

## Guidelines for the Prevention of Stroke in Women A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

*The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons*

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**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 on the data provided in prior stroke guidelines and cardiovascular prevention guidelines for women. This guideline focuses on the risk factors unique to women, such as reproductive factors, and those that are more common in women, including migraine with aura, obesity, metabolic syndrome, and atrial fibrillation.

**Methods**—Writing group members were nominated by the committee chair on the basis of their previous work in relevant topic areas and were approved by the American Heart Association (AHA) Stroke Council's Scientific Statement Oversight Committee and the AHA's Manuscript Oversight Committee. 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. The document underwent extensive AHA internal peer review, Stroke Council Leadership review, and Scientific Statements Oversight Committee review before consideration and approval by the AHA Science Advisory and Coordinating Committee.

**Results**—We provide current evidence, research gaps, and recommendations on risk of stroke related to preeclampsia, oral contraceptives, menopause, and hormone replacement, as well as those risk factors more common in women, such as obesity/metabolic syndrome, atrial fibrillation, and migraine with aura.

**Conclusions**—To more accurately reflect the risk of stroke in women across the lifespan, as well as the clear gaps in current risk scores, we believe a female-specific stroke risk score is warranted. (*Stroke*. 2014;45:000-000.)

**Key Words:** AHA Scientific Statements ■ atrial fibrillation ■ hormone replacement therapy ■ menopause ■ metabolic syndrome X ■ preeclampsia/eclampsia ■ sex differences ■ stroke

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on December 13, 2013. A copy of the document is available at <http://my.americanheart.org/statements> by selecting either the "By Topic" link or the "By Publication Date" link. To purchase additional reprints, call 843-216-2533 or e-mail [kelle.ramsay@wolterskluwer.com](mailto:kelle.ramsay@wolterskluwer.com).

The American Heart Association requests that this document be cited as follows: Bushnell C, McCullough LD, Awad IA, Chireau MV, Fedder WN, Furie KL, Howard VJ, Lichtman JH, Lisabeth LD, Piña IL, Reeves MJ, Rexrode KM, Saposnik G, Singh V, Towfighi A, Vaccarino V, Walters MR; 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. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:000-000.

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DOI: 10.1161/01.str.0000442009.06663.48

Stroke has a large negative impact on society, with women disproportionately affected. An estimated 6.8 million (2.8%) of people in the United States are living after having had a stroke, including 3.8 million women and 3 million men.<sup>1</sup> Stroke is the fifth-leading cause of death for men, but the third leading cause for women.<sup>2</sup> By 2030, there will be an estimated 72 million people >65 years old (19% of the population), and women will increasingly outnumber men.<sup>3</sup> These demographics suggest an anticipated increase of the burden of stroke in women.<sup>4</sup> Nearly half of stroke survivors have residual deficits, including weakness or cognitive dysfunction, 6 months after stroke,<sup>5</sup> which translates into ≈200 000 more disabled women with stroke than men. Some of the impact is explained by the fact that women live longer, and thus the lifetime risk of stroke in those aged 55 to 75 years is higher in women (20%) than men (17%).<sup>6</sup> Women are more likely to be living alone and widowed before stroke, are more often institutionalized after stroke, and have poorer recovery from stroke than men.<sup>7–13</sup> Therefore, women are more adversely affected by stroke than men. How our society adapts to the anticipated increase in stroke prevalence in women is vitally important. Now more than ever, it is critical to identify women at higher risk for stroke and initiate the appropriate prevention strategies.

Despite the importance of stroke in women, there has never been an American Heart Association (AHA)/American Stroke Association guideline dedicated to stroke risk and prevention in women. This endeavor is important because women differ from men in a multitude of ways, including genetic differences in immunity,<sup>14,15</sup> coagulation,<sup>16,17</sup> hormonal factors,<sup>18</sup> reproductive factors including pregnancy and childbirth, and social factors,<sup>5,9</sup> all of which can influence risk for stroke and impact stroke outcomes. This document provides a new stroke prevention guideline that covers topics specific to women in more detail than has been included in current primary and secondary stroke prevention guidelines<sup>19,20</sup> and provides more emphasis on stroke-specific issues in women than are included in the current cardiovascular prevention guideline for women.<sup>21</sup>

Writing group members were nominated by the committee chair on the basis of their previous work in relevant topic areas and were approved by the AHA Stroke Council's Scientific Statement Oversight Committee and the AHA's Manuscript Oversight Committee. Multiple disciplines are represented, including 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 (Tables 1 and 2). The document underwent extensive AHA internal peer review, Stroke Council Leadership review, and Scientific Statements Oversight Committee review before consideration and approval by the AHA Science Advisory and Coordinating Committee. Each topic was assigned to a primary author

and a secondary reviewer. In this guideline, we focus on the risk factors unique to women, such as reproductive factors, and those that are more common in women, including migraine with aura, obesity, metabolic syndrome, and atrial fibrillation (AF). Topics that are not covered in detail include management of diabetes mellitus and cholesterol, because there are no recommendations for these risk factors that are specific to women. We therefore direct readers to the most recent primary and secondary prevention guidelines for specific detailed recommendations.<sup>19,20</sup>

One of the writing group's goals was to review risk factors that are unique to women or might affect women's risk of stroke differentially, as well as to determine whether there is a need for a stroke risk score for women that incorporates female-specific factors such as reproductive and menopausal factors (Table 3). Recommendations that are unique to women are included, as well as gaps in knowledge where additional research is needed to inform risk identification and thus improve stroke prevention in women. To demonstrate the importance of enhancing stroke risk scores for women, we have reviewed existing stroke risk scores and assessed their relevance on the basis of our summary of the literature on specific risk factors. Evidence from this guideline will inform providers and researchers of the current understanding of stroke risk and prevention in women. More importantly, this guideline may empower women and their families to understand their own risk and how they can minimize the chances of having a stroke.

## Epidemiology of Ischemic and Hemorrhagic Stroke in Women

### Overview

In the United States, more than half (53.5%) of the estimated 795 000 new or recurrent strokes occur among women annually, resulting in ≈55 000 more stroke events in women than men.<sup>1</sup> Results from the Framingham cohort show that women have a higher lifetime risk of stroke than men.<sup>6,12</sup> Although stroke incidence rates have declined, data suggest that the decline may be smaller for women than men.<sup>22–24</sup> Data from epidemiological studies demonstrate that the majority (87%) of strokes are ischemic (IS), with the remainder hemorrhagic (10% intracerebral [ICH] and 3% subarachnoid [SAH]).<sup>1</sup> With an anticipated increase in the aging population, the prevalence of stroke survivors is projected to increase, particularly among elderly women.<sup>4</sup> Because the United States lacks a national surveillance system for cardiovascular disease (CVD),<sup>25</sup> and sex-specific or age- and sex-specific stroke incidence data have not been routinely reported in published studies, there are important gaps in our understanding of sex differences in incident and recurrent stroke events, temporal patterns of stroke events, and outcomes after stroke. Most of what is known about the epidemiology of stroke comes from mortality data. As noted previously, the higher stroke mortality for women is often attributed to the longer life expectancy of women. Of 128 842 deaths related to stroke in 2009, 76 769 (59.6%) occurred in women.<sup>1</sup>

Table 1. Applying Classification of Recommendation and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT				
	CLASS I Benefit >>> Risk Procedure/Treatment <b>SHOULD</b> be performed/ administered	CLASS IIa Benefit >> Risk Additional studies with focused objectives needed <b>IT IS REASONABLE</b> to per- form procedure/administer treatment	CLASS IIb Benefit ≥ Risk Additional studies with broad objectives needed; additional registry data would be helpful  Procedure/Treatment <b>MAY BE CONSIDERED</b>	CLASS III No Benefit or CLASS III Harm	
				Procedure/ Test	Treatment
				COR III: No benefit	No Proven Benefit
				COR III: Harm	Excess Cost w/o Benefit or Harmful to Patients
<b>LEVEL A</b> Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Some conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Greater conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>	
<b>LEVEL B</b> Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Some conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Greater conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Evidence from single randomized trial or nonrandomized studies</li> </ul>	
<b>LEVEL C</b> Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Only expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Only diverging expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Only diverging expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Only expert opinion, case studies, or standard of care</li> </ul>	
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit  is not recommended is not indicated should not be performed/ administered/ other  is not useful/ beneficial/ effective	COR III: Harm  potentially harmful causes harm associated with excess morbid- ity/mortality should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B			

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

\*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

## Incidence

### Ischemic Stroke

Within most age strata, women have a lower IS incidence than men, and as such, the overall age-adjusted incidence of IS is lower for women than men<sup>4,24,26–31</sup>; however, sex differences in IS incidence rates differ across the age strata. In the oldest age groups (generally >85 years of age), women tend to have higher<sup>12,24,27–30</sup> or similar incidence of IS as men.<sup>4,26</sup> Because women tend to be older when they have their stroke events, and women have a longer life expectancy than men, age-adjusted rates can be misleading and may underestimate the total burden of stroke in women. Differences by race/ethnicity

have also been noted, with higher rates among blacks and Hispanics<sup>31</sup> than among whites for both women and men.<sup>1,28–31</sup>

### Hemorrhagic Stroke (SAH and ICH)

The majority of studies show that women have higher rates of SAH incidence than men<sup>26,32–43</sup>; however, sex differences are modified by age such that SAH rates are higher in men at younger ages but higher in women relative to men beginning at ≈55 years of age.<sup>44,45</sup> Data reported from non-US populations have shown differing sex-related patterns across countries, with higher SAH incidence among men in Finland and eastern Europe, possibly because of regional differences in risk factor prevalence in men and women.<sup>46</sup> The incidence



**Table 2. Definition of Classes and Levels of Evidence Used in AHA/ASA Recommendations**

Class I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective.
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
Class IIa	The weight of evidence or opinion is in favor of the procedure or treatment.
Class IIb	Usefulness/efficacy is less well established by evidence or opinion.
Class III	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful.
Therapeutic recommendations	
Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of Evidence B	Data derived from a single randomized trial or nonrandomized studies
Level of Evidence C	Consensus opinion of experts, case studies, or standard of care
Diagnostic recommendations	
Level of Evidence A	Data derived from multiple prospective cohort studies using a reference standard applied by a masked evaluator
Level of Evidence B	Data derived from a single grade A study or 1 or more case-control studies, or studies using a reference standard applied by an unmasked evaluator
Level of Evidence C	Consensus opinion of experts

AHA/ASA indicates American Heart Association/American Stroke Association.

of ICH has been reported to be lower in women than men in most<sup>26,39–41,47</sup> but not all<sup>42</sup> studies. Differences by race/ethnicity have been noted, with higher ICH incidence rates in blacks than whites<sup>30,31,48</sup> and in Hispanics than whites for both women and men.<sup>31</sup>

#### **Increased Prevalence of SAH in Women: Risks Related to Cerebral Aneurysms**

There has been significant debate about the potential cause of the increased risk of SAH in women. Autopsy and angiographic studies have documented a higher prevalence of cerebral aneurysms in women,<sup>49</sup> as well as a higher risk of rupture.<sup>50</sup> These findings are in agreement with results of a recent study from the Nationwide Inpatient Sample, which claimed that more than twice as many women as men were discharged with both ruptured and unruptured cerebral aneurysms.<sup>51</sup> There is also a difference in the distribution of aneurysm locations in women versus men, and this may convey a higher hemorrhagic risk, especially with greater prevalence of aneurysms at the posterior communicating artery.<sup>52</sup> Other studies have suggested similar trigger factors for aneurysm rupture in men and women.<sup>53</sup> There is also no convincing evidence of increased risk of aneurysmal SAH in pregnancy or the puerperium,<sup>54</sup> and before age 50 years, aneurysmal SAH

**Table 3. Stroke Risk Factors, Categorized by Those That Are Sex-Specific, Stronger or More Prevalent in Women, or Similar Between Women and Men**

Risk Factor	Sex-Specific Risk Factors	Risk Factors That Are Stronger or More Prevalent in Women	Risk Factors With Similar Prevalence in Men and Women but Unknown Difference in Impact
Pregnancy	X		
Preeclampsia	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 mellitus		X	
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	

is more common in men.<sup>55</sup> A population-based case-control study showed that the risk of SAH was lower in women with first pregnancy after 23 years of age and in those who had ever used hormone therapy (HT).<sup>56</sup> The literature certainly confirmed a higher incidence of SAH and a higher prevalence of cerebral aneurysms in women, but not necessarily a higher risk for rupture of aneurysms with similar characteristics.

#### **Prevalence**

On the basis of self-report data from the US 2010 National Health Interview Survey, it is estimated that just more than half (51.8%, 3.223 million) of the 6.226 million adults (3%) in the United States who have been told they had a stroke were women.<sup>57</sup> Data from the Behavioral Risk Factor Surveillance System for the time period 2006 to 2010 showed that the age-adjusted self-reported prevalence of stroke survivors did not change significantly for women (2.5%–2.6%), whereas it did for men, with prevalence declining from 2.8% in 2006 to 2.5% in 2009 and then increasing to 2.7% in 2010.<sup>58</sup>

#### **Mortality**

In the United States, ≈60% of deaths related to stroke in 2010 occurred in women (77 109 of 129 476 deaths).<sup>1,2,59</sup>

Age-specific stroke mortality is higher for men than women for all age groups except  $\geq 85$  years, and this pattern is consistent across all racial/ethnic groups (Figures 1 and 2).<sup>1,2,59</sup> In 2010, age-adjusted stroke mortality (based on *International Classification of Diseases, 10th Revision*, codes I60–I69) for women was 38.3 per 100 000 compared with 39.3 per 100 000 for men (relative risk [RR], 0.97).<sup>59</sup> For most of the past century, age-adjusted stroke mortality rates declined dramatically in the United States,<sup>60</sup> and between 1996 and 2005, these declines were marginally greater for men (–28.2%) than women (–23.9%).<sup>1,61</sup> Stroke is a major cause of death worldwide, accounting for an estimated 10% of all deaths in 2002. Similar to the United States, women worldwide have lower stroke mortality than men except in the older age groups,<sup>62–65</sup> and IS mortality has declined for both men and women, with some acceleration in the rate of decline in the 1990s for certain age-sex groups.<sup>66</sup>

### Ischemic Stroke

An analysis of US death certificate data from 1995 to 1998 found that IS constitutes a larger percentage of stroke mortality overall in women than men (82% of stroke deaths in women versus 78% in men), with the greatest difference seen for older women.<sup>67</sup> The overall age-adjusted IS death rate in women is slightly lower (74.3 per 100 000 compared with 78.8 per 100 000 for men; RR, 0.94; 95% confidence interval [CI], 0.93–0.95). Younger women have lower age-specific IS mortality than men, but there is a crossover at  $\approx 65$  years of age, at which point older women have higher age-specific IS mortality than men.<sup>67</sup> This study also reported that the age-adjusted death rate for IS was higher for white women than white men (RR, 1.21; 95% CI, 1.21–1.22), but for all other racial/ethnic groups, the age-adjusted death rate for IS was lower or similar for women and men.<sup>67</sup>

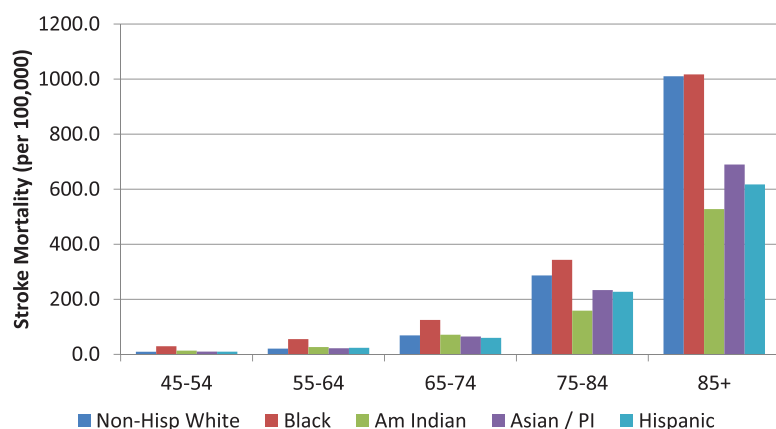
### Hemorrhagic Stroke

Women have higher age-adjusted SAH mortality than men (4.9 versus 3.1 per 100 000; RR, 1.59; 95% CI, 1.54–1.62).<sup>67</sup> Sex differences persisted across racial/ethnic groups and were highest among Asian Americans. In addition, the risk ratio of mortality in women versus men increased with age.<sup>67,68</sup> In contrast to SAH, women have lower age-adjusted ICH mortality rates than men (13.3 per 100 000 for women and 16.2 per 100 000 for men; RR, 0.82; 95% CI, 0.81–0.83). Mortality was lower for women aged  $<65$  years, but there

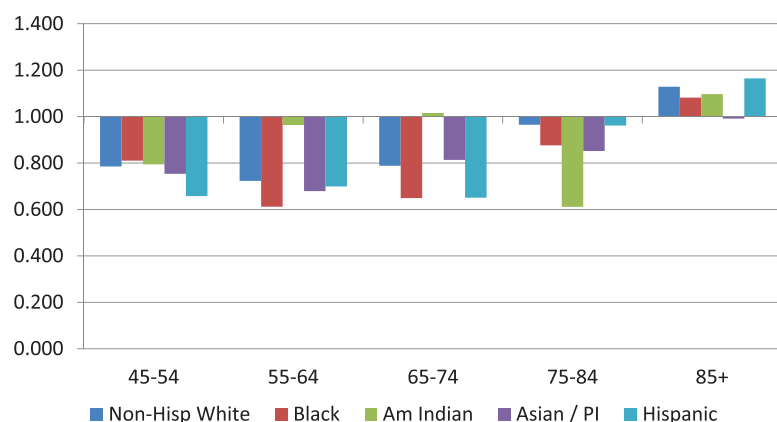
was no sex difference in ICH mortality risk for adults  $\geq 65$  years of age.<sup>67</sup>

### Total Stroke Case Fatality

The findings of studies that have examined sex differences in short-term case-fatality rates (commonly defined as within 30 days of onset and inclusive of all strokes) have been quite variable and are complicated by a lack of age adjustment. Some studies have reported that women have higher case fatality than men,<sup>26,27,30,69,70</sup> whereas others have not.<sup>9,13,42,71</sup> Although a recent systematic review found that short-term case fatality was higher in women than men in 26 of 31 studies (with a pooled rate of 24.7% versus 19.7%),<sup>26</sup> these results were based on crude unadjusted data. Much of the higher case fatality in women is likely to be attributable to the fact that women tend to be older at the time of their stroke.<sup>4</sup> Studies that have adjusted for age (as well as other characteristics) show that the sex difference in short-term mortality can actually reverse, with women having lower mortality after adjustment.<sup>72,73</sup> A study of temporal trends (1950–2004) in the US Framingham Study found that age-adjusted 30-day fatality decreased significantly for men but not women.<sup>22</sup> Non-US populations have also reported mixed results in terms of sex differences in stroke case fatality over time,<sup>69</sup> which may be attributable to differences in the time periods studied, underlying demographics, lack of age adjustment, and other factors. Case-fatality studies for IS have shown either no sex differences or higher rates in men.<sup>27,30</sup> A study from the Netherlands that examined trends in IS 30-day case fatality for the period 1997 to 2005 showed that in all age-sex groups, the case fatality declined significantly; the largest decline for men was from 12.5% to 6.9% (–0.42 change) in the 65- to 74-year-old age group, and the largest decline for women was from 6.4% to 3.5% (–0.45) in the 35- to 64-year-old age group.<sup>66</sup> Data are limited to assess case fatality for hemorrhagic strokes. A study restricted to a younger population (20–44 years of age) reported lower 30-day case fatality after SAH in women than in men (9% versus 17%).<sup>41</sup> Studies have shown differing patterns of ICH case fatality by sex. The Atherosclerosis Risk in Communities study (ARIC) reported a lower 30-day ICH case fatality for women than for men (30.4% versus 34.5%),<sup>30</sup> but the Northern Manhattan Stroke Study found slightly higher 1-month case fatality for women than men (40% versus 35%).<sup>41</sup> Temporal trends in case fatality for hemorrhagic stroke are largely unreported. A Finnish study



**Figure 1.** US stroke mortality rates for women, 2009. Am Indian indicates American Indian; Non-Hisp, non-Hispanic; and PI, Pacific Islander.



