


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.


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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


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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


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Sex-Specific Risk Factors

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


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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	

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Epidemiology of Stroke in Women

Women are disproportionately 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


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Mortality

- In the US, in 2010, approximately 60% of stroke related deaths occurred in woman (77,109 of 129,476 deaths)
- Age specific stroke mortality is higher for men than women across all groups except ≥ 85 years. This is consistent across all race-ethnic groups.


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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


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Epidemiology Gap Summary

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


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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


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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 non-fatal CV events (one meta-analysis of predominantly white women)


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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


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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


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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


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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


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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


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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 effective antihypertensive medications such as methyldopa, labetalol and nifedipine, with consideration of maternal and fetal side effects.	Class I, LOE A


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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 blood pressure cutoffs, as well as evidence for decreased risk for the development of severe hypertension with treatment (although maternal-fetal risk/benefit ratios have not been established).	Class IIa, LOE B

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Recommendations: Treatment of HTN in Pregnancy and Postpartum

Class III Recommendations	Class, (LOE)
Atenolol, ARB's and direct renin inhibitors are contraindicated in pregnancy and should not be used	Class III, 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 30 years after delivery in women with a history of preeclampsia (Level 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.	Class IIa, LOE C



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



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)


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

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


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Class I Recommendations: Oral Contraceptives

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


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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


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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

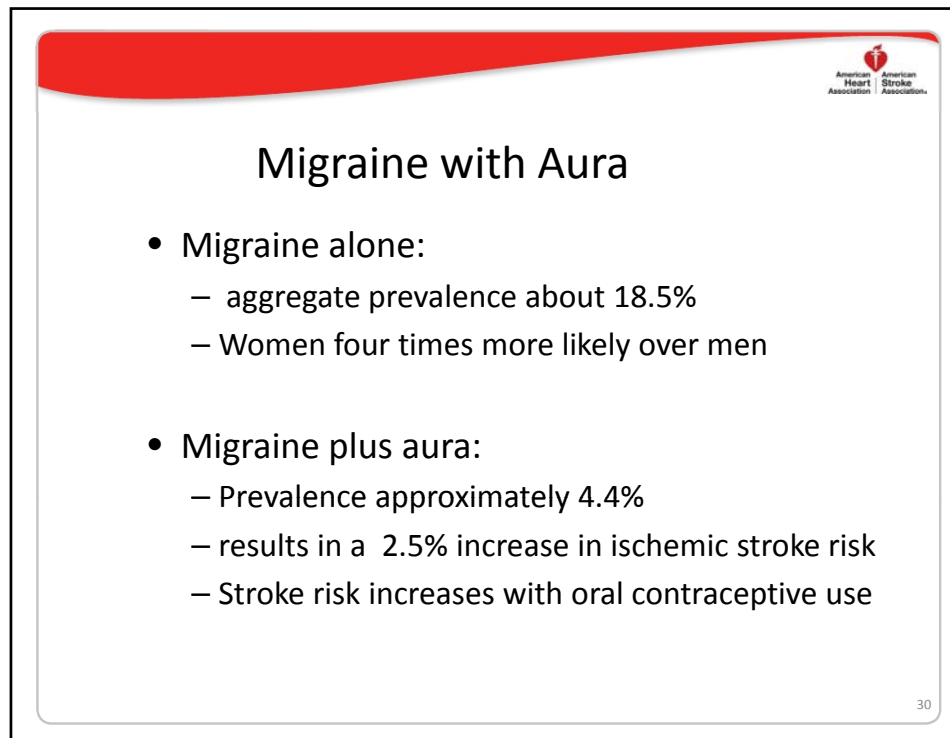
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Recommendations: Menopause and Postmenopausal Hormone Therapy

