIb
and stroke risk, treatments to reduce migraine frequency might be	LOE C
reasonable, through evidence is lacking that this treatment reduces	
the risk of first stroke.	
Class IIa Recommendations	Class, (LOE)
Due to the increased stroke risk seen in women with migraine	Class IIa
headaches with aura and smoking, it is reasonable to strongly	LOE B
recommend smoking cessation in women with migraine headaches	
and aura.	



Obesity

- By 2030 it is estimated that 86% of Americans will be overweight or obese
- Higher stroke risk associated with increasing BMI
- Postmenopausal women are likely to have abdominal obesity.
- The larger the waist circumference
 - the greater the chance of stroke
 - associated with insulin resistance



Obesity

- Obesity:
 - Is a risk factor for stroke (after considering other risk factors such as age, physical activity, smoking, alcohol consumption, diabetes and HTN
 - Epidemic may counter other advances made in smoking cessation, HTN and dyslipidemia awareness in the US
 - Is highly prevalent in non-hispanic black women



Metabolic Syndrome (MetSD)

- Affects 1/3 of the US population
- Stroke events in women (30% vs 4%) over men with Met SD
- Characterized as:
 - Abdominal adiposity
 - Dyslipidemia
 - Hypertension
 - Insulin resistance



Lifestyle

- Adherence to healthy lifestyle behaviors has shown to decrease stroke incidence in women.
- Lifestyle behaviors include:
 - Healthy diet
 - Physical activity
 - Moderate alcohol intake
 - Abstinence from smoking
 - Healthy BMI



Recommendations: Obesity, Metabolic Syndrome and Lifestyle

Class I Recommendations	Class, (LOE)
A healthy lifestyle consisting of regular physical activity, moderate	Class I,
alcohol consumption (< 1drink per day for non-pregnant women),	LOE B
abstention from cigarette smoking, a diet rich in fruit, vegetables,	
grains, nuts, olive oil and low saturated fat is recommended for primary	
stroke prevention in women with cardiovascular risk factors.	
Lifestyle interventions focusing on diet and exercise are recommended	Class I,
for Primary stroke prevention among individuals at high risk for stroke	LOE B



Atrial Fibrillation (AF)

- Most common arrhythmia
- Modifiable stroke risk factor
- AF increases stroke risk (4-5 fold)
- AF stroke associates with higher death and disability
- Stroke risk From AF increases with age
 - 1.5% for persons 50-59 years
 - 25% for persons 80 years or older



Atrial Fibrillation (AF) - continued

- Non-Hispanic whites have the highest prevalence of AF compared to Blacks, Hispanic whites, Asians or other ethnic groups.
- Overall number of AF cases are equal between men and women
- 60% of AF patients over 75 are women



Risk Stratification for Women with AF

CHADS2 Risk Stratification Tool		
CHF	1 POINT	
HTN	1 POINT	
AGE ≥ 75	1 POINT	
DIABETES MELLITUS	1 POINT	
PRIOR STROKE/TIA	2 POINTS	

 Risk assessment of women for stroke should take into account age and sex-specific differences

STROKE RISK SCORE		
0 POINT LOW RISK		
1 POINT	MODERATE RISK	
≥2 POINTS	HIGH RISK	



Risk Stratification for Women with AF - continued

- Female sex is an independent predictor of stroke in patients with AF.
- CHA2DS2-Vasc score is an extension of the CHADS2 adding extra points for female sex

CHA2DS2-VASc Risk Stratification Tool		
Female Sex	1 POINT	
Hx MI, PAD, or AORTIC PLAQUE	1 POINT	
AGE 65-74	1 POINT	
AGE > 75	2 POINT	
EJECTION FRACTION < 35	(pending presently under consideration)	



Anticoagulation and AF

- Anticoagulation is the most effective treatment strategy to decrease the risk of stroke
- Risk stratification tools such as CHADS-VASc are useful to stratify risk of stroke thus assisting clinicians with initiating anticoagulation therapies.



Recommendation: Atrial Fibrillation

Class I Recommendations	Class, (LOE)
New oral anticoagulants are a useful alternative to warfarin for the	Class I,
prevention of stroke and systemic thromboembolism in women with	LOE A
paroxysmal or permanent AF and pre-specified risk factors (according to	
CHADS2-VASc) who do not have a prosthetic heart valve or	
hemodynamically significant valve disease, severe renal failure	
(creatinine clearance 15 mL/min., lower weight (<50 kg), or advanced	
liver disease (impaired baseline clotting function).	
Considering the increased prevalence of AF with age and the higher risk	Class I,
of stroke in elderly women with AF, active screening-in particular of	LOE B
women >75 years of age-in primary care settings using pulse taking	
followed by an ECG as appropriate is recommended.	
Risk stratification tools in AF that account for age-and sex-specific	Class I, LOE A
differences in the incidence of stroke are recommended. Class I, Level of	
evidence A.	
	55



Recommendations: Atrial Fibrillation

Class IIa Recommendations	Class, (LOE)
Oral anticoagulation in women aged 65 and younger with AF alone	Class IIa,
(no other risk factors) (Note: women with CHADS2=0 or	LOE B
CHADS2-VASc =1) is not recommended	
(Class III, Level of Evidence B)	
Antiplatelet therapy is a reasonable therapeutic option for	
selected low-risk women	



Depression and Psychosocial Stress

 Depression increases the risk of stroke on both men and women

Psychlogical stress incurs a 30% higher risk of stroke

 Women should be assessed for depression and psychosocial stress since both are more common in women



Recommendation: Depression and Psychosocial Stress

 Further research is needed to determine the mechanisms underlying the association between depression and stroke as well as to test whether depression might contribute to a stroke risk prediction score in women.