**Figure 2.** Female-male US stroke mortality ratio, 2009. Am Indian indicates American Indian; Non-Hisp, non-Hispanic; and PI, Pacific Islander.

found similar declines in 28-day case fatality for women and men over a 12-year period from 1991 to 2002.<sup>74</sup>

### Sex Differences 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. Most studies have not found important sex differences in delayed hospital arrival,<sup>4,75</sup> but a few found women have longer prehospital delay than men.<sup>76–80</sup> Most studies that have explored knowledge and awareness of stroke symptoms in either stroke patients or at-risk populations have not compared results by sex; however, several population-based studies have shown that knowledge and awareness of stroke warning signs and symptoms are somewhat higher in women than men.<sup>81–83</sup> 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 that it must be administered within 3 hours.<sup>84</sup> Population-based surveys of women conducted by the AHA have identified an overall poor level of knowledge about CVD and stroke, particularly in minority women<sup>85,86</sup>; however, the studies excluded men and were therefore unable to report on sex differences.

### Epidemiology of Ischemic and Hemorrhagic Stroke in Women: Summary and Gaps

Stroke epidemiology research predominantly describes IS events. Additional research is needed to understand sex differences for hemorrhagic stroke events.

Data are limited in terms of sex-, race-, and age-specific rates of stroke incidence, mortality, and case fatality. This represents an important gap, because disease patterns and outcomes have been shown to vary by these characteristics. Future studies should report data separately for men and women, stratify by age when examining sex differences in disease rates, and clarify whether first-ever stroke events, recurrent events, or both are being reported. In addition to reporting by sex and age, for each stroke subtype, the incidence, mortality, and case fatality should be reported by race/ethnicity. In general, stroke event rates are lower in women than men, but sex comparisons based on age-adjusted rates mask important differences by age. There is a higher lifetime risk of stroke

in women than men and a greater number of stroke deaths in women than men.

### Vascular Differences 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.<sup>2,19</sup> There are a number of important sex differences in the prevalence, treatment, and pathophysiology of hypertension that should be highlighted to improve awareness and treatment of this risk factor in women.

#### Sex Differences in Stroke Risk With Hypertension

Among stroke patients, some studies,<sup>9,13,71,72,88,89</sup> but not all,<sup>90,91</sup> have shown that women are more likely to have hypertension than men. Similarly, women may have a higher risk of first stroke with hypertension. For example, the INTERSTROKE study showed that women had a higher risk of stroke with self-reported blood pressures (BPs) of 160/90 mm Hg (odds ratio [OR], 4.89; 95% CI, 3.79–6.32) than men (OR, 3.88; 95% CI, 3.22–4.68), although the CIs overlapped.<sup>92</sup> In addition, older women (mean age 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.<sup>93</sup>

### Efficacy of Hypertension Treatment and Reduction of Stroke in Women

The effects of pharmacological intervention to lower BP and thereby reduce the risk of stroke on cardiovascular outcomes and surrogate cardiovascular end points have been studied extensively,<sup>94–107</sup> 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 analyses and meta-analyses 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 (90% of whom were white) was associated with a 38% risk reduction in fatal and nonfatal cerebrovascular events (95% CI, 27%–47%). A reduction of 25% in fatal and nonfatal cardiovascular events (95% CI, 17%–33%) was

also reported, together with a 17% reduction in cardiovascular mortality (95% CI, 3%–29%).<sup>108</sup> Therefore, women benefit significantly from these interventions, as do men, and the type of medication used to lower the BP may be less relevant than the achievement of target BP goals.

Analyses of women of different racial/ethnic and age groups have suggested particular benefit of BP reduction in younger and black women. In 1 large systematic review of prospective studies, BP treatment in those aged 30 to 54 years (of whom 79% were white) yielded a reduction in risk of fatal and nonfatal cerebrovascular events of 41% (95% CI, 8%–63%), as well as a 27% reduction in fatal and nonfatal cardiovascular events (95% CI, 4%–44%).<sup>109</sup> In this same study, when black women were considered as a separate group, BP treatment reduced the risk of fatal and nonfatal cerebrovascular events by 53% (95% CI, 29%–69%), and all-cause mortality by 34% (95% CI, 14%–49%).<sup>109</sup>

### Sex, BP, Antihypertensive Treatment, and Achieving BP Goals

Numerous studies have shown that females have lower BP levels over much of their life span than their age-matched male counterparts,<sup>110</sup> but this changes with age. For example, 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 than men after the age of 55 years, which suggests an important role of sex hormones in the regulation of BP.<sup>1</sup> The lifetime risk of developing hypertension in the United States is ≈29% for women and 31% for men<sup>1</sup>; however, ≈75% of women >60 years of age become hypertensive.<sup>2</sup> Age-adjusted hypertension prevalence, both diagnosed and undiagnosed, from 1999 to 2002 was 78% for older women and only 64% for older men.<sup>111</sup>

Sex differences in the pattern of prescribed antihypertensive medications have been seen across several large studies. For example, in the Framingham Heart Study, 38% of women but only 23% of men were prescribed thiazide diuretics,<sup>112</sup> and similar rates were seen in the National Health and Nutrition Examination Survey (NHANES) cohorts, with higher diuretic (31.6% versus 22.3%) and angiotensin receptor blocker (11.3% versus 8.7%) use in women.<sup>113</sup>

Currently, there is no compelling evidence that there are differences in the response to BP medications between the sexes<sup>111</sup>; however, in large-scale reviews that examined the efficacy of  $\beta$ -blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and diuretics,<sup>114</sup> 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.

Some studies have suggested that antihypertensive medication use is significantly higher among women than men (61.4% versus 56.8%). Among treated hypertensive people, the proportion taking  $\geq 3$  antihypertensive drugs was lower among women than men, especially among older people (60–69 years old: 12.3% versus 19.8%; 70–79 years old: 18.6% versus 21.2%; and  $\geq 80$  years old: 18.8% versus 22.8%). Only 44.8% of treated women achieved BP control versus 51.1% of treated men.<sup>113</sup> Notably, hypertensive women are significantly more likely to be treated than men but less likely to have achieved

BP control. This may be because of unknown physiological mechanisms (ie, arterial stiffness, overactivation of the renin-angiotensin system) or poorer compliance in women. The recent PARITE study, which examined 3440 patients, found that in French office-based cardiology practices, the antihypertensive regimen is adjusted as often in female as in male patients. Hypertension was uncontrolled in 76% of both men and women, and 69% were at high global cardiovascular risk (75% of men, 62% of women;  $P < 0.001$ ).<sup>113,115</sup>

Unfortunately, control of hypertension is poor in high-risk elderly women. Data from the Framingham Heart Study showed an age-related decrease in BP control rates that was more pronounced in women than men.<sup>112</sup> Among participants >80 years of age with hypertension, only 23% of women (versus 38% of men) had BP <140/90 mm Hg.<sup>112</sup>

In analyses from the NHANES III and IV cohorts, the age-adjusted prevalence of uncontrolled BP was  $50.8 \pm 2.1\%$  in men and  $55.9 \pm 1.5\%$  in women, which was not significantly different; women had a higher prevalence of other concomitant cardiovascular risk factors,<sup>110</sup> which likely contributed to poorer BP control in elderly women. These included central obesity, elevated total cholesterol, and low high-density lipoprotein cholesterol levels.<sup>110</sup> Among adults with hypertension in NHANES from 1999 to 2004, women were at higher risk of cardiovascular events than men, such that 53% of women but only 41% of men had >3 of the 6 risk factors studied ( $P < 0.001$ ).

Sex differences in hypertension and BP regulation are complex, because ovarian hormones influence BP considerably. Therefore, studies that examine vascular function and BP must take hormonal status into account.<sup>111,116</sup> Sex differences in sympathetic activity, vascular reactivity, water regulation (arginine vasopressin signaling), and autonomic control have been well documented,<sup>116</sup> but most of these studies were performed in young women. Efforts to assess the effects of hormonal effects on the vasculature have examined specific points in the menstrual cycle or suppressed ovarian function using gonadotropin-releasing hormone agonists or antagonists. In addition to hormone-dependent effects, these investigations have demonstrated hormone-independent sex differences in the vasculature.<sup>116</sup> Hormone-independent approaches to BP regulation may be more relevant to older, postmenopausal women and may provide important information that will inform future clinical trials of different BP reduction strategies.

Several nonpharmacological recommendations for BP management are relevant to both men and women. A recent meta-analysis showed that even a modest reduction in salt intake for  $\geq 4$  weeks led to significant and important decreases in BP in both hypertensive and normotensive individuals, irrespective of sex and ethnic group. This was accompanied by a small physiological increase in plasma renin activity, aldosterone, and noradrenaline. Therefore, reductions in salt intake from 9 to 12 g/d to 3 g/d have been recommended.<sup>117</sup>

Side effects of antihypertensive therapy tend to be encountered with a higher degree of frequency in women than men. Diuretic-induced disturbances of electrolyte concentration are seen more frequently in women,<sup>118,119</sup> as is angiotensin-converting enzyme inhibitor-induced cough and calcium channel blocker (CCB)-related dependent edema.<sup>120</sup>



## Hypertension in Women of Childbearing Age

Prepregnancy hypertension increases the risk for preeclampsia/eclampsia and stroke during pregnancy. The choice of BP-lowering medications before pregnancy should be made based on a woman's intentions for future pregnancy, because some categories of medications are associated with various risks if continued during pregnancy (Table 4).<sup>120a,121\*</sup>

$\alpha$ -Blockers,  $\beta$ -blockers, CCBs, hydralazine, and thiazide diuretics have been used in pregnancy; all transfer across the placenta. There are no data from large, well-controlled, randomized controlled trials directly comparing specific antihypertensive agents in pregnancy. Methyldopa has been extensively used in pregnancy and appears to be safe,<sup>122–127</sup> including for neonates in a long-term pediatric study.<sup>128</sup> A Cochrane review of the use of  $\beta$ -blockers in pregnancy noted that these drugs decreased the risk of progression to severe hypertension but may have increased risk for fetal growth restriction (n=1346; RR, 1.36; 95% CI, 1.02–1.82),<sup>125,126</sup> although this may have been confounded in part by the inclusion of trials that used atenolol, which is not recommended in pregnancy because of its known association with fetal growth restriction.<sup>129,130</sup> Pindolol and metoprolol appear safe for use in pregnancy.<sup>131</sup> CCBs appear to be safe in pregnancy, with the most commonly used CCB being nifedipine.<sup>132,133</sup> A 2007 Cochrane review indicated that there was a small increase in the risk for preeclampsia with the use of CCBs versus no therapy (725 women; RR, 1.40; 95% CI, 1.06–1.86).<sup>132</sup> Diuretics, predominantly thiazide-type, have been indicated to be safe in pregnancy,<sup>124,134</sup> and women taking thiazides before pregnancy do not need to discontinue them; however, a 2007 Cochrane review examined the use of diuretics to prevent preeclampsia.<sup>135</sup> For thiazides, the reviewers noted that several studies were of uncertain quality and that there was insufficient evidence for any differences between treatment and control groups (4 trials, 1391 women; RR, 0.68; 95% CI, 0.45–1.03).<sup>135</sup>

Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and direct renin inhibitors are

contraindicated at all stages of pregnancy because of teratogenicity and adverse fetal outcomes.<sup>136–139</sup>

## Sex and Hypertension in Relation to Prevention of Stroke: Summary and Gaps

There is insufficient evidence to warrant a different approach to BP treatment in women from that used for men; as such, the existing guidelines for measurement, identification, and management of BP in adults should be followed. Existing guidelines for nonpharmacological intervention (predominantly dietary modification) to lower BP and to reduce stroke risk in adults should be followed.<sup>19,140</sup> It is unclear whether the age-related decline in BP control among women is related to inadequate intensity of treatment, inappropriate drug choices, lack of compliance, true treatment resistance, biological factors, or other factors. Further research to resolve these questions is needed. In addition, hormone-dependent and -independent approaches to BP treatment require further study.

## Sex and Hypertension in Relation to Prevention of Stroke: Recommendations

The recommendations for BP treatment to prevent stroke are currently the same for women as for men and can be found in the AHA/American Stroke Association “Guidelines for the Primary Prevention of Stroke,”<sup>19</sup> the European Society of Hypertension/European Society of Cardiology guidelines,<sup>141</sup> and the “Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.”<sup>142</sup>

## Sex-Specific Risk Factors

### Pregnancy and Stroke

Pregnancy is a condition unique to women. Although stroke is uncommon in pregnancy (34 strokes per 100 000 deliveries),<sup>143</sup> the risk for stroke is higher in pregnant than in non-pregnant young women (21 per 100 000<sup>144</sup>), with the highest stroke risk occurring in the third trimester and post partum. The physiological changes of pregnancy, specifically venous stasis, edema, and hypercoagulability caused by activated

\*American College of Obstetricians and Gynecologists Bulletin withdrawn in lieu of a newer version. Access date was May 15, 2013.

**Table 4. Summary of Antihypertensive Drugs Used During Pregnancy**

Category	Maternal Side Effects	Teratogenicity or Fetal-Neonatal Adverse Effects	Class/Level of Evidence (see Table 2)
$\alpha$ -Blockers (eg, methyldopa)	Sedation, elevated LFTs, depression	No	Ia/C
Diuretics (thiazide)	Hypokalemia	No	III/B
$\beta$ -Blockers (atenolol)	Headache	Associated with fetal growth restriction	III/B
$\beta$ -Blockers (pindolol, metoprolol)	Headache	Possible fetal growth restriction, neonatal bradycardia	Ia/B
Calcium channel blockers (eg, nifedipine)	Headache; possible interaction with magnesium sulfate; may interfere with labor	No	I/A
Combined $\alpha$ - $\beta$ blockers (labetalol)	May provoke asthma exacerbation	Possible neonatal bradycardia	Ia/B
Hydralazine	Reflex tachycardia, delayed hypotension	Neonatal thrombocytopenia, fetal bradycardia	III/B
ACE inhibitors, angiotensin receptor blockers, renin inhibitors		Skeletal and cardiovascular abnormalities, renal dysgenesis, pulmonary hypoplasia	III/C

ACE indicates angiotensin-converting enzyme; and LFTs, liver function tests.

Modified from Umans et al<sup>120a</sup> with permission from Elsevier, Copyright © 2009.



protein C resistance, lower levels of protein S, and increased fibrinogen, combine to make pregnancy and the postpartum period a time of increased risk for stroke. Pregnancy-related hypertension is the leading cause of both hemorrhagic stroke and IS in pregnant and postpartum women.<sup>145–147</sup>

### **Hypertensive Disorders of Pregnancy**

Preeclampsia/eclampsia and pregnancy-induced hypertension are the 2 most important hypertensive disorders of pregnancy. Preeclampsia is defined as progressively worsening high BP in pregnancy that occurs in the setting of proteinuria ( $\geq 300$  mg of protein in a 24-hour urine specimen).<sup>148</sup> Preeclampsia may be of early onset (before 37 weeks' gestation) or late onset (after 37 weeks). Eclampsia is preeclampsia that progresses to seizures. Preeclampsia is a multisystem disorder, and abnormalities such as HELLP (hemolysis, elevated liver enzymes, or low platelets), disseminated intravascular coagulation, acute renal failure, myocardial infarction (MI), pulmonary edema, and stroke may occur. Preeclampsia is hypothesized to be caused by as-yet-unnamed placental factors that enter the maternal circulation, provoking the signs, symptoms, and laboratory findings associated with this disorder.<sup>149</sup>

Pregnancy-induced (sometimes called gestational) hypertension is defined as an elevation in BP, usually near term, that occurs without the other signs and symptoms of preeclampsia. Although gestational hypertension may or may not progress to preeclampsia, it can result in markedly elevated BPs. By definition, gestational hypertension usually resolves by 12 weeks post partum.<sup>150</sup>

Recognized risk factors for pregnancy-induced hypertension include obesity, age ( $>40$  years), chronic hypertension, personal or family history of preeclampsia or gestational hypertension, nulliparity, multiple pregnancy, preexisting vascular disease, collagen vascular disease, diabetes mellitus, and renal disease.<sup>131</sup> By far the most important predisposing factor is chronic hypertension, because superimposed preeclampsia develops in  $\approx 25\%$  of pregnant women with this condition. Regardless of its origin, high BP during pregnancy is associated with risk to both mother and baby, and BP-related complications remain a leading cause of maternal morbidity and mortality, as well as preterm birth, fetal growth restriction, and stillbirth.<sup>121,151</sup>

Women with high BP during pregnancy who have given birth continue to be at risk for preeclampsia and stroke. Although less common than preeclampsia during pregnancy, postpartum preeclampsia is more insidious and potentially more dangerous, because women may be unaware of its development and are no longer being seen regularly, as they were for prenatal care. Postpartum preeclampsia is associated with a high risk for stroke and may be the underlying cause of severe postpartum headaches.<sup>152</sup> Transient elevations in BP are common post partum because of volume redistribution, iatrogenic administration of fluid, alterations in vascular tone, and use of nonsteroidal anti-inflammatory drugs,<sup>153–155</sup> but persistently elevated BP should be categorized and treated according to the adult guidelines.<sup>140</sup>

A 2010 Cochrane review noted that the RR of hypertension in pregnancy was decreased with calcium supplementation of  $\geq 1$  g/d (RR, 0.65; 95% CI, 0.53–0.81).<sup>156</sup> A reduction

in preeclampsia/eclampsia was also noted (RR, 0.45; 95% CI, 0.31–0.65). Low-dose aspirin can also lower the risk for preeclampsia, on the basis of a meta-analysis of 46 trials and 32 891 women (RR, 0.83; 95% CI, 0.77–0.89; number needed to treat, 72).<sup>157</sup> Recent research suggests that vitamin D3 deficiency may be associated with increased risk for preeclampsia,<sup>158</sup> but there are insufficient data to support a recommendation.