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

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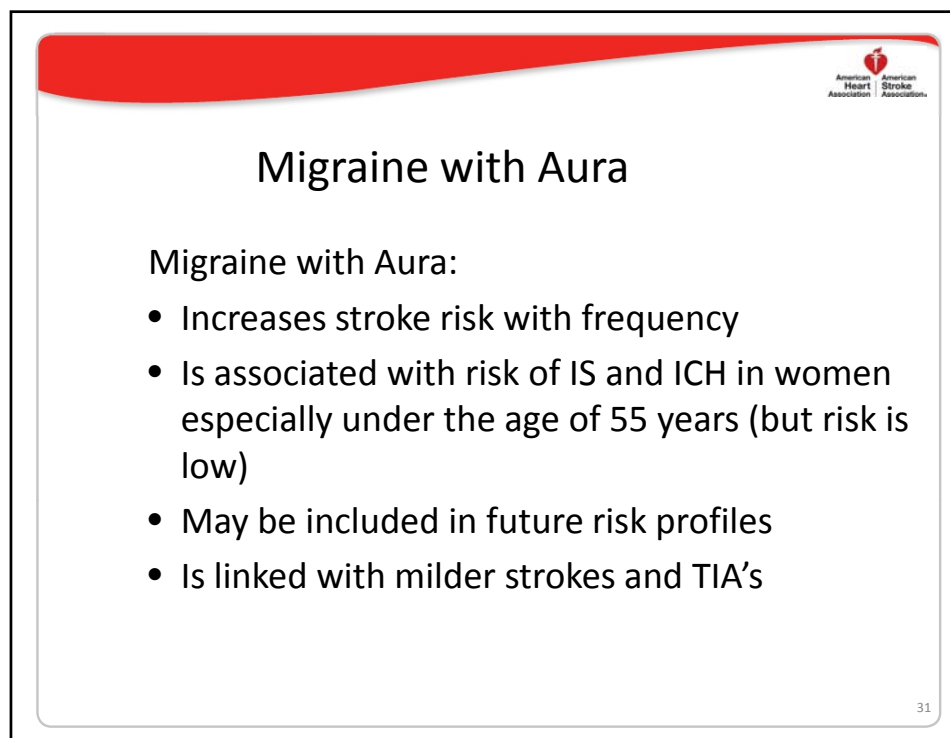


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Migraine with Aura

- 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

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A slide titled "Migraine with Aura" with a red decorative header. The slide contains a section header "Migraine with Aura:" followed by a bulleted list of clinical implications. The American Heart Association and American Stroke Association logos are in the top right corner. The number 31 is in the bottom right corner.

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


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Recommendations: Migraine with Aura

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


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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


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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

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Risk Stratification for Women with AF

CHADS2 Risk Stratification Tool	
CHF	1 POINT
HTN	1 POINT
AGE \geq 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
\geq 2 POINTS	HIGH RISK

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Risk Stratification for Women with AF - continued

- Female sex is an independent predictor of stroke in persons 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)


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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.

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Recommendation: Atrial Fibrillation

Class I Recommendations	Class, (LOE)
New oral anticoagulants are a useful alternative to warfarin for the prevention of stroke and systemic thromboembolism in women with 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).	Class I, LOE A
Considering the increased prevalence of AF with age and the higher risk of stroke in elderly women with AF, active screening-in particular of women >75 years of age-in primary care settings using pulse taking followed by an ECG as appropriate is recommended.	Class I, LOE B
Risk stratification tools in AF that account for age-and sex-specific differences in the incidence of stroke are recommended. Class I, Level of evidence A.	Class I, LOE A



Recommendations: Atrial Fibrillation


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



Depression and Psychosocial Stress

- Depression increases the risk of stroke on both men and women
- Psychological stress incurs a 30% higher risk of stroke
- Women should be assessed for depression and psychosocial stress since both are more common in women


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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.


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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

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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 Intervention Trials		Representation of Women in Antiplatelet Trials	
TRIAL	Total patients enrolled (% of women)	TRIAL	Total patients enrolled (% of women)
NASCET	663 (32)	ACE	2806 (30)
NASCET moderate	2303 (29)	ESPC- 2	6604 (42)
ECST	1535 (28)	CAPRIE	15480 (30)
ACAS	1662 (34%)	MATCH	7624 (37)
ACST	3165 (34)	AAASPS	1824 (53)
EVA-3s	520 (25%)	ESPRIT	2714 (35)
SPACE	1207 (28%)	ProFESS	20438 (37)
CREST	2502 (35)	SPS3	3021 (37)


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Stroke Risk Factors Unique to Women in Review