Women in Stroke Clinical Trials

- Women account for < ½ of subjects enrolled in NIH stroke prevention clinical drug trials
- Low participation of women in stroke prevention clinical trials limits the generalization of results
- Women have been under-represented in clinical trials related to:
 - Surgery
 - Overall cardiovascular disease
 - Cancer



Representation of Women in Clinical Trials

This paper recommends the inclusion of women into all primary and secondary stroke prevention clinical trials to obtain statistical power to provide future valid recommendations.

Representation of Women in Carotid		Representation of Women in Antiplatelet Tria	
Intervention Tr	Total patients enrolled (% of women)	TRIAL	Total patients enrolled (% of women)
NASCET	663 (32)	ACE	2806 (30)
NASCET		ESPC- 2	6604 (42)
moderate	2303 (29)	CAPRIE	15480 (30)
ECST	3035 (28)	МАТСН	7624 (37)
ACAS	1662 (34%)	AAASPS	1824 (53)
ACST	3165 (34)	ESPRIT	2714 (35)
EVA-3s	520 (25%)	ProFESS	20438 (37)
SPACE	1207 (28%)	SPS3	3021 (37)
CREST	2491 (35)		



Carotid Stenosis

- Gender differences:
 - Women have smaller caliber ICA's
 - Women have shorter stenotic segments
 - Carotid endarterectomy (CEA) is performed less often in women (36.4% vs.53.8% in men)
 - Being female is an independent predictor of not receiving a CEA



Medical and Surgical Management of Carotid Stenosis

 Women appeared to derive less benefit from surgery (comparing medical mgmt. to surgical)

 Benefits and risks of carotid procedures in women with high grade stenosis remain unanswered.



Class I Recommendations	Class, (LOE)
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	Class I, LOE C
In women who are to undergo CEA, aspirin is recommended unless contraindicated, because aspirin was used in every major trial that demonstrated efficacy of CEA	Class I, LOE C
For women with recent TIA or IS and ipsilateral moderate (50%-69%) carotid stenosis, CEA is recommended depending on patient-specific factors, such as age and comorbidities, if the perioperative morbidity and mortality risk is estimated to be <6%.	Class I, LOE B



Class I Recommendations	Class, (LOE)
For women with recent TIA or IS within the past 6 months and ipsilateral severe (70%-99%) carotid artery stenosis, CEA is recommended if the perioperative morbidity and mortality risk is estimated to be <6%.	Class I, LOE A
If a high-risk (i.e. 10 year predicted CVD risk ≥10-%) women has an indication for aspirin but is intolerant of aspirin therapy, clopidogrel should be substituted.	Class I, LOE B



Class IIa Recommendations	Class, (LOE)
Prophylactic carotid endarterectomy performed with <3%	Class IIa,
morbidity/mortality can be useful in highly selected patients with an	LOE A
asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasound).	
The benefit of surgery may now be lower than anticipated based on	
randomized trial results, and the cited 3% threshold for complication	
rates may be high owing to interim advances in medical therapy.	
Aspirin therapy (75-325 mg/d is reasonable in women with diabetes	Class IIa,
mellitus unless contraindicated.	LOE B
When CEA is indicated for women with TIA or stroke, surgery within 2	Class IIa,
weeks is reasonable rather that delaying surgery if there are no contraindications to early revascularization.	LOE B



Class IIb Recommendations	LOE
Aspirin therapy can be useful in women ≥ 65 years of age (81 mg daily or 100 mg every other day) if blood pressure is controlled and benefit for ischemic and myocardial infarction prevention is likely to outweigh risk of gastrointestinal bleeding and hemorrhagic stroke (Class IIa Level of Evidence B) and may be reasonable for women <65 years of age for ischemic stroke prevention.	Class IIb, LOE B



Stroke Risk Factors Unique to Women in Review

- Pregnancy factors
 - Pre-clampsia
- Hormonal exposure
 - Oral contraceptives, postmenopausal hormone therapy
- Changes in hormone status across the lifespan
- Menarche, menopause an oophorectomy
- Depression
- Atrial fibrillation in the elderly



Conclusion/Summary

- Improve the accuracy of stroke risk assessment
- Assess stroke risk in women with a history of pre-eclampsia and other pregnancy-related complications.
- Prospective data on the long-term stroke risk with pregnancy complications is needed.
- Development of stroke prediction models



Conclusion/Summary

- Future epidemiological studies on:
 - Stroke substypes, especially hemorrhagic stroke
 - Age
 - Sex
- Improve stroke awareness at younger ages:
 - stroke risk factors, obesity, HTN, and diabetes at younger ages
 - risks associated with pregnancy, gestational HTN, hormonal contraception etc.



Conclusion/Summary

- Future focus on risk profile development and tailor prevention strategies for women
- Recognition of sex-specific stroke risk factors and a risk score that includes these factors.