### **Treatment of Elevated BP During Pregnancy, Including Preeclampsia**

The central autoregulatory plateau in pregnancy is estimated at 120 mmHg, and women with moderate to severe high BP in pregnancy, especially those with preeclampsia, are at risk for loss of central cerebral vascular autoregulation. The association between high BP and stroke risk in women with preeclampsia is not linear, such that stroke can occur at moderately elevated BPs, which suggests that current thresholds for treatment may not be sufficiently stringent.<sup>159</sup> Pharmacological treatment to lower BP during pregnancy should be chosen after consideration of tolerability, preexisting therapy, and risk of teratogenicity, because all agents cross the placenta. (Table 4).

High BP during pregnancy may be defined as mild (diastolic BP 90–99 mmHg or systolic BP 140–149 mmHg), moderate (diastolic BP 100–109 mmHg or systolic BP 150–159 mmHg), or severe (diastolic BP  $\geq 110$  mmHg or systolic BP  $\geq 160$  mmHg). The goal of BP management in pregnancy is to maintain systolic BP between 130 and 155 mmHg and diastolic BP between 80 and 105 mmHg, with lower target ranges in the context of comorbidity; however, the treatment rationale for women with mild to moderate high BP in pregnancy is not as clear-cut as for severe high BP in pregnancy because maternal and fetal risk-benefit ratios have not been established.<sup>125</sup> For example, a meta-analysis that examined the association between reduction in maternal BP and fetal growth found that a 10-mmHg decrement in maternal mean arterial pressure was associated with a 176-g decrease in neonatal birth weight, regardless of the antihypertensive agent used.<sup>160</sup> In addition, Abalos et al<sup>132</sup> performed a meta-analysis of randomized controlled trials of treatment versus no treatment of mild to moderate high BP in pregnancy. Although the risk for development of severe hypertension in pregnancy was reduced by 50% in the treatment group (19 trials, 2409 women; RR, 0.50; 95% CI, 0.41–0.61; number needed to treat, 10), there was no statistically significant difference in risk for preeclampsia (22 trials, 3081 women; RR, 0.73; CI 0.50–1.08) and no evidence for benefit or harm to the fetus.

Severe hypertension in pregnancy is categorized with the same criteria as for stage 2 hypertension in nonpregnant adults according to the “Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure” (BP  $\geq 160/110$  mmHg) and is associated with high risk for stroke and eclampsia.<sup>131,161</sup> The American College of Obstetricians and Gynecologists recommends treatment of severe hypertension and suggests labetalol as first-line therapy,<sup>121</sup> and it recommends avoidance of atenolol, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers.

In addition to pharmacological control of hypertension, the use of magnesium sulfate for seizure prophylaxis is well established and has been demonstrated in randomized trials to decrease risk of stroke in women with severe high BP in pregnancy and eclampsia. A Cochrane review showed a >50% reduction in eclampsia with the use of magnesium sulfate versus placebo (6 trials, 11 444 women; RR, 0.41; 95% CI, 0.29–0.58; number needed to treat for additional benefit, 100), with a nonsignificant decrease in maternal death (RR, 0.54; 95% CI, 0.26–1.10).<sup>162</sup> Although modest decrements in BP can be observed with magnesium sulfate alone, the latter has not been shown to effectively decrease BP in moderate to severe high BP in pregnancy, and there is no evidence to support its use as monotherapy.<sup>125</sup>

### **Pregnancy Complications and the Long-term Risk of Stroke**

An expanding body of research has shown that complications of pregnancy (preeclampsia, gestational diabetes, and pregnancy-induced hypertension) are associated with higher risk for future CVD and stroke beyond the childbearing years than among women without these disorders<sup>163</sup> (Tables 5 and 6). For example, women with a history of preeclampsia have a markedly increased risk for developing renal disease and a 2- to 10-fold increase in risk for development of chronic hypertension, a major risk factor for stroke. In addition, 50% of women with gestational diabetes will develop type 2 diabetes mellitus, a major risk factor for stroke, within 5 to 10 years of their pregnancy (although only 1 study has suggested an increased risk for CVD after a pregnancy complicated by gestational diabetes; CVD was defined as a composite outcome of admission to hospital for acute MI, coronary bypass, coronary angioplasty, stroke, or carotid endarterectomy [CEA]).<sup>180–182</sup> A 2012 study of long-term risk for CVD reported that 18.2% of women with a history of preeclampsia versus 1.7% of women with uncomplicated pregnancies had a CVD event in 10 years (OR, 13.08; 95% CI, 3.38–85.5). Likewise, the 30-year risk (OR, 8.43; 95% CI, 3.48–23.2) and lifetime risk (OR, 3.25; 95% CI, 1.76–6.11) for CVD for women who formerly had preeclampsia were significantly increased compared with

women with uncomplicated pregnancies.<sup>183</sup> A 2008 systematic review and meta-analysis by McDonald et al<sup>181</sup> noted that women with a history of preeclampsia/eclampsia had twice the risk of cerebrovascular disease (not further defined) as women without these disorders (RR, 2.03; 95% CI, 1.54–2.67). Another meta-analysis by Bellamy et al<sup>180</sup> combined 4 cohort studies and reported a cumulative OR of 1.81 for any stroke (OR, 1.81; 95% CI, 1.37–2.33) in women with a history of preeclampsia, whereas Brown et al<sup>184</sup> noted an OR of 1.76 for cerebrovascular disease (95% CI, 1.43–2.21) for women with a history of pregnancies with preeclampsia. In one study, the mean age at stroke onset was ≤50 years in women with these disorders, which suggests an accelerated time course to severe CVD or cerebrovascular disease, as well as loss or attenuation of women's premenopausal cardiovascular advantage.<sup>185</sup> Early-onset preeclampsia (before 32 weeks' gestation) in particular has been noted to increase risk for stroke 5-fold compared with later-onset preeclampsia.<sup>186</sup> Early-onset preeclampsia is also associated with an increase in white matter lesions independent of hypertension in women years after pregnancies complicated by preeclampsia or eclampsia, which suggests a vulnerability to future events.<sup>187</sup>

The basis of the association between preeclampsia and future stroke is not entirely known but is hypothesized to be possibly related to genetic factors; shared risk factors (hypertension, dyslipidemia, endothelial dysfunction) between preeclampsia/eclampsia or other pregnancy complications and stroke; unmasking of underlying metabolic or vascular disease; or the induction during pregnancy of cardiovascular or cerebrovascular abnormalities that persist long-term.<sup>188</sup> To assess the contribution by preeclampsia/eclampsia to future risk for CVD and stroke and the possible impact that lifestyle interventions may have on this risk, Berks et al<sup>189</sup> performed a series of literature-based calculations on risk estimates. First, using a meta-analysis cumulative OR for stroke as the starting point, they found that preeclampsia increased the odds of stroke by 1.55-fold after correction for cardiovascular risk factors (interquartile range 1.76–1.98). This result suggests

**Table 5. Adverse Pregnancy Outcomes and Future Hypertension**

Study Date and First Author	Total No. of Subjects	Study Design	Pregnancy Outcome	Mean Follow-up, y	RR or OR of Hypertension (95% CI)
Sibai 1986 <sup>164</sup>	815	Prospective cohort	Preeclampsia and eclampsia	7.3	2.64 (1.66–4.17)
Nisell 1995 <sup>165</sup>	138	Retrospective cohort	Preeclampsia	7	8.8 (1.16–66.59)
North 1996 <sup>166</sup>	100	Retrospective cohort	Preeclampsia	5	20.0 (2.79–143.38)
Hannaford 1997 <sup>167</sup>	23 000	Prospective cohort	Preeclampsia	12.5	2.35 (2.08–2.65)
Marin 2000 <sup>168</sup>	359	Prospective and retrospective cohort	Preeclampsia	14.2	3.70 (1.72–7.97)
Hubel 2000 <sup>169</sup>	60	Retrospective cohort	Preeclampsia and eclampsia	32.7	5.00 (1.19–20.92)
Wilson 2003 <sup>170</sup>	1312	Retrospective cohort	Preeclampsia	32	2.62 (1.77–3.86)
Sattar 2003 <sup>171</sup>	80	Retrospective cohort	Preeclampsia	19	3.50 (0.77–15.83)
Diehl 2008 <sup>172</sup>	202	Retrospective cohort	Preeclampsia	27.4	2.2 (1.45–3.36)

CI indicates confidence interval; OR, odds ratio; and RR, risk ratio.

Adapted from Garovic et al<sup>149</sup> with kind permission from Springer Science+Business Media. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

**Table 6. Adverse Pregnancy Outcomes and Risk for Stroke**

Study Date and Author	Total No. of Subjects	Study Design	Pregnancy Outcome	Cerebrovascular Outcome	Follow-up, y	HR or OR for Outcome (95% CI)
Mannistö et al, 2013 <sup>173</sup>	10 314	Prospective cohort study	Gestational hypertension	Ischemic cerebrovascular disease	40	1.67 (1.13–2.45)
Bonamy et al, 2011 <sup>174</sup>	923 686	Retrospective cohort study	Preterm birth; SGA	Cerebrovascular events (infarction, hemorrhage, subarachnoid hemorrhage, TIA, other stroke)		Preterm birth 2.41 (1.4–4.17); SGA birth 1.68 (1.46–2.06); preterm and SGA birth 3.11 (1.91–5.09)
Irgens et al, 2001 <sup>175</sup>	626 272	Retrospective cohort study	Preeclampsia	Stroke mortality		Term preeclampsia 0.98 (0.5–1.91); preterm preeclampsia* 5.08 (2.09–12.35)
Wilson et al, 2003 <sup>170</sup>	1312	Retrospective cohort study	Preeclampsia	Stroke mortality	32	3.59 (1.04–12.4)
Ray et al, 2005 <sup>176</sup>	1 026 265	Retrospective cohort study	Maternal placental syndrome	Cerebrovascular disease		1.90 (1.42–2.54)
Funai et al, 2005 <sup>177</sup>	37 061	Retrospective cohort study	Preeclampsia	Stroke		3.07 (2.18–4.33)
Kestenbaum et al, 2003 <sup>178</sup>	124 141	Case-control study	Preeclampsia	Cerebrovascular disease		2.53 (1.70–3.77)
Lykke et al, 2009 <sup>179</sup>	782 287	Retrospective cohort	Gestational hypertension, mild preeclampsia, severe preeclampsia	Stroke	12.9–14.6	Gestational hypertension 1.58 (1.32–1.89); mild preeclampsia 1.50 (1.36–1.66); severe preeclampsia 1.66 (1.29–2.14)

CI indicates confidence interval; HR, hazard ratio; OR, odds ratio; SGA, small for gestational age; and TIA, transient ischemic attack.

\*Defined as preeclampsia between 16 and 36 weeks.

that CVD risk factors antecedent to pregnancy did not fully explain the risk for CVD after preeclampsia. They hypothesized that preeclampsia/eclampsia is a risk factor rather than a marker for stroke and CVD. The authors then calculated the effect of literature-based cumulative benefits of lifestyle interventions (dietary habits, exercise, and smoking cessation) on this risk for stroke with preeclampsia. They found the OR for the effect of lifestyle interventions on the risk for CVD after a preeclamptic pregnancy to be 0.91 (interquartile range, 0.87–0.96), which suggests that these interventions could reduce the risk of stroke in this population. Although one limitation of this research was the extrapolation of lifestyle interventions performed in older populations to a younger population of women 1 to 30 years after preeclampsia, prospective studies are warranted on the basis of the implication that lifestyle interventions in these women might be effective.<sup>189</sup>

#### **Preeclampsia and Pregnancy Outcomes: Summary and Gaps**

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. This risk has been quantified in large retrospective studies, mostly in northern European populations. Prospective studies on the pathophysiology underlying the association between hypertensive disorders of pregnancy and stroke, especially in diverse populations, are needed, because it is not known whether prepregnancy risk factors or pregnancy-associated factors predispose these women to subsequent risk of stroke. Research also 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.<sup>190</sup> Although a limited number of studies have examined cardiovascular and stroke risk factors and documented increased risk for events long-term in women with these disorders, there are no prospective randomized controlled trials assessing interventions to reduce stroke risk in this population with clear risk factors (preeclampsia, gestational diabetes). There is a need for high-quality studies of women with a history of adverse pregnancy outcomes to define their trajectory for the development of cerebrovascular disease and then to develop screening, risk stratification, and preventive strategies. Insufficient evidence exists to inform any recommendation for screening, prevention, or treatment in women with a history of pregnancy complications or adverse pregnancy outcomes.

#### **Preeclampsia and Pregnancy Outcomes: Recommendations**

##### **Prevention of Preeclampsia**

- 1. 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 (Class I; Level of Evidence A).**
- 2. Calcium supplementation (of  $\geq 1$  g/d, orally) should be considered for women with low dietary intake of calcium ( $<600$  mg/d) to prevent preeclampsia (Class I; Level of Evidence A).**

##### **Treatment of Hypertension in Pregnancy and Post Partum**

- 1. 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; Level of Evidence A*).

2. 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 BP 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; Level of Evidence B*).
3. Atenolol, angiotensin receptor blockers, and direct renin inhibitors are contraindicated in pregnancy and should not be used (*Class III; Level of Evidence C*).
4. After giving birth, women with chronic hypertension should be continued on their antihypertensive regimen, with dosage adjustments to reflect the decrease in volume of distribution and glomerular filtration rate that occurs after delivery. They should also be monitored carefully for the development of postpartum preeclampsia (*Class IIa; Level of Evidence C*).

#### *Prevention of Stroke in Women With a History of Preeclampsia*

1. Because of the increased risk of future hypertension and stroke 1 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 1 year post partum, 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; Level of Evidence C*).

#### **Cerebral Venous Thrombosis**

Cerebral venous thrombosis (CVT) is a stroke type that is caused by thrombus formation in  $\geq 1$  of the venous sinuses and manifests primarily as headache. CVT makes up 0.5% to 1% of all strokes but is the stroke type that shows the most prominent differential sex prevalence.<sup>191,192</sup> In adulthood, the majority of affected individuals are women, who represent >70% of cases in most studies<sup>193–200</sup> (Table 7). The overall adult incidence of CVT is 1.32 per 100 000 person-years (95% CI, 1.06–1.61) and is higher in women (1.86 per 100 000; 95% CI, 1.44–2.36) than men (0.75 per 100 000; 95% CI, 0.49–1.09).<sup>198</sup> This sex difference is even more notable in women aged 31 to 50 years, in whom the incidence may be as high as 2.78 per 100 000 person-years (95% CI, 1.98–3.82). Women tend to be younger (median age 34 years) than men (median age 42 years) at the time of diagnosis.<sup>193,198</sup> Guidelines for the evaluation and treatment of CVT were published recently.<sup>200</sup> Therefore, only interim studies with an emphasis on sex-specific factors are presented in this guideline.

#### **Risk Factors**

The female predominance of CVT has been attributed to hormonal factors (primarily oral contraceptive [OC] use and

**Table 7. CVT and Recurrence Rates in Published Studies**

Study	Subjects Enrolled, n	% Female	Recurrence Rate, %		
			CVT	Other Thrombosis	Length of Follow-up
ISCVT <sup>194</sup>	624	74.5	2.2	4.3	16 mo
VENOPORT <sup>196</sup>	142	71	2.0	8.0	16 y
Martinelli et al <sup>197</sup>	145	73	3.0	7.0	6 y
Coutinho et al <sup>193</sup>	94	72	NA	NA	NA
Dentali et al <sup>199</sup>	706	73.7	4.4	6.5	40 mo

CVT indicates cerebral venous thrombosis; ISCVT, International Study on Cerebral Vein and Dural Sinus Thrombosis; NA, not available; and VENOPORT, Cerebral Venous Thrombosis Portuguese Collaborative Study Group.

pregnancy), because the incidence is sex-independent in children and in the elderly.<sup>201,202</sup> A link between thrombophilia and CVT has been relatively well established for several inherited conditions, including antithrombin III, protein C, and protein S deficiency and factor V Leiden.<sup>200</sup> Many exogenous provoking factors for venous thrombosis have been described, such as cancer, infection, and hematologic and autoimmune conditions.<sup>191,192</sup> However, 2 major risk factors are female specific: OC use and pregnancy. The use of OCs is associated with an increased risk of CVT,<sup>200</sup> a risk that is increased significantly in women with an underlying hereditary prothrombotic factor, such as factor V Leiden or prothrombin gene mutation.<sup>203</sup> Pregnancy and OC use are considered transient risk factors and do not necessarily indicate a higher risk for recurrence. Most pregnancy-related CVT occurs in the third trimester or puerperium.<sup>200,204</sup>

#### **Treatment and Recurrence**

The standard therapy for acute CVT is anticoagulation with intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin (LMWH) followed by oral anticoagulation.<sup>200</sup> There are no large studies of the use of newer anticoagulants that are currently only approved for use in patients with nonvalvular AF or deep venous thrombosis<sup>205</sup>; therefore, warfarin is usually recommended. Management and imaging recommendations are provided in detail in prior guidelines<sup>200</sup> and are summarized below. There are no secondary prevention trials of duration of anticoagulation in adults with CVT; therefore, guidelines are based solely on observational data.

Recurrence rates range from 2% to 5% in most studies, although many of these studies did not provide long-term follow-up of patients, and the level of anticoagulation at the time of recurrence was often not reported. In the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), recurrence of CVT was seen in 2.2% of patients, and other recurrent thrombotic events were seen in 4.3%, with a mean follow-up of 16 months<sup>194,196</sup> (Table 7). A recent large, retrospective, multinational study performed follow-up of 706 patients for a median of 40 months and tracked prespecified risk factors and conditions such as infections, trauma, OC use, pregnancy, puerperium, HT, recent neurosurgical procedures, and the presence of myeloproliferative neoplasms.<sup>199</sup> Significantly more women than men had at least 1 risk factor

(61.0% versus 45.7%;  $P < 0.05$ ). Recurrence rates were again low (4.4% for recurrent CVT and 6.5% with a recurrent venous thromboembolism [VTE] in a different site), which led to an overall incidence of recurrence of 23.6 events per 1000 patient-years (95% CI, 17.8–28.7). Most events occurred after anticoagulation discontinuation. Somewhat surprisingly, the recurrence rate was similar in patients with unprovoked CVT and in patients with CVT secondary to known risk factors (22.8 events/1000 patient-years [95% CI, 15.9–32.6] versus 27.0 events/1000 patient-years [95% CI, 20.4–36.0]). A previous VTE was the only significant predictor of recurrence with multivariate analysis (hazard ratio [HR], 2.70; 95% CI, 1.25–5.83;  $P < 0.011$ ).<sup>199</sup> Many of the recurrent VTEs occurred in women when the first CVT occurred during pregnancy/ puerperium or was secondary to OC or HT use; however, neither female sex (HR, 1.37; 95% CI, 0.83–2.25), pregnancy/ puerperium (HR, 1.05; 95% CI, 0.48–2.28), or use of OC/HT (HR, 0.72; 95% CI, 0.45–1.14) was an independent risk factor for VTE recurrence.<sup>199</sup> This was in contrast to the results from a study by Martinelli et al,<sup>197</sup> which found that male sex was a risk factor for recurrence (HR, 9.66; 95% CI, 2.86–32.7). The higher risk in men could potentially be attributable to more correctable or transient risk factors in women (use of OCs, pregnancy, etc) or may simply reflect the fact that this study enrolled fewer patients ( $n=145$ ) and may have been underpowered for sex-specific analysis.<sup>197</sup>

Recurrence tends to occur within the first year of the index CVT. Patients with severe thrombophilia (antithrombin, protein C, or protein S deficiency; antiphospholipid antibodies; or combined abnormalities) have an increased risk of VTE (adjusted HR, 4.71; 95% CI, 1.34–16.5).<sup>200,203,206</sup> The recurrent event is more often a VTE than a recurrent CVT, and providers should have a high index of suspicion for other thrombotic complications (pulmonary embolism, deep venous thrombosis) in patients with a prior CVT.