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

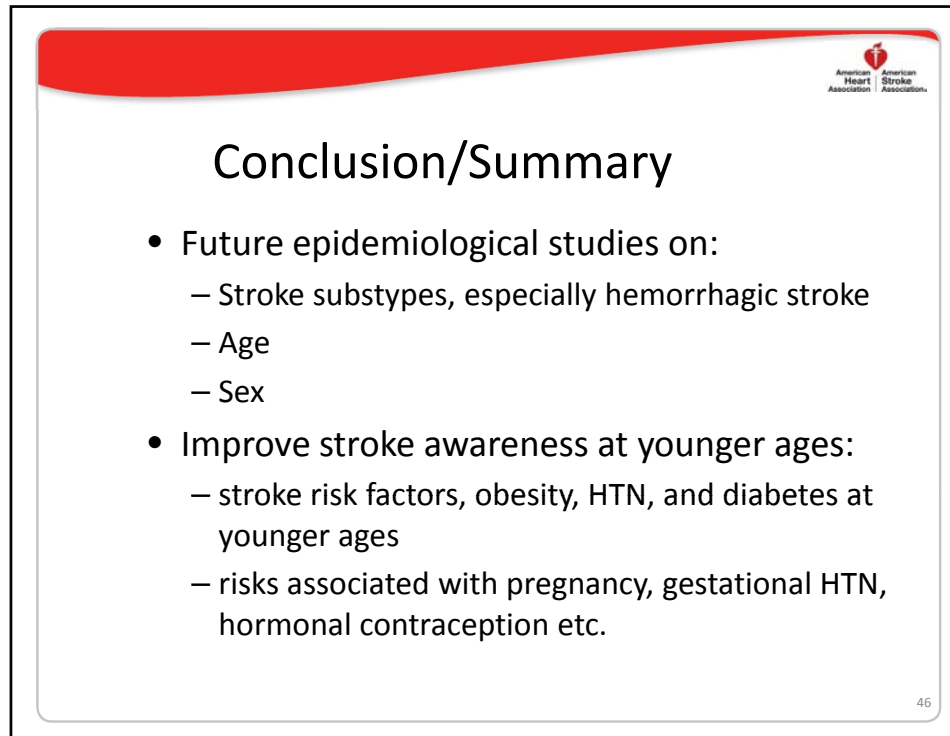
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Conclusion/Summary

- 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

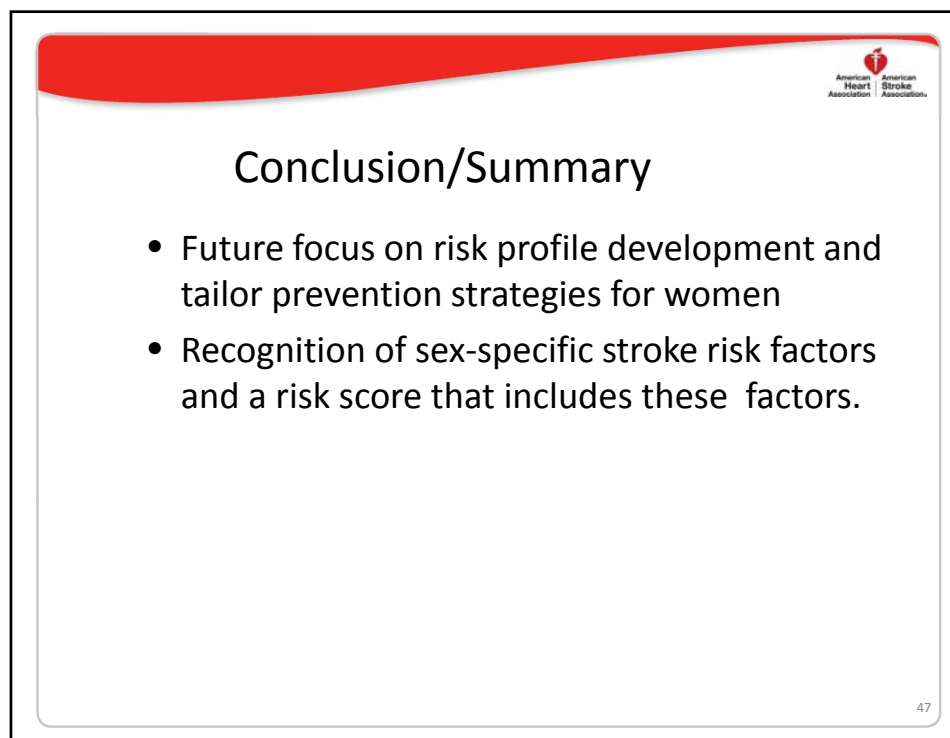
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Slide 46 features a red decorative header at the top. In the top right corner, there are logos for the American Heart Association and the American Stroke Association. The main title is "Conclusion/Summary". The content consists of two main bullet points with sub-points:

- Future epidemiological studies on:
 - Stroke subtypes, 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.

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Slide 47 features a red decorative header at the top. In the top right corner, there are logos for the American Heart Association and the American Stroke Association. The main title is "Conclusion/Summary". The content consists of two main bullet points:

- 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.

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