### Sex Differences in Outcome

Overall, patients with CVT have lower mortality and better functional outcomes than most stroke subtypes.<sup>191,192</sup> Predictors for poor outcome include age, malignancy, central nervous system infection, and intracranial hemorrhage.<sup>191</sup> The mortality rate was only 2.8% in the most recent large study, and in general, patients had good functional outcomes (89.1% of patients had a complete recovery, with a modified Rankin score of 0–1).<sup>199</sup> A post hoc analysis of patients followed up in the ISCVT found that male sex was associated with poorer outcomes at follow-up (HR, 1.59; 95% CI, 1.01–2.52) and that significantly more women recovered completely after 6 months (81% versus 71%,  $P=0.01$ ).<sup>193</sup> This was driven in large part by improved outcomes in a subset of women who had an identified “gender-specific risk factor” (OC use, pregnancy, puerperium, and hormone replacement therapy), present in 65% of women.<sup>193</sup> Women with other underlying risk factors for CVT unrelated to these sex-specific factors had similar outcomes as males. Logistic regression analysis confirmed that the absence of sex-specific risk factors was a strong and independent predictor of poor outcome in women with CVT (OR, 3.7; 95% CI, 1.9–7.4). Although there was a trend toward higher mortality in males, this was not significant.<sup>193</sup>

No association between sex and mortality rates was seen in the recent Nationwide Inpatient Sample of 3488 patients; however, the mortality was higher in that cohort (4.39%), which contained a surprisingly large number of patients with pyogenic CVT.<sup>207,208</sup> In a larger sample of 11 400 records from the Nationwide Inpatient Sample data set, the most common condition associated with CVT was pregnancy/puerperium (seen in 24.6% of patients). These women had a low mortality rate (0.4%), but despite this, male sex was associated with decreased mortality (2.1%) on multivariate analysis (OR, 0.62; 95% CI, 0.43–0.87,  $P=0.006$ ).<sup>209</sup> The use of the Nationwide Inpatient Sample data is limited, because only inpatient data are recorded, results may be prone to coding errors, initial stroke severity is not recorded, and information on the presence of sex-specific risk factors is undoubtedly incomplete. Currently, data on sex specific functional outcomes are lacking.

### Pregnancy-Associated CVT

Pregnancy and the puerperium period are times of increased risk for venous thrombosis for women, including CVT. The incidence of CVT during pregnancy and the puerperium is estimated at 1 in 2500 deliveries to 1 in 10000 deliveries in Western countries, with increased odds ranging from 30% to 13-fold higher (ORs, 1.3–13).<sup>210–212</sup> The greatest risk periods for CVT include the third trimester and the first 4 postpartum weeks.<sup>211</sup> Up to 73% of CVTs in women occur during the puerperium.<sup>212</sup> Cesarean delivery appears to be associated with a higher risk of CVT after adjustment for age, vascular risk factors, presence of infections, hospital type, and location (OR, 3.10; 95% CI, 2.26–4.24).

### Future Pregnancies and Recurrence

Prior guidelines have summarized the studies examining the outcome and complication rates of pregnancy in women who had CVT.<sup>200</sup> These studies found that the risk of complications during future pregnancies was low. There was a high proportion of spontaneous abortion, consistent with emerging observational trials.<sup>213</sup> On the basis of the available evidence, CVT is not a contraindication for future pregnancies; however, many of the patients followed up for recurrences were maintained on preventive antithrombotic medication. Considering the additional risk that pregnancy confers to women with a history of CVT, prophylaxis with LMWH during future pregnancies and the postpartum period may be beneficial.<sup>200</sup>

### CVT: Summary and Gaps

There is a striking sex difference in CVT incidence that is related to hormonal factors and pregnancy. Long-term oral anticoagulation is recommended for patients at high risk of recurrence because of thrombophilia, but overall recurrence rates are low, even with subsequent pregnancy. Long-term data on sex differences in recurrence and on functional outcomes are lacking.

### CVT: Recommendations

1. 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; Level of Evidence C*).

2. 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; Level of Evidence C*).
3. Testing for prothrombotic conditions, including protein C, protein S, or antithrombin deficiency; antiphospholipid syndrome; prothrombin 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 (*Class IIa; Level of Evidence B*).
4. In patients with provoked CVT (associated with a transient risk factor), vitamin K antagonists may be continued for 3 to 6 months, with a target international normalized ratio of 2.0 to 3.0 (*Class IIb; Level of Evidence C*).
5. In patients with unprovoked CVT, vitamin K antagonists may be continued for 6 to 12 months, with a target international normalized ratio of 2.0 to 3.0 (*Class IIb; Level of Evidence C*).
6. For patients with recurrent CVT, VTE after CVT, or first CVT with severe thrombophilia (ie, homozygous prothrombin G20210A; homozygous factor V Leiden; deficiencies of protein C, protein S, or antithrombin; combined thrombophilia defects; or antiphospholipid syndrome), indefinite anticoagulation may be considered, with a target international normalized ratio of 2.0 to 3.0 (*Class IIb; Level of Evidence C*).
7. For women with CVT during pregnancy, LMWH in full anticoagulant doses should be continued throughout pregnancy, and LMWH or vitamin K antagonist with a target international normalized ratio of 2.0 to 3.0 should be continued for  $\geq 6$  weeks post partum (for a total minimum duration of therapy of 6 months) (*Class I; Level of Evidence C*).
8. It is reasonable to advise women with a history of CVT that future pregnancy is not contraindicated. Further investigations regarding the underlying cause and a formal consultation with a hematologist or maternal fetal medicine specialist are reasonable (*Class IIa; Level of Evidence B*).
9. It is reasonable to treat acute CVT during pregnancy with full-dose LMWH rather than unfractionated heparin (*Class IIa; Level of Evidence C*).
10. For women with a history of CVT, prophylaxis with LMWH during future pregnancies and the postpartum period is reasonable (*Class IIa; Level of Evidence C*).

### Oral Contraceptives

On the basis of a US Department of Health and Human Services survey conducted from 2006 to 2008, 10.7 million women aged 15 to 44 years in the United States used the pill form of contraception.<sup>214</sup> As alternative forms of hormonal

contraception such as the transdermal patch, vaginal ring, and intrauterine devices are increasingly used, the risk of stroke with these formulations also needs to be evaluated. The risk of stroke is very low in the age group of women who use contraception, but the incidence rises steeply from 3.4 per 100 000 at ages 15 to 19 years to 64.4 per 100 000 in women aged 45 to 49 years.<sup>144</sup>

### IS Risk

The cumulative risk of stroke in women using OC pills has been summarized in 4 different meta-analyses, with many of the same individual cohort or case-control studies included in each. A meta-analysis of 16 case-control and cohort studies between 1960 and 1999 estimated a 2.75-fold increased odds (95% CI, 2.24–3.38) of stroke associated with any OC use.<sup>215</sup> A later meta-analysis of 20 studies published between 1970 and 2000 that separated the studies by design (case-control versus cohort) found no increased risk of stroke in the cohort studies but an increased risk with OC use in case-control studies (OR, 2.13; 95% CI, 1.59–2.86).<sup>216</sup> Importantly, only 2 of the 4 cohort studies reported strokes by subtype, and risk was increased for IS but not hemorrhagic strokes.<sup>216</sup> An additional meta-analysis of studies from 1980 to 2002 limited only to low-dose combined OCs (second and third generation only) also showed a comparable increased risk with OC use (OR, 2.12; 95% CI, 1.56–2.86).<sup>217</sup> Lastly, a systematic review of progestogen-only OCs revealed no significant increased risk of stroke with this form of contraceptive.<sup>218</sup>

Two additional large cohort studies have been published since these meta-analyses. The first is the Women's Lifestyle and Health Cohort Study. This cohort comprised 49 259 Swedish women who were followed up from 1991 to 1992 until 2004.<sup>219</sup> In the 285 cases of incident stroke that included ischemic, hemorrhagic, and unknown types, there was no significant association between OC use, duration, or type of OC. Reproductive factors, such as age at first birth, duration of breastfeeding, age at menarche, mean menstrual cycle days at age 30 years, and parity, were not associated with stroke after adjustment for cigarette smoking, hypertension, diabetes mellitus, alcohol, body mass index (BMI), education, and physical activity.<sup>219</sup>

The second study estimated rates of IS only (excluding hemorrhagic stroke and transient ischemic attacks [TIAs]) in women aged 15 to 49 years and the RRs associated with use of various doses and formulations of hormonal contraception in Denmark.<sup>144</sup> In this population-based cohort of  $\approx 1.6$  million women, the crude incidence of IS in contraceptive users was 21.4 per 100 000 person-years. The adjusted RR for ethinyl estradiol doses from 30 to 40  $\mu\text{g}$  ranged from 1.40 (95% CI, 0.97–2.03) to 2.20 (1.79–2.69), whereas the RR for the 20- $\mu\text{g}$  dose ranged from 0.88 (0.22–3.53) to 1.53 (1.26–1.87). Progestin-only formulations were not associated with IS. The transdermal patch was associated with a nonsignificant increased risk in a small number of cases (RR, 3.15; 95% CI, 0.79–12.60), whereas the vaginal ring was associated with a 2.49-fold increased risk (95% CI, 1.41–4.41). In addition, duration of use did not change the risk estimates.<sup>144</sup> Although this study followed a very large number of women, it is limited because risk factors and stroke cases were based



on administrative data. The authors concluded that the RR of IS with intermediate-dose ethinyl estradiol and different progestin types was lower than that reported in other studies and that the transdermal and vaginal ring routes of contraception conferred a similar risk as pills.<sup>144</sup>

### Hemorrhagic Stroke Risk

Data regarding risk with OC use have been less consistent for hemorrhagic stroke. The World Health Organization reported an overall slightly increased risk of hemorrhagic stroke (both intracerebral and subarachnoid) with OC use; however, this risk was present in developing countries but not in Europe.<sup>220</sup> Also, European women >35 years of age were at increased risk of SAH, whereas women in developing nations were at increased risk of both ICH and SAH. Women with hypertension and who smoked cigarettes were also at increased risk.<sup>221</sup> In the Swedish Women's Lifestyle and Health Cohort, there was a significant decrease in hemorrhagic stroke among women who were parous (versus nulliparous; HR, 0.5; 95% CI, 0.2–0.8) and a nonsignificant increase in women who started OC use after 30 years of age (HR, 2.3; 95% CI, 0.8–6.8) and stopped using OCs based on doctor recommendation for medical reasons (adjusted HR, 2.1; 95% CI, 0.9–5.0).<sup>219</sup>

Hemorrhagic stroke in young women is relevant in Asia, where the risk of this type of stroke is disproportionately higher than in Europe and North America. A recent case-control study of Chinese women evaluated the association between the single-nucleotide polymorphisms rs10958409 GA/AA (located near *SOX17*, a transcription factor that modulates cardiovascular development and endothelial cell biology) and rs1333040 CT/TT (located near *CDKN2A*, *CDKN2B*, and *ANRIL*, which regulate p53 activity) and risk of ischemic and hemorrhagic stroke in OC users and nonusers.<sup>222</sup> Women with the rs10958409 GA/AA or rs1333040 CT/TT genotypes (associated with susceptibility of intracranial aneurysm) had an increased overall risk of stroke, which increased to an OR of 6.06 (95% CI, 1.69–21.81) and 14.48 (95% CI, 1.56–134.43), respectively, in OC users <50 years of age. The rs1333040 single-nucleotide polymorphism was a significant risk with OC use only for hemorrhagic stroke, not IS.<sup>222</sup> This study is important because it demonstrates not

only the gene-drug interaction but also some potential mechanisms for how OCs might lead to hemorrhage in specific at-risk populations.<sup>222</sup>

### Additional Risk Factors for Stroke in Women Using OCs

Besides the well-established risk associated with older age, cigarette smoking, hypertension, and migraine headaches,<sup>223</sup> the Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) study from the Netherlands showed that women who were obese (OR, 4.6; 95% CI, 2.4–8.9) and had a history of hypercholesterolemia (OR, 10.8; 95% CI, 2.3–49.9) were also at an increased risk from OC use compared with women with these risk factors who did not use OCs.<sup>224</sup>

The RATIO investigators have performed multiple analyses to identify prothrombotic mutations in women with stroke who were and were not OC users (Table 8). They found that women using OCs who were heterozygous for factor V Leiden (OR, 11.2; 95% CI, 4.2–29.0) and methyl tetrahydrofolate reductase or MTHFR 677TT mutation (OR, 5.4; 95% CI, 2.4–12.0) were at increased risk of IS. There may have been some synergism between OCs and these mutations, because the increased risk was not evident in nonusers with these mutations.<sup>225</sup> In addition, this study also showed an association with a genetic variation of factor XIII.<sup>226</sup> In the assessment of acquired antiphospholipid antibodies, the presence of  $\beta 2$  glycoprotein-1 antibodies was associated with 2.3-fold increased odds of stroke (95% CI, 1.4–3.7), but there was no association with anticardiolipin or antiprothrombin antibodies. The prevalence of lupus anticoagulant was 17% in women with IS, and the OR was very high at 43.1 (95% CI, 12.2–152.0).<sup>227</sup> The OR increased to 201 (95% CI, 22.1–1828.0) in women who were also using OCs, although this was based on a very small number of outcomes. This is another example of the amplification of IS risk in a condition that is already associated with arterial thromboembolism and VTE.<sup>227</sup>

The RATIO investigators also assessed the association between OC use and endothelial dysfunction. They reported that an increase in von Willebrand factor levels and low ADAMTS13 levels were associated with increased odds of IS and MI in young women in the RATIO cohort, with a further

**Table 8. Odds of Ischemic Stroke With the Presence of Genetic or Acquired Prothrombotic Factors With and Without OC Use in the RATIO Cohort**

Study	Case/Control, n	Biomarker (Genetic or Acquired)	Adjusted OR (95% CI)	
			Non-OC Users	OC Users
Slooter et al <sup>225</sup>	193/767	FVL	0.4 (0.1–1.9)*	11.2 (4.3–29.0)*
		MTHFR 677TT	1.1 (0.5–2.4)*	5.4 (2.4–12.0)*
Pruissen et al <sup>226</sup>	190/767	FXIII Tyr204Phe	8.8 (4.3–18)†	20 (9–46)†
Urbanus et al <sup>227</sup>	175/628	Lupus anticoagulant (Ratio <sub>sic</sub> $\geq 1.15$ )	33.6 (6.8–167)*	201.0 (22.1–1828.0)*
Andersson et al <sup>228</sup>	175/638	vWF >90th percentile	1.6 (0.8–3.5)‡	11.4 (5.2–25.3)‡
		ADAMTS13 $\leq 10$ th percentile	1.8 (0.8–4.3)‡	5.1 (2.4–11.2)‡

ADAMTS13 indicates a disintegrin and metalloproteinase with the thrombospondin type I repeat 13; CI, confidence interval; FVL, factor V Leiden mutation; FXIII, factor XIII; MTHFR, methylenetetrahydrofolate reductase; OC, oral contraceptive; OR, odds ratio; RATIO, Risk of Arterial Thrombosis in Relation to Oral Contraceptives; Ratio<sub>sic</sub>, normalized ratios for lupus anticoagulant screen and lupus anticoagulant–confirm coagulation times; and vWF, von Willebrand factor.

\*Adjusted for age, residence area, and index year.

†Adjusted for age at index date, index year, area of residence, hypercholesterolemia, hypertension, diabetes mellitus, and smoking.

‡Adjusted for age, year of event/index year, area of residence, hypercholesterolemia, hypertension, diabetes mellitus, and smoking.

increase in the OR with OC use.<sup>228</sup> The largest effect of OC use was in women with von Willebrand factor levels >90th percentile, for whom the OR for stroke was 1.6 (95% CI, 0.8–3.5) in nonusers and increased to 11.4 (95% CI, 5.2–25.3) in OC users. The results of this study demonstrate that OC use appears to further increase the risk of stroke in the setting of endothelial dysfunction. Additional research should be focused on the validation of von Willebrand factor and ADAMTS13 as risk factors for stroke with OC use in other racial/ethnic and geographic populations, as well as exploration of the value of measuring these biomarkers in women before initiation of OCs.

Should women be screened for thrombophilia before hormonal contraception is prescribed for them? This question has been addressed in a large systematic review and meta-analysis of the risk of VTE in the high-risk settings of OC use and pregnancy.<sup>229</sup> Although there are 15-fold odds of VTE in women with the factor V Leiden mutation who are using OCs (95% CI, 8.66–28.15), the absolute risk is low because of the low prevalence of this and other thrombophilias and VTE. For other hereditary thrombophilias, including prothrombin gene mutation, as well as protein C and antithrombin deficiencies, the odds of VTE increased in combination with OC use, but the odds of VTE stayed the same with protein S deficiency.<sup>229</sup> IS and CVT are much less common than VTE,<sup>144</sup> so the yield of routine screening would be even lower for these conditions. Selective screening based on prior personal or family history of VTE is proposed to be more cost-effective than universal screening in women who initiate OCs or desire to become pregnant.<sup>229</sup> The cost-effectiveness analysis in this meta-analysis was designed for prevention of VTE, but adaptation to stroke screening in young women should also include obesity, diabetes mellitus, hyperlipidemia, hypertension, and cigarette smoking.

Another very important risk factor for stroke in young women is migraine aura, which has some evidence supporting a further increase in risk for women who also use OCs. An analysis of the Stroke Prevention in Young Women study, a population-based, case-control study of 386 women aged 15 to 49 years with incident stroke and 614 age- and ethnicity-matched control subjects, showed that women with probable migraine with visual aura were at 1.5-fold increased odds (95% CI, 1.1–2.0) of stroke compared with control subjects.<sup>230</sup> Women with this migraine type who also smoked cigarettes and used OCs had 7.0-fold higher odds (95% CI, 1.3–22.8) of stroke than women with probable migraine with visual aura who did not smoke or use OCs; however, women with probable migraine with visual aura who were OC users but nonsmokers did not have a significantly increased odds of stroke, which suggests the risk with both OC use and smoking in women with probable migraine with visual aura is additive.<sup>230</sup> This was a biethnic cohort of black (representing a higher proportion of cases) and white women, whereas many of the large cohorts were limited to a northern European population. A consensus statement from both headache and stroke experts suggests screening for and treatment of all traditional stroke risk factors in women with migraine but does not state that low-dose OC use is contraindicated.<sup>231</sup>

### **Hormonal Contraception and BP**

The impact of OC use on BP, an important stroke risk factor, and other hemodynamic parameters is somewhat controversial. A study of BP and hemodynamic measurements in young women (mean age 20 years) in the United Kingdom (ENIGMA Study) showed that women using OCs had a marginal but significantly higher systolic BP (mean 112±12 versus 110±11 mmHg in nonusers;  $P=0.04$ ) and an increased arterial pulse wave velocity, a measure of aortic stiffness<sup>232</sup>; however, in the multivariate model, mean arterial pressure, age, and heart rate were associated with arterial pulse wave velocity but not OC use.<sup>232</sup>

Several systematic reviews cover the topic of OC use and hypertension in women. Summarizing the data through 2005, one review estimated the odds of IS for women with hypertension using OCs were 1.73 (95% CI, 0.83–3.60) and concluded that there was no synergistic increase in risk because the odds of stroke in normotensive women using OCs were similar.<sup>233</sup> A systematic review of studies that examined BP after initiation of OCs demonstrated mixed results from studies of follow-up BPs. Generally, the mean BPs were most often well below 140/90 mmHg. Importantly, only a very small percentage ( $\approx 2\%$ ) of women developed hypertension.<sup>234</sup> A systematic review of studies that collected outcomes based on measurement of BP before initiation of OCs<sup>235</sup> found 2 case-control studies that met criteria for inclusion.<sup>220,236</sup> Both studies demonstrated a higher OR of IS in women without versus with BP measurement before initiation of OCs, although the CIs overlapped.<sup>220,236</sup> A separate case-control study showed no difference in hemorrhagic stroke based on preinitiation BP measurement.<sup>221</sup> Taken together, these limited data suggest that OCs appear to marginally increase BP, albeit infrequently leading to hypertension, and that measurement of BP before OC initiation may be an important preventive measure to detect women at risk of stroke.

### **OCs: Summary and Gaps**

The relative increase in stroke risk with low-dose OCs is small, approximately 1.4 to 2.0 times that of non-OC users.<sup>144</sup> On the basis of the longitudinal data from the Danish population-based study, among 10 000 women who use the 20- $\mu$ g dose of desogestrel with ethinyl estradiol for 1 year, 2 women will have arterial thrombosis and 6.8 will have venous thrombosis.<sup>144</sup> The risk of stroke with OC use also appears to be lower than the risk associated with pregnancy ( $\approx 3$  per 10 000 deliveries).<sup>143</sup>

Despite the overall low risk of stroke from hormonal contraception, certain subgroups of women, particularly those who are older, smoke cigarettes, or have hypertension, diabetes mellitus, obesity, hypercholesterolemia, or prothrombotic mutations, may be at higher risk for stroke. Estimates are based primarily on case-control studies and a smaller number of cohort studies primarily from northern European countries, which limits generalizability to other populations. Further research is needed to better understand the subgroups of women who may be at risk for hemorrhagic stroke associated with OCs based on age, race/ethnicity, genetic makeup, and parity. In addition, research assessing the value of specific biomarkers of endothelial function, such as von Willebrand

factor and ADAMTS13, before and during OC use, as well as after an arterial thrombotic event, is warranted.

### OCs: Recommendations

1. OCs may be harmful in women with additional risk factors (eg, cigarette smoking, prior thromboembolic events) (*Class III; Level of Evidence B*).<sup>224,225</sup>
2. Among OC users, aggressive therapy of stroke risk factors may be reasonable (*Class IIb; Level of Evidence C*).<sup>224,225,231</sup>
3. Routine screening for prothrombotic mutations before initiation of hormonal contraception is not useful (*Class III; Level of Evidence A*).<sup>229</sup>
4. Measurement of BP before initiation of hormonal contraception is recommended (*Class I; Level of Evidence B*).<sup>220,235,236</sup>

### Menopause and Postmenopausal HT

#### Menopause Onset

Exposure to endogenous estrogen has been hypothesized to be protective for stroke in premenopausal women; however, given logistical difficulties in collecting longitudinal data on endogenous hormones and the large sample sizes that would be required to study stroke in younger women, no study has investigated the relationship between endogenous hormones and stroke as women transition through menopause. The association between onset of menopause and stroke risk has been the subject of 2 recent reviews, one focusing on the association of age at menopause and stroke risk and the other focusing on the association of premature or early menopause and stroke risk.<sup>237,238</sup> In the first review by Lisabeth and Bushnell,<sup>237</sup> the authors concluded that the few studies that considered the association between age at menopause and incident stroke had inconsistent findings. The findings of these studies were summarized briefly. Hu et al<sup>239</sup> found that age at natural menopause was not associated with risk of total stroke, IS, or hemorrhagic stroke among 35 616 women in the Nurse's Health Study who reported no use of HT. In a cohort study of 5731 postmenopausal Korean women who did not use HT, no association was found between age at natural menopause and risk of total stroke, IS or hemorrhagic stroke.<sup>240</sup> Lisabeth et al,<sup>241</sup> using data from the Framingham Heart Study (n=1430), found that women with natural menopause before age 42 years had twice the IS risk (RR, 2.03; 95% CI, 1.16–3.56) as women who had natural menopause at ≥42 years of age after adjustment for age, risk factors, and postmenopausal estrogen use. Results from a Japanese cohort also suggested that women who underwent menopause before 40 years of age were more likely to have an IS than those with menopause between 50 and 54 years of age after adjustment for age and risk factors (RR, 2.57; 95% CI, 1.20–5.49); however, findings appeared to be largely driven by women with surgical menopause.<sup>242</sup> A case-control study conducted in Spain found no association between menopause at <53 years of age and the odds of noncardioembolic stroke after accounting for age and risk factors.<sup>243</sup>

In the review by Rocca et al,<sup>238</sup> 7 observational cohort studies were summarized to determine whether early or premature

menopause is associated with stroke. The findings from 3 of the studies not yet discussed previously are briefly summarized.<sup>244</sup> Using data from the Nurse's Health Study, Parker et al<sup>245</sup> found that after multivariable adjustment, women with hysterectomy with bilateral oophorectomy had a slightly elevated risk of total stroke compared with women with hysterectomy with ovarian conservation (HR, 1.14; 95% CI, 0.98–1.33), and this association did not reach significance. In further analysis of these data limited to women with hysterectomy who had never used estrogen therapy, the authors found a larger statistically significant association between oophorectomy and total stroke (HR, 1.85; 95% CI, 1.09–3.16) in all women and in women with hysterectomy before age 50 years (HR, 2.19; 95% CI, 1.16–4.14). A more recent analysis of a Swedish cohort found that women who underwent an oophorectomy before age 50 years had an increased risk of total stroke (HR, 1.47; 95% CI, 1.16–1.87) compared with women with no hysterectomy and no oophorectomy.<sup>246</sup> Finally, in a recent analysis of data from the WHI focused on women with a history of hysterectomy (without capture of age before natural menopause), no association was found for oophorectomy versus ovarian conservation and risk of total stroke in all women (HR, 1.04; 95% CI, 0.87–1.24) or those women without a history of hormone use (HR, 1.31; 95% CI, 0.92–1.87) after multivariable adjustment.<sup>247</sup>

#### Menopause Onset: Summary and Gaps

Results of existing studies of the association between age at menopause or premature or early menopause, whether natural or surgical, and stroke risk appear to suggest increased risk of stroke with earlier onset of menopause, although the evidence is not entirely consistent. Few data on the association of other surrogate markers for endogenous hormone exposures, such as lifetime estrogen exposure, duration of ovarian activity, or time since menopause, and stroke risk exist. Additional studies are needed to determine the influence of the onset of menopause on stroke risk. Studies should aim to determine whether the association between menopause onset and stroke is limited to ischemic events and whether and how the type of menopause (natural or surgical) may impact this association.

#### Postmenopausal HT

Early observational evidence suggested a potential benefit of HT on cerebrovascular disease<sup>248</sup>; however, even as early as 2002, evidence was emerging that HT may have detrimental effects. A review of 29 observational studies found no clear evidence that HT use benefited stroke risk in postmenopausal women.<sup>249</sup> Subsequent randomized clinical trials for both the primary and secondary prevention of stroke in women randomized to HT have been universally negative (Table 9). Two large clinical trials examined women with established vascular disease: the Heart and Estrogen/Progestin Replacement Study (HERS) and Women's Estrogen for Stroke Trial (WEST).<sup>250,251</sup> Stroke events (including any stroke and IS) were similar for women allocated to an estrogen or to placebo.

Findings from the WHI HT trials were reported soon after those from HERS and WEST. The multicenter WHI randomized women into groups according to use of conjugated equine estrogen (CEE) and medroxyprogesterone or CEE alone, based on hysterectomy status.<sup>253–256</sup> These women, unlike those in previous randomized trials, did not have documented vascular



disease (no self-reported history of acute MI, stroke, or TIA in the previous 6 months); however, they were considerably older than women in previous observational trials, with a mean age of 63 years. Additional analyses of the WHI focused on specific subgroups of women to determine those at particularly high risk; the subgroups were outlined in previous AHA guidelines.<sup>19</sup> The risk of stroke with CEE was limited to IS (HR, 1.55; 95% CI, 1.19–2.01) and not hemorrhagic stroke (HR, 0.64; 95% CI, 0.35–1.18). There was no difference based on stroke pathogenic subtype, severity, or mortality. Women with no prior history of CVD were at higher risk (HR, 1.73; 95% CI, 1.28–2.33) than women with a prior history (HR, 1.01; 95% CI, 0.58–1.75). Women using HT who were 50 to 59 years of age had a lower risk (HR, 1.09; 95% CI, 0.54–2.21) than those 60 to 69 years of age (HR, 1.72; 95% CI, 1.17–2.54) or those 70 to 79 years of age (HR, 1.52; 95% CI, 1.02–2.29) compared with nonusers. These risk estimates did not vary by race or other baseline risk factors, including aspirin or statin use or BP.<sup>19</sup>

There is also little compelling evidence that HT is effective at preventing deterioration of cognitive function in postmenopausal women. The Women's Health Initiative Memory Study (WHIMS), a subgroup of women enrolled in the WHI, found that for women  $\geq 65$  years of age, HT did not reduce the incidence of either dementia or mild cognitive impairment.<sup>260,261</sup>

HT had an adverse effect on global cognitive function,<sup>262,263</sup> which was greater among women with lower cognitive function at initiation of treatment. Subsequent magnetic resonance imaging studies in a subset of these women found greater brain atrophy<sup>264</sup> but not a significantly higher volume of subclinical cerebrovascular lesions in treated women.<sup>265</sup> The adverse effects were most evident in women experiencing cognitive deficits before initiation of HT.

Similar results have been reported in randomized clinical trials for selective estrogen receptor modulators and other hormonally active compounds (including raloxifene<sup>266,267</sup> and tibolone,<sup>268</sup> a commonly used therapy in Europe with both estrogenic and androgenic properties). Raloxifene (60 mg versus placebo) had no effect on the risk of nonfatal stroke (HR, 1.10; 95% CI, 0.92–1.32) but increased the risk of fatal strokes (HR, 1.49; 95% CI, 1.00–1.24;  $P=0.05$ ).

There has been an increasing recognition that the timing of HT initiation may play a critical role in the overall effect of HT.<sup>269,270</sup> An analysis of the WHI subjects was performed to test this hypothesis, and interestingly, women <10 years from menopause had no increased risk of coronary heart disease events with any CEE (alone or CEE plus medroxyprogesterone; HR, 0.76; 95% CI, 0.50–1.16), whereas women  $\geq 20$  years post menopause had an elevated risk (HR, 1.28; 95%

**Table 9. Association Between HT Use and Stroke Risk in Randomized Controlled Trials of Perimenopausal and Postmenopausal Women**

Trial	Total No.	Average Age, y	HT Regimen	Vascular Disease	Follow-up	Any Stroke, HR (95% CI)
HERS (2001) <sup>250</sup>	2763	66.7	0.625 mg of CEE plus 2.5 mg of MPA (n=1380) vs placebo (n=1383)	Yes (CAD)	4.1 y	1.1 (0.9–1.7)
WEST <sup>251</sup>	664	71	Estrogen (1 mg of estradiol) vs placebo	Yes (CVD); nondisabling ischemic stroke or TIA within preceding 90 d (CVD)		1.1 (0.8–1.6)
HERS II <sup>252</sup>	2321	66.7	0.625 mg of CEE plus 2.5 mg of MPA (n=1380) vs placebo (n=1383)	Yes (CAD)	6.8 y (2.7–y unblinded follow-up to HERS)	1.09 (0.75–1.6)
WHI <sup>253–256</sup>	16 608	63	CEE+MPA	No*		1.3 (1.0–1.7)
WHI <sup>253–256</sup>	10 739	63	CEE	No*		1.4 (1.1–1.7)
Estonian trial <sup>257</sup>	Open HT, 494; open control, 494; blind HT, 404; blind placebo, 373	Open HT, 58.6; open control, 58.9; blind HT, 58.5; blind placebo, 59	CEE 0.625 mg/d plus 2.5 mg/d MPA or CEE 0.625 mg/d plus 5 mg/d MPA, if <3 y had passed since menopause at recruitment	No*	2.0–5.0 y	1.24 (0.85–1.82)
DOPS <sup>258</sup>	Randomly allocated (open label, n=1006) to HT (n=502) or no treatment (n=504)	49.7	Intact uterus: 2 mg of synthetic 17 $\beta$ -estradiol for 12 d, 2 mg of 17 $\beta$ -estradiol plus 1 mg of norethisterone acetate for 10 d, and 1 mg of 17 $\beta$ -estradiol for 6 d. Prior hysterectomy: 17 $\beta$ -estradiol 2 mg/d. Enrolled within 24 mo of last menses.	No*	11 y (randomized treatment phase) and continued observational follow-up (16 y)	11-y follow-up, 0.77 (0.35–1.70); 16-y follow-up, 0.89 (0.48–1.65; $P=0.71$ )

CAD indicates coronary artery disease; CEE, conjugated equine estrogen; CI, confidence interval; CVD, cardiovascular disease; DOPS, Danish Osteoporosis Prevention Study; HERS, Heart and Estrogen/Progestin Replacement Study; HR, hazard ratio; HT, hormone therapy; MPA, medroxyprogesterone acetate; WEST, Women's Estrogen for Stroke Trial; and WHI, Women's Health Initiative trial for women with a uterus (CEE+MPA) or without a uterus (CEE).

\*Self-reported as no history of acute myocardial infarction, stroke, or transient ischemic attack in the previous 6 months.<sup>259</sup>

CI, 1.03–1.58;  $P$  for trend=0.02). There was, however, no trend for increased stroke based on years since menopause.<sup>267</sup> The Estonian trial of HT, a study of women 50 to 64 years of age, also confirmed the findings of the WHI, with a trend toward an increase in cerebrovascular events in women taking HT<sup>257</sup> (Table 9). The Kronos Early Estrogen Prevention Study (KEEPS) is an ongoing trial of women 42 to 58 years of age who are within 36 months of their final menstrual period and who were randomized to estrogen replacement in low doses (0.45 mg of CEE), transdermal formulation (50 µg/wk), or combined with cyclic oral, micronized progesterone 200 mg for 12 days each month.<sup>271</sup> The primary outcomes are progression of subclinical atherosclerosis as measured by carotid intima-media thickness and coronary calcium scores, rather than stroke; however, this study will directly assess HT initiated soon after menopause. This study has completed enrollment, and initial results were presented at the meeting of the North American Menopause Society on October 3, 2012 (<http://www.keepstudy.org>); however, until the full data are available, no statements can be made regarding the safety of HT in this subset of women. The effective duration of use for benefit is currently unknown.

Only 1 randomized trial, the open-label Danish Osteoporosis Prevention Study (DOPS),<sup>258</sup> specifically examined healthy women aged 45 to 58 years who were recently postmenopausal or had perimenopausal symptoms in combination with recorded postmenopausal serum follicle-stimulating hormone values ( $n=1006$ ). Women had a mean time since menopause of 0.6 years, with last menstrual bleeding 3 to 24 months before study entry. Stroke was a designated (secondary) end point. A total of 502 women were randomly allocated to receive HT and 504 to receive no treatment (control; Table 9). Importantly, this study had an open-label design, and the patients in the control arm did not receive placebo, which could have influenced compliance in the HT arm. After 11 years, the trial was stopped secondary to concerns of potentially harmful effects of HT that had been seen in other trials, such as the WHI. Women were followed up as an observational cohort for an additional 5 years. There was no increase in stroke, VTE, or breast cancer in treated women. HT initiated in these recently postmenopausal, younger women significantly reduced the risk of the combined end point of mortality, MI, or heart failure. Stroke rates did not differ between groups.<sup>258</sup>

Transdermal estradiol may represent a safer alternative than oral estrogens, because treatment does not appear to increase the risk of VTE and stroke and may reduce the risk of MI compared with nonusers. In a nested case-control study examining patients in general practices in the United Kingdom that included 15710 cases of stroke and almost 60000 randomly selected, matched control subjects from women aged 50 to 79 years, transdermal estradiol was not associated with an increased risk of stroke, whereas oral estrogens significantly increased stroke risk.<sup>272</sup> Importantly, dose effects, even from transdermal use, were seen in this population, because low-dose products that contained  $\leq 50$  µg of estrogen did not increase stroke risk (rate ratio, 0.81; 95% CI, 0.62–1.05) compared with no use, but high-dose patches that contained  $>50$  µg did increase risk (rate ratio, 1.89; 95% CI, 1.15–3.11). Until randomized blinded studies are performed

that demonstrate the safety of transdermal therapy, this treatment is not recommended for stroke prevention on the basis of available evidence, although this treatment is approved for relief of menopausal symptoms.

### Postmenopausal HT: Summary and Gaps

An increased risk of stroke is associated with the tested forms of HT, which include CEE/medroxyprogesterone in standard formulations. A recent analysis and review of 9 randomized controlled trials,<sup>273</sup> a review of HT trials by Henderson and Lobo,<sup>274</sup> and a Cochrane review that included 23 studies<sup>275</sup> all reached the conclusion that HT, in the formulations prescribed in prior studies, does not reduce stroke risk and may increase the risk of stroke. There are insufficient data to assess the risk of long-term HT use initiated in perimenopausal women or postmenopausal women  $<50$  years of age; however, the data on this subject are often conflicting, and information regarding risk with newer HT regimens continues to emerge. There is no benefit of raloxifene or tamoxifen for stroke prevention, and raloxifene may increase the risk of fatal stroke. Tibolone is also associated with an increased risk of stroke. Prospective randomized trials of alternative forms of HT are ongoing, although the primary outcomes are an intermediate measurement of subclinical atherosclerosis and not stroke. The use of HT for other indications needs to be informed by the risk estimate for vascular outcomes provided by the clinical trials that have been reviewed. HT is associated with a small to moderate improvement in sexual function, particularly in pain, when used in women with menopausal symptoms or in early postmenopause (within 5 years of amenorrhea), but this treatment cannot be recommended currently for stroke prevention in unselected postmenopausal women.<sup>276</sup> Limitations of prior trials included low adherence, high attrition, inadequate power to detect risks for low-incidence outcomes such as stroke, and evaluation of few regimens. Further research is needed to better understand the subgroups of women who may be at risk for stroke associated with HT and to optimize the timing and route of administration, as well as the dose and type of hormone used. Much less is known about the use of HT and the risk of either ICH or SAH.

### Postmenopausal HT: Recommendations

1. HT (CEE with or without medroxyprogesterone) should not be used for primary or secondary prevention of stroke in postmenopausal women (Class III; Level of Evidence A).
2. Selective estrogen receptor modulators, such as raloxifene, tamoxifen, or tibolone, should not be used for primary prevention of stroke (Class III; Level of Evidence A).

### Risk Factors More Common in Women Than Men

#### Migraine With Aura

The prevalence of migraine in the population is  $\approx 18.5\%$ , and for migraine with aura, it is  $4.4\%$ .<sup>277</sup> Women are 4 times more

likely to have migraines than men.<sup>277</sup> Very rarely are migraines associated with stroke, however. Migraine with aura is defined as a typical migraine headache plus the presence of homonymous visual disturbance, unilateral paresthesias or numbness, unilateral weakness, or aphasia or unclassifiable speech difficulty that might typically precede the migraine headache.<sup>278</sup> This type of migraine is associated with double the risk for IS based on meta-analyses of diverse cohorts of patients. The most recently published meta-analysis reported a 2.5-fold increase in IS in patients with migraine with aura (OR, 2.51; 95% CI, 1.52–4.14),<sup>279</sup> similar to a previous analysis that showed an OR of 2.16 (95% CI, 1.53–3.03).<sup>280</sup> The association between migraine aura and IS is higher in women than men. In women with migraine with aura, the risk increases even more in those using oral contraceptives (OR, 7.02; 95% CI, 1.51–32.68) and in cigarette smokers (OR, 9.03; 95% CI, 4.22–19.34).<sup>280</sup>

The absolute risk of migraine-associated stroke is relatively low. On the basis of data from the Women's Health Study (WHS), migraine with aura accounted for 4 additional IS cases per 10000 women per year when migraine with aura was the assumed underlying cause of stroke.<sup>281</sup> The risk is higher with increasing frequency of migraine<sup>282</sup> and if the aura does not include nausea and vomiting.<sup>283</sup> Data from the WHS suggest that migraine with aura is associated with increased risk of TIA (RR, 1.56; 95% CI, 1.03–2.36) and nondisabling stroke (RR, 2.33; 95% CI, 1.37–3.97) compared with women with no history of migraine<sup>284</sup> and that the presence of migraine with aura does not modify the beneficial effects of aspirin.<sup>285</sup> Therefore, migraine aura appears to be associated with a better prognosis because of the link to milder strokes and TIAs than with non-migraine-associated strokes in the WHS.

Migraines with aura have also been associated with a risk of hemorrhagic stroke in the WHS, but this association was stronger in the subset of women with fatal hemorrhagic stroke and in women <55 years of age.<sup>286</sup> In pregnant women with an *International Classification of Diseases, 9th Revision*, hospital code for migraine, there was a large association with hemorrhagic stroke (OR, 9.1; 95% CI, 3.0–27.8); however, in the pregnant population, the risk of vascular diseases was closely associated with a concomitant diagnosis of preeclampsia/eclampsia.<sup>287</sup>

Interestingly, there is an emerging literature on the association between migraines and preeclampsia.<sup>288–290</sup> The most recent analysis of the United Kingdom Obstetric Surveillance System found 30 cases of antenatal stroke, for an estimated incidence of 1.5 cases per 100000 women who delivered babies (95% CI, 1.0–2.1). Factors associated with increased risk of antenatal stroke were history of migraine (adjusted OR, 8.5; 95% CI, 1.5–62.1), gestational diabetes (adjusted OR, 26.8; 95% CI, 3.2–∞), and preeclampsia or eclampsia (adjusted OR, 7.7; 95% CI, 1.3–55.7).<sup>146</sup>

### **Migraine With Aura: Summary and Gaps**

Migraine with aura (but not without aura) is associated with risk for IS and hemorrhagic stroke in women, especially those <55 years of age, although the absolute risk is low, and these women appear to have a good poststroke prognosis. Not only do the majority of studies with both men and women

support this as a predominantly female issue, but the largest cohorts that have been studied are limited to women. There are not sufficient data to recommend specific approaches to treat migraine with the intention of lowering risk of stroke. Migraine treatment with triptans is contraindicated in patients with a history of cerebrovascular disease or coronary heart disease,<sup>291</sup> as explicitly stated in guidelines from the American Academy of Neurology. As for the risk of treatment with triptans in women with migraine with aura, there are no data to guide this decision other than the observational data related to higher risk of stroke among those who smoke cigarettes or use OCs (see “Oral Contraceptives”). Given the number of studies that consistently show a higher risk of stroke in younger women with migraine with aura, it may be reasonable to include this in a woman-specific risk profile. The general recommendations for men and women with migraine with aura and stroke are as stated in the primary prevention guideline.<sup>19</sup>

### **Migraine With Aura: Recommendations**

- 1. Because there is an association between higher migraine frequency and stroke risk, treatments to reduce migraine frequency might be reasonable, although evidence is lacking that this treatment reduces the risk of first stroke (Class IIb; Level of Evidence C).**
- 2. Because of 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 with aura (Class IIa; Level of Evidence B).**

### **Obesity, Metabolic Syndrome, and Lifestyle Factors**

By the year 2030, an estimated 86% of Americans will be overweight or obese.<sup>292</sup> Obesity affects a disproportionate number of women in the United States; in 2007 to 2008, the age-adjusted prevalence of obesity in the United States was 35.2% in women compared with 32.0% in men.<sup>293</sup> Non-Hispanic black women have the highest prevalence of obesity (49.6% in 2007–2008).<sup>294</sup>

The distribution of obesity has important cardiovascular ramifications. In 1947, Vague<sup>295</sup> coined the term *android obesity* to describe the high-risk form of obesity, at that time more frequently found in men, in which the body fat is concentrated in the abdominal area; he introduced the term *gynoid obesity* to describe the low-risk lower-body adiposity, more frequently found in premenopausal women. Abdominal obesity (defined as waist circumference >88 cm in women and >102 cm in men), however, is now far more prevalent in women than men, and android obesity is a misnomer. In fact, data from NHANES in 2007 to 2008 revealed that among adults ≥20 years old, age-adjusted prevalence of abdominal obesity was 61.8% in women compared with 43.7% in men.<sup>293</sup> In addition, premenopausal women are increasingly likely to have abdominal obesity; a recent study of women aged 35 to 54 years in the United States revealed that from 1988–1994 until 1999–2004, the prevalence of abdominal obesity increased from 47.4% to 58.9%.<sup>296</sup> The escalating obesity epidemic may counter the tremendous advances that have been made



in smoking cessation and hypertension and dyslipidemia awareness and control in the United States. Understanding the effects of obesity and abdominal adiposity on stroke risk, and the potentially differential impact of these conditions on women compared with men, may elucidate avenues for reducing the incidence and morbidity of stroke.

#### **Association Between Obesity and Abdominal Adiposity and Stroke Risk and Outcomes**

Obesity is an independent risk factor for stroke. Studies have revealed a graded association between BMI and stroke risk; the risk of total stroke or IS rises linearly with increasing BMI and in a stepwise fashion for higher BMI categories.<sup>297–299</sup> Obesity affects stroke risk in both men and women, even after adjustment for factors such as age, physical activity, smoking, alcohol consumption, and comorbid conditions such as hypertension and diabetes mellitus<sup>297–307</sup> (Table 10). There is no clear evidence that obesity has a stronger impact on stroke risk in women than in men (Table 10).

Numerous epidemiological and metabolic studies have shown that abdominal obesity has a stronger correlation with insulin resistance, atherogenic dyslipidemia, diabetes mellitus, and CVD than other distributions of body fat.<sup>309</sup> Abdominal obesity can be measured by use of waist circumference, waist-to-hip ratio, and waist-to-stature ratio. As with BMI, there is a graded association between abdominal obesity and stroke risk. A study of 67 000 women found a 2% relative increase in total stroke risk with each 1-unit increase in waist circumference.<sup>303</sup> Other studies have shown similar associations between abdominal obesity and stroke risk.<sup>304,307,310,311</sup> Although many studies have shown that abdominal obesity is associated with stroke in women, even after adjustment for age, lifestyle habits, and medical comorbidities,<sup>301,303,307,310–312</sup> some studies have shown that the association is no longer significant in multivariable models<sup>300,313,314</sup> (Table 11). Studies of sex differences in the effect of abdominal obesity on stroke risk have had conflicting results (Table 11).

The impact of obesity on poststroke outcomes remains unclear. One retrospective analysis of cross-sectional and prospective data from a nationally representative survey of the US adult population followed up from survey participation in 1988 to 1994 through mortality assessment in 2000 revealed that the overall risk for all-cause mortality among stroke survivors increased per 1 kg/m<sup>2</sup> of higher BMI ( $P=0.030$ ), but an interaction between age and BMI ( $P=0.009$ ) revealed that the association of higher BMI with mortality risk was strongest in younger individuals and declined linearly with increasing age.<sup>315</sup> On the other hand, a post hoc analysis of the Telemedical Project for Integrative Stroke Care (TEMPiS) revealed that mortality risk was lower in overweight patients (HR, 0.69; 95% CI, 0.56–0.86) and lowest in obese (HR, 0.50; 95% CI, 0.35–0.71) and very obese (HR, 0.36; 95% CI, 0.20–0.66) patients compared with those with normal BMI.<sup>316</sup> It is unclear whether obesity has a differential impact on stroke outcomes in women compared with men.<sup>317</sup>

#### **Metabolic Syndrome**

Metabolic syndrome, a combination of cardiometabolic risk factors that tend to cluster together (insulin resistance, abdominal adiposity, dyslipidemia, and hypertension) affects

approximately one third of the US adult population.<sup>318</sup> Analysis of data from NHANES 2003 to 2006 revealed that 36.1% of men and 32.4% of women in the United States had metabolic syndrome ( $P=0.063$ ).<sup>318</sup> Numerous studies have shown an association between metabolic syndrome and stroke in both men and women<sup>303,310,311,314,319–326</sup> (Table 12). The exact mechanism whereby metabolic syndrome affects cardiovascular risk is unknown; it is thought that components of the syndrome synergistically increase vascular risk through mechanisms that include insulin resistance, hypercoagulability, endothelial dysfunction, and inflammation. Studies suggest that metabolic syndrome confers a higher stroke risk on women than men,<sup>303,310,320,321</sup> and metabolic syndrome accounts for a larger percentage of stroke events in women than in men (30% versus 4%, respectively).<sup>310</sup> The mechanisms for this difference are not completely understood.

#### **Pathophysiologic Mechanisms of Obesity, Abdominal Adiposity, and Metabolic Syndrome That Affect Stroke Risk**

The pathophysiological mechanisms by which general obesity increases stroke risk remain unclear. One proposed mechanism is that obesity is associated with a prothrombotic and proinflammatory state.<sup>328–332</sup> BMI is directly associated with fibrinogen, factor VII, plasminogen activator inhibitor, and tissue-type plasminogen activator antigen levels in both men and women.<sup>328</sup> Similar associations are present between abdominal obesity and hemostatic factors. These associations persist after controlling for age, smoking, total and high-density lipoprotein cholesterol, triglycerides, glucose level, BP, and use of antihypertensive medications.<sup>328</sup> In addition, higher levels of acute phase reactants such as C-reactive protein may decrease endothelial cell production of nitric oxide, which may in turn instigate a cascade of events leading to vasoconstriction, leukocyte adherence, platelet activation, oxidation, and thrombosis.<sup>333,334</sup> Attenuation of the protective effect of high-density lipoprotein cholesterol<sup>314</sup> attributable to general obesity may also play a role. The biological pathways by which abdominal adiposity increases stroke risk are also not yet understood, but platelet activation, inflammation, endothelial dysfunction, or an overactive endocannabinoid system<sup>335</sup> may all serve key roles in the process. In addition, increased very low-density lipoprotein production caused by the high lipolytic activity of abdominal adipose tissue<sup>304,312</sup> may increase stroke risk.

#### **Lifestyle**

Lifestyle factors such as a healthy diet,<sup>336–338</sup> physical activity,<sup>339–343</sup> abstinence from smoking,<sup>344–346</sup> moderate alcohol intake,<sup>347,348</sup> and maintenance of a healthy BMI<sup>299,308</sup> reduce the risk of CVD and mortality. Adherence to a combination of healthy lifestyle practices has been shown to decrease stroke incidence in women<sup>327</sup> and improve outcomes after stroke in both men and women.<sup>349</sup> All-cause mortality after stroke decreases with higher numbers of healthy behaviors (1–3 factors versus none: HR, 0.12 [95% CI, 0.03–0.47]; 4–5 factors versus none: HR, 0.04 [95% CI, 0.01–0.20]; 4–5 factors versus 1–3 factors: HR, 0.38 [95% CI, 0.22–0.66]; trend  $P=0.04$ ). Similar effects are observed for cardiovascular mortality after stroke (4–5 factors versus none: HR, 0.08 [95% CI, 0.01–0.66]; 1–3 factors versus none: HR, 0.15 [95% CI, 0.02–1.15]; 4–5 factors versus 1–3 factors: HR, 0.53 [95% CI, 0.28–0.98]; trend  $P=0.18$ ).<sup>349</sup>

**Table 10. Relationship Between Elevated BMI and Stroke**

First Author	Study Site	n	Follow-up, y	Study Type	End Point	BMI, kg/m <sup>2</sup>	HR (95% CI)	
							Women	Men
Bazzano <sup>297</sup>	China	154 736	Mean: 8.3	Prospective cohort	Clinically defined total stroke*	25–29.9 vs 18.5–24.9 ≥30	1.35 (1.24–1.47)	1.49 (1.39–1.61)
Hu <sup>300</sup>	Finland	49 996	Mean: 19.5	Prospective cohort	Clinically defined total stroke†	25–29.9 vs 18.5–24.9 ≥30	1.73 (1.51–1.98)	1.68 (1.43–1.97)
							1.02 (0.90–1.16)	1.13 (1.01–1.27)
Winter <sup>307</sup>	Germany	1137	≈1	Case-control	Clinically defined total stroke, TIA‡	25–29.9 vs <25.0 30–34.9 vs <25.0	1.12 (0.97–1.29)	1.32 (1.14–1.53)
							1.17 (0.60–2.28)	1.36 (0.82–2.25)
Saito <sup>298</sup>	Japan	71 722	Median: 7.9	Prospective cohort	Clinically defined total stroke§	27–29.9 vs 23.0–24.9 ≥30 vs 23.0–24.9	1.63 (0.78–3.37)	0.99 (0.55–1.80)
							1.29 (1.01–1.65)	1.09 (0.88–1.36)
Kurth <sup>299</sup>	USA	39 053	Mean: 10	Prospective cohort	Clinically defined total stroke	30–34.9 vs <20.0 ≥35 vs <20.0	2.16 (1.60–2.93)	1.25 (0.86–1.84)
							1.37 (0.83–2.28)	NA
Kurth <sup>308</sup>	USA	21 414	12.5	Prospective cohort	Clinically defined total stroke¶	27–29.9 vs <23 ≥30 vs <23	2.05 (1.18–3.55)	1.51 (1.19–1.92)
							N/A	1.51 (1.19–1.92)
Yatsuya <sup>301</sup>	USA	13 549	Median: 16.9	Prospective cohort	Clinically defined ischemic stroke#	28.6–32.0 ≥32	N/A	2.00 (1.48–2.71)
							Black: 1.15 (0.62–2.13) White: 1.49 (0.89–2.50)	Black: 1.33 (0.70–2.55) White: 1.85 (1.17–2.94)
Zhang <sup>303</sup>	China	67 083	Mean: 7.3	Prospective cohort	Clinically defined total stroke**	24.4–26.5 vs <21.1 ≥26.6 vs <21.1	Black: 1.43 (0.81–2.53) White: 1.78 (1.08–2.93)	Black: 2.12 (1.13–4.00) White: 1.85 (1.08–3.17)
							1.51 (1.30–1.74)	NA
Lu <sup>304</sup>	Sweden	33 578	Mean: 11	Prospective cohort	Clinically defined total stroke††	25–29.9 vs 20.0–24.9 ≥30 vs 20.0–24.9	1.71 (1.49–1.97)	NA
							1.2 (0.9–1.7)	NA
Rexrode <sup>305</sup>	USA	116 759	16	Prospective cohort	Clinically defined total stroke‡‡	29–31.9 vs <21.0 ≥32 vs <21.0	1.4 (0.8–2.4)	NA
							1.90 (1.28–2.82)	NA
Wang <sup>306</sup>	China	26 607	11	Prospective cohort	Clinically defined total stroke§§	25–29.9 vs 18.5–24.9 ≥30 vs 18.5–24.9	2.37 (1.60–3.50)	NA
							1.42 (1.16–1.73)	1.63 (1.35–1.96)
							1.57 (1.06–2.31)	2.20 (1.47–3.30)

BMI indicates body mass index; CI, confidence interval; HR, hazard ratio; NA, not available; and TIA, transient ischemic attack.

\*Adjusted for age, smoking, alcohol consumption, physical inactivity, education, residence in northern China, and residence in urban area.

†Adjusted for age, study year, smoking, physical activity, educational level, family history of stroke, alcohol consumption, systolic blood pressure, total cholesterol level, and history of diabetes mellitus.

‡Matched for age and sex and adjusted for physical inactivity, smoking, history of hypertension, and history of diabetes mellitus.

§Adjusted for age, smoking, alcohol consumption, sports and physical exercise, medications or past history of hypertension or diabetes mellitus, and Japan Public Health Center community.

||Adjusted for age, smoking status, exercise, alcohol consumption, and postmenopausal hormone use.

¶Adjusted for age, smoking, alcohol consumption, exercise, history of angina, parental history of myocardial infarction at age <60 y, and randomized treatment assignment.

#Adjusted for age, education, smoking status, cigarette-years, alcohol consumption, and physical activity.

\*\*Adjusted for age; education; occupation; family income; menopausal status; use of oral contraceptives, hormone therapy (HT), and aspirin; amount of exercise; cigarette smoking; alcohol consumption; and intakes of saturated fat, vegetables, fruits, and sodium comparing the highest versus lowest quintiles of BMI.

††Adjusted for age, smoking, alcohol intake, age at first childbirth, years of education, and oral contraceptive use.

‡‡Adjusted for age, smoking, oral contraceptive use, menopausal status, HT, and time period.

§§Adjusted for age, educational level, smoking status, and alcohol consumption.

A multitude of randomized controlled trials of lifestyle interventions targeting individuals at high risk for diabetes mellitus and CVD have been conducted.<sup>350–362</sup> Although many of the studies have proved effective in improving lifestyle habits and vascular risk factors in the short term, it has proved more challenging to maintain such changes and reduce cardiovascular events. For example, in the WHI Randomized Controlled Dietary Modification Trial, over a mean of 8.1 years, the dietary intervention reduced total fat intake and increased intakes of

vegetables, fruits, and grains but did not significantly reduce the risk of coronary heart disease, stroke, or cardiovascular death in postmenopausal women and achieved only modest effects on cardiovascular risk factors.<sup>358</sup> In addition, a 2-year behaviorally based physical activity and diet program implemented to reduce obesity in a primary care setting showed a significant reduction in waist circumference at 6 and 12 months, but the reduction in waist circumference was sustained in men but not women at 24 months.<sup>361</sup> On the other hand, a recent primary

**Table 11. Abdominal Obesity and Stroke in Women and Men**

First Author	Study Site	No. of Subjects	Follow-up, y	Study Type	End Point	Stroke Subtypes	Measure of Abdominal Obesity	HR or OR (95% CI)	
								Women	Men
Hu <sup>300</sup>	Finland	49 996	Mean: 19.5	Prospective cohort	Clinically defined stroke*	Ischemic, hemorrhagic	WC 4th vs 1st quartile WHR 4th vs 1st quartile	HR: 1.25 (0.78–2.01) HR: 1.07 (0.70–1.63)	HR: 1.57 (1.10–2.25) HR: 1.55 (1.06–2.26)
Winter <sup>307</sup>	Germany	1137	Undefined	Case-control	Clinically defined stroke, TIA†	Ischemic, hemorrhagic	F: WC ≥88 cm vs <80 cm M: WC >102 cm vs <94 cm	OR: 4.49 (2.13–9.46)	OR: 3.71 (2.18–6.32)
							F: WHR ≥0.85 vs <0.85 M: WHR ≥1.0 vs <1.0	OR: 7.77 (3.87–15.61)	OR: 4.13 (2.70–6.30)
Suk <sup>312</sup>	USA	1718	≈4	Case-control	Clinically defined stroke‡	Ischemic	F: WHR ≥0.86 vs <0.86 M: WHR ≥0.93 vs <0.93	OR: 2.6 (1.7–4.2)	OR: 3.2 (1.9–5.5)
Yatsuya <sup>301</sup>	USA	13 549	Median: 16.9	Prospective cohort	Clinically defined stroke§	Ischemic	WC 5th vs 1st quintile	Black HR: 1.65 (1.03–2.65) White HR: 1.97 (1.23–3.15)	Black HR: 3.19 (1.53–6.67) White HR: 2.15 (1.14–4.03)
							WHR 5th vs 1st quintile	Black HR: 2.45 (1.55–3.87) White HR: 1.76 (1.08–2.88)	Black HR: 1.69 (0.91–3.15) White HR: 2.55 (1.42–4.57)
Zhang <sup>303</sup>	China	67 083	Mean: 7.3	Prospective cohort	Clinically defined stroke¶	Ischemic, hemorrhagic	WC 5th vs 1st quintile	HR: 1.77 (1.53–2.05)	NA
							WHR 5th vs 1st quintile	HR: 1.59 (1.37–1.85)	NA
							WSR 5th vs 1st quintile	HR: 1.91 (1.61–2.27)	NA
Lu <sup>304</sup>	Sweden	33 578	Mean: 11	Prospective cohort	Clinically defined stroke¶	Ischemic, hemorrhagic	WC 4th vs 1st quartile	HR: 2.3 (1.2–4.3)	NA
							WHR ≥0.88 5th vs 1st quintile	HR: 2.4 (1.3–4.2)	NA
							WSR 5th vs 1st quintile	HR: 2.5 (1.5–4.3)	NA
Furukawa <sup>313</sup>	Japan	5474	Mean: 11.7	Prospective cohort	Clinically defined stroke#	Not stated	WC 4th vs 1st quartile	HR: 2.64 (1.16–6.03)	HR: 1.40 (0.82–2.41)

CI indicates confidence interval; HR, hazard ratio; F, female; M, male; NA, not applicable; OR, odds ratio; TIA, transient ischemic attack; WC, waist circumference; WHR, waist-hip ratio; and WSR, waist-to-stature ratio.

\*Adjusted for age; study year; smoking; physical activity; education level; family history of stroke; alcohol, vegetable, fruit, sausage, and bread consumption; systolic blood pressure; total cholesterol level; and history of diabetes mellitus.

†Matched for age and sex and adjusted for physical inactivity, smoking, history of hypertension, and history of diabetes mellitus.

‡Matched by age, sex, and race/ethnicity, and adjusted for hypertension, diabetes mellitus, any cardiac disease, current smoking status, no physical activity, moderate alcohol drinking, level of LDL cholesterol, level of HDL cholesterol, and education.

§Adjusted for age, education, smoking status, cigarette-years, usual alcohol consumption, and physical activity.

¶Adjusted for age; education; occupation; family income; menopausal status; use of oral contraceptives; hormone therapy; aspirin; amount of exercise; cigarette smoking; alcohol consumption; and intakes of saturated fat, vegetables, fruits, and sodium comparing the highest versus lowest quintiles.

¶Adjusted for age, smoking, alcohol intake, age at first birth, years of education, and ever use of oral contraceptives by the time of cohort enrollment.

#Adjusted for age, smoking, and drinking status.

prevention trial of an energy-unrestricted Mediterranean diet supplemented with either extra-virgin olive oil or nuts in high-risk people without CVD revealed that the groups randomly assigned to a Mediterranean diet with extra-virgin olive oil and to a Mediterranean diet with nuts had lower odds of MI,

stroke, or cardiovascular death (HR, 0.70 [95% CI, 0.54–0.92] and HR 0.72 [95% CI, 0.54–0.96], respectively) compared with usual care.<sup>362</sup> Regarding components of the primary end point, only the comparisons of stroke risk reached statistical significance (HR, 0.61; 95% CI, 0.44–0.86).<sup>362</sup> Prespecified



**Table 12. Metabolic Syndrome and Stroke**

First Author	Study Site	n	Follow-up, y	Type of Study	End Point	Stroke Subtypes	MetSD Definition	HR, OR, or RR (95% CI)	
								Women	Men
Boden-Albala <sup>310</sup>	USA	3298	Median: 6.4	Prospective cohort	Clinically defined stroke*	Ischemic	NCEP-ATP III	HR: 2.0 (1.3–3.1)	HR: 1.1 (0.6–1.9)
Chen <sup>319</sup>	Taiwan	3453	Mean: 10.4	Prospective cohort	Clinically defined stroke†	Ischemic	NCEP-ATP III	HR: 2.5 (0.7–8.4)	HR: 5.8 (2.0–16.5)
Ninomiya <sup>320</sup>	USA	10 357	NA	Cross-sectional	Self-reported stroke‡	Undefined	NCEP-ATP III	OR: 2.20 (1.56–3.11)	OR: 1.93 (1.34–2.78)
Najarian <sup>321</sup>	USA	2097	14	Prospective cohort	Clinically defined stroke§	Ischemic, hemorrhagic	NCEP-ATP III	RR: 2.81 (1.48–5.33)	RR: 1.57 (0.88–2.79)
Takahashi <sup>324</sup>	Japan	1493	Mean: 6.4	Prospective cohort	Clinically defined stroke	Ischemic	Other	RR: 23.1 (2.7–196)	NA
Li <sup>326</sup>	USA, Europe, Asia	92 732	Variable	Review of prospective cohort	Clinically defined stroke	Ischemic, hemorrhagic	NCEP-ATP III, WHO	RR: 1.54 (1.28–1.82)	RR: 1.46 (1.28–1.65)

ATP III indicates Adult Treatment Panel III; CI, confidence interval; EGIR, European Group for the Study of Insulin Resistance; HR, hazard ratio; IDF, International Diabetes Federation; MetSD, metabolic syndrome; NA, not available; NCEP, National Cholesterol Education Program; OR, odds ratio; RR, relative risk; and WHO, World Health Organization.

\*Adjusted for MetSD, age, education, insurance status, any physical activity, smoking, moderate alcohol use, and cardiac disease.

†Adjusted for age, age squared, residential township, smoking, alcohol intake, physical activity level, parental history of stroke, and education level.

‡Adjusted for age, sex, race, and cigarette smoking.

§Adjusted for age; systolic blood pressure; treatment for hypertension; history of cardiovascular disease, atrial fibrillation, and/or left ventricular hypertrophy; and smoking status.

||Adjusted for age and smoking.

subgroup analyses revealed that men derived a significant benefit, whereas women did not. Further studies are needed to determine whether these results can be replicated, particularly because they are based on subgroup analyses. In addition, the pathophysiology underlying these potential sex differences is poorly understood and deserves additional exploration.

Although lifestyle habits have an important impact on post-stroke outcomes, there are no published trials of lifestyle interventions for secondary stroke prevention. The Healthy Eating and Lifestyle After Stroke (HEALS) trial, a randomized controlled trial of an occupational therapist–led series of 6 group clinics aimed at changing lifestyle habits among stroke survivors, is attempting to address this knowledge gap.<sup>363</sup> Finally, little is known regarding how and whether lifestyle interventions should be tailored in women.

#### **Obesity, Abdominal Adiposity, and Metabolic Syndrome: Summary and Gaps**

In the United States, ≈1 in 3 individuals is obese. The prevalence of obesity is higher in women than men and is expected to increase over time in both sexes. Prospective studies have shown that obesity, abdominal adiposity, and metabolic syndrome are independent risk factors for stroke in both men and women. Further research is needed to determine whether sex modifies the impact of these conditions on stroke risk and outcomes. Healthy lifestyle practices, including maintaining a normal BMI, eating a diet rich in fruits and vegetables, moderate alcohol use, abstaining from smoking, and regular exercise, are associated with lower stroke incidence and better outcomes after stroke; however, little is known about sex differences in the effect of healthy lifestyle on stroke incidence and outcomes. Further research is needed to determine effective lifestyle interventions for preventing stroke occurrence and recurrence

in women. Research is needed to develop lifestyle interventions that are effective for both primary and secondary stroke prevention and for tailoring such interventions in women.

#### **Obesity, Metabolic Syndrome, and Lifestyle Factors: Recommendations**

- 1. A healthy lifestyle consisting of regular physical activity, moderate alcohol consumption (<1 drink/d for nonpregnant women), abstinence 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] diet) is recommended for primary stroke prevention in women with cardiovascular risk factors (Class I; Level of Evidence B).**
- 2. Lifestyle interventions focusing on diet and exercise are recommended for primary stroke prevention among individuals at high risk for stroke (Class I; Level of Evidence B).**

#### **Atrial Fibrillation**

AF is the most common arrhythmia and a major modifiable risk factor for stroke. AF increases 4- to 5-fold the risk of IS and is associated with higher death and disability.<sup>19</sup> The attributable risk of stroke from AF increases with age, from 1.5% for those aged 50 to 59 years to nearly 25% for those aged ≥80 years.<sup>19,364</sup> Whites carry the highest prevalence of AF compared with blacks, Hispanics, Asians, and other ethnic groups.<sup>365–367</sup> The overall number of men and women with AF is similar, but ≈60% of AF patients aged >75 years are women.<sup>368,369</sup>

Given that AF increases with age and that women have greater life expectancy, there will be an increasing number of

elderly women with AF as the population ages.<sup>19</sup> For example, in *Get With The Guidelines—Stroke*, one third of hospital admissions for stroke were for stroke patients  $\geq 80$  years of age, and AF was identified in 15.6% of men and 20.4% of women ( $P < 0.0001$ ).<sup>370</sup> Moreover, women with AF are slightly less likely to receive anticoagulation therapy than men (88% versus 89.7%; adjusted OR, 0.93; 95% CI, 0.88–0.98).<sup>371</sup> Similar findings were observed in other studies.<sup>71,372–376</sup>

### **Risk Stratification for Women With AF**

The occurrence of stroke is one of the most feared complications in patients with AF. Risk stratification tools, such as the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASC scores, are useful in guiding the decision making for anticoagulation therapy.<sup>377,378</sup> The CHADS<sub>2</sub> score uses a point system that includes congestive heart failure (1 point), hypertension (1 point), age  $\geq 75$  years (1 point), diabetes mellitus (1 point), and 2 points for prior stroke/TIA.<sup>378</sup> This scheme has been tested in several independent cohorts of patients with AF, with a score of 0 points indicating low risk (0.5% to 1.7%); 1 point, moderate risk (1.2% to 2.2% per year); and  $\geq 2$  points, high risk (1.9% to 7.6% per year).<sup>364</sup>

Female sex is an independent predictor of stroke in patients with AF.<sup>379–383</sup> This has been incorporated into other risk stratification tools used in the decision making for anticoagulation prophylaxis.<sup>380</sup>

The CHA<sub>2</sub>DS<sub>2</sub>-VASC score can be considered an extension of the CHADS<sub>2</sub> with extra points added for female sex (1 point), previous MI, peripheral arterial disease or aortic plaque (1 point), and age 65 to 74 years (1 point) or  $\geq 75$  years (2 points). The American College of Cardiology/AHA/European Society of Cardiology guidelines included similar risk stratification strategies as CHADS<sub>2</sub>, with the inclusion of left ventricular ejection fraction  $< 35\%$  in the high-risk category. The CHA<sub>2</sub>DS<sub>2</sub>-VASC score has been recommended recently by the European Society of Cardiology for risk classification.<sup>368,384–387</sup>

Two large cohort studies have both confirmed an age-sex interaction in patients with AF, which suggests a higher risk of stroke in women  $\geq 75$  years with AF compared with men.<sup>372,382</sup> For example, in a large study that included 100 802 patients with nonvalvular AF in Sweden, the incident risk of IS was greater in women than in men (6.2% versus 4.2% per year,  $P < 0.0001$ ).<sup>382</sup>

Another large population-based study comprising 39 398 men (47.2%) and 44 115 women (52.8%) aged  $\geq 65$  years with AF from Canada showed a higher crude stroke incidence in women (2.02 per 100 person-years; 95% CI, 1.95–2.10) than men (1.61 per 100 person-years; 95% CI, 1.54–1.69;  $P < 0.001$ ). The observed difference was mainly driven by women aged  $\geq 75$  years. The stroke incidence per 100 person-years among participants aged  $\geq 75$  years was 2.38 (95% CI, 2.28–2.49) in women and 1.95 (95% CI, 1.84–2.07) in men ( $P < 0.001$ ). The stroke risk was significantly higher for women both for those taking or not taking warfarin. The multivariable analysis also revealed a similar increased risk of stroke in women (adjusted HR, 1.14 [95% CI, 1.07–1.22];  $P < 0.001$ ) after adjustment for baseline comorbid conditions, individual components of the CHADS<sub>2</sub> score, and warfarin treatment.<sup>372</sup> There was a significant ( $P = 0.02$ ) interaction of age with sex, with the increased stroke risk confined to women aged  $\geq 75$  years. The age-sex

interaction on stroke risk in patients with AF was again confirmed recently in a large Swedish nationwide drug registry study.<sup>372,382</sup> Interestingly, warfarin use was associated with greater stroke reduction in women (60%; RR, 0.4; 95% CI, 0.3–0.5) than in men (40%; RR, 0.6; 95% CI, 0.5–0.8).<sup>380</sup>

### **Appropriateness of Anticoagulation by Sex**

The appropriateness of anticoagulation in women with AF  $< 65$  years of age with no other major or clinically relevant risk factors is controversial. The European Society of Cardiology recommends anticoagulation for patients with AF and a CHA<sub>2</sub>DS<sub>2</sub>-VASC score  $\geq 1$ .<sup>387</sup> The Canadian Cardiovascular Society recommends anticoagulation for AF patients with a CHADS<sub>2</sub> score  $\geq 1$ .<sup>388</sup> According to these guidelines, anticoagulation would be recommended for all women with AF alone (and no other risk factors).

Two large observational studies provide some guidance. The Swedish study ( $n = 100\,802$ ) found that the risk of stroke among patients with AF aged  $\leq 65$  years without risk factors was comparably low in both women (0.7%) and men (0.5%).<sup>382</sup> Another nationwide study from Denmark that included 73 538 patients with AF looked at the short- and long-term risk of thromboembolic events by combining the risk factors included in CHA<sub>2</sub>DS<sub>2</sub>-VASC.<sup>389</sup> The authors found that female sex alone was the weaker risk factor, showing a nonsignificant increase in the risk of thromboembolic events at 1- (HR, 1.24; 95% CI, 0.89–1.73), 5- (HR, 0.86; 95% CI, 0.70–1.06) and 10-year (0.82; 95% CI, 0.68–1.00) follow-up. The increased risk of thromboembolic events rose in women aged 65 to 74 years to 2.82 (95% CI, 2.21–3.60) at 1 year, 2.10 (95% CI, 1.81–2.45) at 5 years, and 2.06 (95% CI, 1.80–2.36) at 10 years.<sup>389</sup>

The AHA provides recommendations based on CHADS<sub>2</sub>. The great majority of patients being assessed at stroke prevention clinics have a CHADS<sub>2</sub> score  $\geq 2$ , the clinical situation with strong evidence in favor of anticoagulation for high-risk patients (Class I; Level of Evidence A).<sup>377</sup> These data suggest that women, especially those aged  $\geq 75$  years, have a higher stroke risk, and most benefit from anticoagulation therapy. Younger women ( $< 65$  years old) with AF alone (no other risk factors) have a lower risk of stroke. No specific sex benefits were observed when rate versus rhythm control strategies were compared.<sup>390</sup>

### **Evidence From Randomized Clinical Trials of New Oral Anticoagulants**

Most recent randomized clinical trials of new oral anticoagulants showed better stroke risk reduction and lower risk of intracranial bleeding. The benefit in women was comparable to that in men<sup>391–393</sup> (Table 13). The RELY (Randomized Evaluation of Long-term Anticoagulant Therapy) study randomly assigned 18 113 patients (36.4% women) with AF and a risk of stroke (mean CHADS<sub>2</sub> score 2.2) to receive fixed doses of dabigatran (110 or 150 mg twice daily) or adjusted-dose warfarin. The median follow-up period was 2.0 years. The primary outcome was stroke or systemic embolism.

ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation) was a randomized, double-blind trial comparing apixaban (5 mg twice daily) versus

warfarin (target international normalized ratio, 2.0–3.0) in 18201 patients with AF and at least 1 additional risk factor for stroke (mean CHADS<sub>2</sub> score 2.1). Women constituted one third (35.3%) of participants. The primary outcome was ischemic or hemorrhagic stroke or systemic embolism.<sup>391,391a</sup>

ROCKET AF (Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) was a double-blind trial that randomly assigned 14264 patients with nonvalvular AF who were at increased risk for stroke to receive either rivaroxaban (20 mg daily) or dose-adjusted warfarin. Women represented 39.7% of the participants. The primary end point was stroke or systemic embolism.<sup>393</sup> Of note, the risk of stroke was greater among participants in ROCKET AF than in RELY or ARISTOTLE, because the mean CHADS<sub>2</sub> score was 3.47, with no patients in the lowest categories. Although all 3 trials using new oral anticoagulants consistently showed a greater number of events per year among women, none demonstrated a differential benefit by sex for the primary or secondary outcomes (*P* value for the interaction was not significant).<sup>391–393</sup> These results should be interpreted with caution, because none of these studies were powered to determine a sex difference in the efficacy of new oral anticoagulants over warfarin.

In addition, women with AF had on average 30% higher concentrations of dabigatran than their male counterparts for the same given dose. The effect is most likely attributable to the average 30% lower creatinine clearance in women. No dose adjustment is required according to the product monograph or approval by regulatory agencies.<sup>394–396</sup> Limited information is available among patients who participated in RELY with a body weight <50 kg.<sup>392</sup> There were no differences in serum concentrations by sex for apixaban and rivaroxaban.<sup>391,393</sup> Finally, some questions remain regarding the incomplete or scarce information on sex differences in the dosing of new oral anticoagulants.

### AF: Summary and Gaps

AF is a major modifiable stroke risk factor, independently associated with a 4- to 5-fold increased risk of IS. AF is responsible for 1.5% to 25% of all IS depending on the age group. Anticoagulation is the most effective therapeutic

strategy to decrease the risk of stroke. Risk stratification tools, such as CHA<sub>2</sub>DS<sub>2</sub>-VASc, are useful to stratify the risk of stroke and assist clinicians in the decision to initiate anticoagulation therapy. New oral anticoagulants are a useful alternative to warfarin for the prevention of stroke and systemic thromboembolism; however, caution about overdosing must be used considering the additive effect of age, sex, renal function, and concomitant medications (acetylsalicylic acid, clopidogrel, nonsteroidal anti-inflammatory drugs, P-glycoprotein inhibitors) in increasing the concentrations of new oral anticoagulants.

Future research is needed to determine the appropriate dose of new oral anticoagulants in older women with a lower weight (eg, <50 kg) who are also exposed to other comorbidities (eg, renal impairment) that influence the pharmacokinetics of these agents. In addition, none of the trials of new anticoagulants were powered to determine a sex difference in efficacy versus warfarin.

### AF: Recommendations

1. 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*).
2. 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; Level of Evidence B*).
3. Oral anticoagulation in women aged ≤65 years with AF alone (no other risk factors; women with CHADS<sub>2</sub>=0 or CHA<sub>2</sub>DS<sub>2</sub>-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; Level of Evidence B*).
4. 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 prespecified risk factors (according to CHA<sub>2</sub>DS<sub>2</sub>-VASc) who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (creatinine clearance 15

**Table 13. Primary and Secondary Outcomes Among Participants in the ARISTOTLE, RELY, and ROCKET AF Trials Stratified by Sex**

	ARISTOTLE			RELY				ROCKET AF		
	No. of Events (%/y)			No. of Events (%/y)				No. of Events (%/y)		
	n	Apixaban	Warfarin	n	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin	n	Rivaroxaban	Warfarin
Primary outcome										
Men	11 785	132 (1.2)	160 (1.5)	11 514	52 (1.35)	42 (1.10)	57 (1.49)	8553	103 (1.52)	136 (1.95)
Women	6416	80 (1.4)	105 (1.8)	6598	40 (1.86)	25 (1.14)	45 (2.03)	5590	86 (1.97)	107 (2.47)
Major bleeding										
Men	11 747	225 (2.3)	294 (3.0)	11 514	113 (2.92)	129 (3.37)	138 (3.63)	8591	260 (3.92)	253 (3.68)
Women	6393	102 (1.9)	168 (3.3)	6598	60 (2.79)	72 (3.23)	77 (3.46)	5645	135 (3.11)	133 (3.10)

ARISTOTLE indicates Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation; RELY, Randomized Evaluation of Long-term Anticoagulant Therapy; and ROCKET AF, Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.



**mL/min), lower weight (<50 kg), or advanced liver disease (impaired baseline clotting function) (Class I; Level of Evidence A).**

### Depression and Psychosocial Stress

In addition to being a well-recognized sequela of stroke,<sup>397</sup> depression is associated with increased risk of stroke incidence among both women and men. In the INTERSTROKE case-control study of stroke participants from 22 countries,<sup>92</sup> investigators found that self-reported depression (defined as feeling sad, blue, or depressed for  $\geq 2$  consecutive weeks during the past 12 months) was associated with a 35% increased odds of stroke (95% CI, 1.10–1.66) after adjustment for age, sex, and region. In addition, psychosocial stress (defined with a combined measure of general stress at home and in the workplace and categorized by permanent or several periods of stress versus no or some periods of stress in the past year) was associated with a 30% increased odds of stroke (95% CI, 1.06–1.60) in the adjusted model. Although the multivariable models were adjusted for sex, there were no sex-specific analyses performed in this cohort. In the Nurses' Health Study, women with a history of depression had a 29% increased risk of incident total stroke (multivariate RR, 1.29; 95% CI, 1.13–1.48).<sup>398</sup> In a meta-analysis of prospective studies of depression and stroke, the pooled adjusted HRs were 1.45 (95% CI, 1.29–1.63) for total stroke and 1.25 (95% CI, 1.11–1.40) for IS. The cumulative ORs for studies that included only men or only women revealed no difference in the strength of association between depression and stroke compared with the cumulative OR for studies that included both sexes.<sup>399</sup>

### Depression and Psychosocial Stress: Summary and Gaps

Depression is associated with increased risk of stroke. More research is needed to understand the mechanisms underlying the association between depression and stroke, as well as to determine which women with depression may be at risk, such as those who are treated versus untreated, and whether self-reported measures such as those used in the INTERSTROKE study are the most accurate to determine stroke risk. There is also a lack of sex-specific analyses in many of the cohorts that have assessed multiple risk factors. Because depression and psychosocial stressors are more common in women, it may be reasonable to test these risk factors in a woman-specific stroke risk score.

## Strategies for Prevention of Stroke: Are They Different in Women?

### Representation of Women in Stroke Clinical Trials

Women account for less than half of all subjects enrolled in National Institutes of Health–funded stroke prevention clinical drug trials of the past decade. It has also been recognized that women have been underrepresented in clinical trials in surgery, overall CVD, and cancer.<sup>400–403</sup> Sex disparities in cerebrovascular disease clinical trial participation have been less well examined.<sup>404</sup> The low proportion of women in clinical stroke prevention trials limits the generalization of results across the sexes. Conventional subgroup analyses in women are commonly flawed by type II error. As a result, it remains

unclear whether current evidence-based practices apply to women, who represent half of all stroke victims.

In response to recognition that overall, women were underrepresented in National Institutes of Health–sponsored trials, the National Institutes of Health Revitalization Act (public law 103-43), which required inclusion of women in clinical trials of diseases affecting women, was enacted in 1993.<sup>402,405</sup> Unfortunately, to date, the legislation appears to have had little impact. A review of articles published in *The New England Journal of Medicine* after enactment of the legislation reported that there was no change in the overall rate of enrollment of females, which remained at roughly 25%.<sup>406</sup> Neurological clinical trials were among the most successful in enrolling women, with a participation rate of 45%. A subsequent review of National Institutes of Health–funded studies found that only 24% of enrolled drug study populations were women.<sup>400</sup> This lack of recruitment continues in recent trials. For example, only 20% of women were recruited in the WARCEF trial (Warfarin Versus Aspirin Use in Patients With Impaired LV Function) as recently as 2012.<sup>407</sup> Factors that may play a role in the apparent underrepresentation of women in clinical trials may be sex differences in disease prevalence and age at onset in women. A systematic review of enrollment of women in trials of coronary artery disease, heart failure, arrhythmia, and primary prevention reported that after accounting for age- and sex-specific differences in disease prevalence, the enrollment gaps for women narrowed, ranging from 3% for primary prevention to 13% for heart failure. Stroke was not included in this analysis, however.<sup>408</sup> The percentage of women enrolled in recent stroke prevention trials of carotid disease and antiplatelet agents ranges from 25% to 53%, with an average of 34%, which is generally below the stroke prevalence rates by sex (Tables 14 and 15).

### CEA Versus Medical Management for Symptomatic or Asymptomatic Carotid Stenosis

Differences in the anatomy of the internal carotid arteries and differences in the composition of plaque between women and men have fueled speculation that there may be differential risk or benefit to intervention. Compared with men, women have smaller-caliber internal carotid arteries and shorter stenotic segments.<sup>425,426</sup> CEA is also performed less often in women, likely because of the lower incidence of high-grade symptomatic stenosis.<sup>427,428</sup> In a retrospective cohort study at Kaiser Permanente Medical Care Plan, for the period 2003 to 2004, 299 patients were identified on the basis of a diagnosis of TIA and carotid stenosis ( $>70\%$ ), that is, symptomatic stenosis.<sup>427</sup> Approximately half (47%) were women. Women were less likely to undergo CEA (36.4% versus 53.8% in men;  $P=0.004$ ). Being female remained an independent predictor for not receiving CEA after adjustment for age, number of TIAs, specificity of TIA symptoms, and degree of stenosis. In patients who underwent CEA, the time to surgery was longer in women (mean of 35 days) than men (mean of 18 days;  $P=0.03$ ),<sup>427</sup> whereas the current recommendations are to perform CEA within 2 weeks of symptoms of TIA or mild stroke.<sup>20</sup> In the surgical subgroup, women were older and less likely to have coronary artery disease. Outcomes were similar in men and women in both the CEA and medical management groups.<sup>427</sup>

In subgroup analyses of some trials comparing medical management to CEA in patients with symptomatic or asymptomatic carotid stenosis, women appeared to derive less benefit from surgery than men, potentially because of an increased risk of perioperative events<sup>411–413</sup>; however, the data were inconclusive because of small sample sizes within sex strata and the post hoc nature of some of the analyses. Only 1 trial, the Asymptomatic Carotid Surgery Trial, conducted a prespecified secondary analysis by sex group.<sup>413</sup> Although for all the subgroup analyses, the results were similar to that first found in the Asymptomatic Carotid Atherosclerosis Study,<sup>412</sup> they were statistically significant only for the European Carotid Surgery Trial, but this was a post hoc analysis.<sup>411</sup>

### CEA Versus Carotid Artery Stenting

Carotid artery stenting (CAS) has emerged as an alternative strategy for the management of carotid stenosis.<sup>414–416,429,430</sup> In a meta-analysis of 3 European trials comparing CEA to CAS in symptomatic patients, there was no interaction between sex and 120-day outcome.<sup>431</sup> The North American Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) assigned 2502 patients with symptomatic and asymptomatic carotid stenosis to either CEA or CAS. Roughly 35% (n=872) of the subjects were women. Rates of stroke, MI, or death of any cause during the periprocedural period or any ipsilateral stroke within 4 years after randomization for CAS compared with CEA were 6.2% versus 6.8% in men (HR, 0.99; 95% CI, 0.66–1.46) and 8.9% versus 6.7% in women (HR 1.35; 95% CI, 0.82–2.23).<sup>416</sup> Periprocedural events (from randomization to 30 days after the procedure) occurred in 4.3% of 807 men versus 6.8% of 455 women assigned to CAS and 4.9% of 823 men versus 3.8% of 417 women assigned to CEA, with significant interaction ( $P=0.064$ ).<sup>432</sup> The CAS-to-CEA treatment difference was also affected by age ( $P=0.02$ ), with older patients faring better with CEA and younger patients faring better with CAS.<sup>433</sup> There was no evidence ( $P=0.45$ ) that this effect by age was

**Table 15. Representation of Women in Antiplatelet Trials**

Trial	Total Patients Enrolled (% Women)
ACE <sup>417</sup>	2806 (30)
ESPS-2 <sup>418</sup>	6604 (42)
CAPRIE <sup>419</sup>	15 480 (30)
MATCH <sup>420</sup>	7624 (37)
AAASPS <sup>421</sup>	1824 (53)
ESPRIT <sup>422</sup>	2714 (35)
PROFESS <sup>423</sup>	20 438 (37)
SPS3 <sup>424</sup>	3021 (37)

AAASPS indicates African American Antiplatelet Stroke Prevention Study; ACE, ASA [acetylsalicylic acid] and Carotid Endarterectomy Trial; CAPRIE, Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events; ESPS-2, European Stroke Prevention Study 2; ESPRIT, European/Australasian Stroke Prevention in Reversible Ischaemia Trial; MATCH, Management of Atherosclerosis With Clopidogrel in High-Risk Patients; PROFESS, Prevention Regimen for Effectively Avoiding Second Strokes; and SPS3, Secondary Prevention of Small Subcortical Strokes.

different for women than men. Although data from CREST suggest that women with CAS (relative to CEA) may be at higher risk for the composite outcome of stroke, death, or MI during the periprocedural period, this finding should be interpreted with caution pending confirmation from other trials.

At present, there may not be sufficient data to conclude that high-grade symptomatic or asymptomatic carotid stenosis should be managed differently in men and women with regard to the type of procedure, or whether it should be managed medically. Without definitive data, the recommendations in the guidelines for prevention of first or recurrent stroke should be applied to women.<sup>19,20,434</sup>

### Aspirin for Prevention of Stroke in Women

One of the seminal trials of primary prevention of CVD, including stroke, in women is the WHS, a randomized trial of 100 mg of aspirin on alternate days versus placebo in 39 876 initially asymptomatic women 45 years of age, followed up for 10 years for a first major vascular event (nonfatal MI, nonfatal stroke, or cardiovascular death).<sup>435</sup> Although there was a nonsignificant 9% reduction (RR, 0.91; 95% CI, 0.80–1.03;  $P=0.13$ ) in the combined primary end point among women, the study found a 17% reduction in the risk of stroke (RR, 0.83; 95% CI, 0.69–0.99;  $P=0.04$ ). This was based on a 24% reduction in the risk of IS (RR, 0.76; 95% CI, 0.63–0.93;  $P=0.009$ ) and a nonsignificant increase in the risk of hemorrhagic stroke (RR, 1.24; 95% CI, 0.82–1.87;  $P=0.31$ ). The overall average stroke rates were 0.11% per year in aspirin-treated women and 0.13% per year in placebo-treated women (RR, 0.02% per year; number needed to treat, 5000). An important adverse outcome, gastrointestinal hemorrhage requiring transfusion, was more frequent in the aspirin group (RR, 1.40; 95% CI, 1.07–1.83;  $P=0.02$  and absolute risk increase, 0.01% per year; number needed to harm, 10000). The most consistent benefit for aspirin was in women  $\geq 65$  years of age at study entry, among whom the risk of major cardiovascular events was reduced by 26% (RR, 0.74; 95% CI, 0.59–0.92;  $P=0.008$ ), including a 30% reduction in the

**Table 14. Representation of Women in Carotid Intervention Trials**

Trial	Total Patients (% Women)
NASCET <sup>409</sup>	663 (32)
NASCET moderate <sup>410</sup>	2303 (29)
ECST <sup>411</sup>	3035 (28)
ACAS <sup>412</sup>	1662 (34)
ACST <sup>413</sup>	3165 (34)
EVA-3S <sup>414</sup>	520 (25)
SPACE <sup>415</sup>	1207 (28)
CREST <sup>416</sup>	2491 (35)

ACAS indicates Asymptomatic Carotid Atherosclerosis Study; ACST, Asymptomatic Carotid Surgery Trial; CREST, Carotid Revascularization Endarterectomy Versus Stenting Trial; ECST, European Carotid Surgery Trial; EVA-3S, Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis; NASCET, North American Symptomatic Carotid Endarterectomy Trial; NASCET moderate, North American Symptomatic Carotid Endarterectomy Trial (patients with moderate stenosis only); and SPACE, Stent-Protected Angioplasty Versus Carotid Endarterectomy.

risk of IS (RR, 0.70; 95% CI, 0.49–1.00;  $P=0.05$ ); however, the benefit was reduced when the combination of IS and hemorrhagic stroke was considered (RR, 0.78; 95% CI, 0.57–1.08;  $P=0.13$ ). On the basis of the WHS results, aspirin is recommended for primary prevention for women after consideration of the 10-year risk of CVD and whether this and age outweigh the risk of hemorrhage.<sup>21</sup>

A large, sex-specific meta-analysis of aspirin for primary prevention of IS (separate from other cardiovascular events) showed that women appeared to benefit from aspirin (OR, 0.76; 95% CI, 0.63–0.93), whereas men showed no benefit (OR, 1.00; 95% CI, 0.72–1.41).<sup>436</sup> For heart disease, however, men benefited from aspirin for prevention against coronary heart disease, whereas women did not. As in men, aspirin allocation in primary prevention trials increased the risk of hemorrhagic stroke and major gastrointestinal and extracranial bleeds among women and resulted in uncertain net value.

There is no evidence of a differential effect of antiplatelet agents for secondary stroke in women compared with men.<sup>418,419,422,423,437</sup> The Antithrombotic Trialists meta-analysis of aspirin for the primary and secondary prevention of vascular events (MI, stroke, vascular death) also included individual patient data from each of the trials.<sup>437</sup> They found similar proportional reductions in risk for men and women for the combined outcome; however, there was a trend toward benefit for primary prevention in women versus men, although this was no longer the case when the  $P$  value was adjusted for multiple comparisons.<sup>437</sup> In secondary prevention (among patients who already have occlusive vascular disease), aspirin appears to result in a greater absolute benefit for stroke prevention, with similar magnitude of effect for women and men, and a 19% reduction in stroke risk.<sup>437</sup>

## Strategies for Prevention of Stroke in Women: Summary and Gaps

In all clinical trials of primary and secondary stroke prevention, women need to be included in sufficient numbers for preplanned subgroup analysis, with reasonable statistical power to provide for valid analysis to test for sex interaction.<sup>405</sup> Questions about the benefits and risks of carotid procedures in women with asymptomatic high-grade carotid stenosis and symptomatic treatment for moderate (50%–69%) carotid stenosis remain unanswered. Until further studies are performed, the recommendations for prevention of stroke in women with carotid disease (symptomatic or asymptomatic) remain the same as for men, as published in the primary and secondary prevention guidelines.<sup>19,20</sup> For aspirin, the recommendations below for women are as published in the AHA's "Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women."<sup>21</sup>

## Strategies for Prevention of Stroke in Women: Recommendations

1. 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; Level of Evidence C*).<sup>19</sup>

2. 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; Level of Evidence C*).
3. Prophylactic CEA performed with <3% morbidity/mortality can be useful in highly selected patients with an asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasound) (*Class IIa; Level of Evidence A*).
4. 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; Level of Evidence A*).<sup>20</sup>
5. 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; Level of Evidence B*).<sup>20</sup>
6. When CEA is indicated for women with TIA or stroke, surgery within 2 weeks is reasonable rather than delaying surgery, if there are no contraindications to early revascularization (*Class IIa; Level of Evidence B*).<sup>20</sup>
7. Aspirin therapy (75–325 mg/d) is reasonable in women with diabetes mellitus unless contraindicated (*Class IIa; Level of Evidence B*).<sup>21</sup>
8. If a high-risk (ie, 10-year predicted CVD risk  $\geq 10\%$ ) woman has an indication for aspirin but is intolerant of aspirin therapy, clopidogrel should be substituted (*Class I; Level of Evidence B*).<sup>21</sup>
9. Aspirin therapy can be useful in women  $\geq 65$  years of age (81 mg/d or 100 mg every other day) if BP is controlled and the benefit for IS and MI prevention is likely to outweigh the risk of gastrointestinal bleeding and hemorrhagic stroke (*Class IIa; Level of Evidence B*) and may be reasonable for women <65 years of age for IS prevention (*Class IIb; Level of Evidence B*).<sup>21</sup>

## Data Shaping Development and Validation of Risk Scores

### Use of Sex-Specific Stroke Risk Prediction Scores

Risk scores have been advocated to clinically classify individuals according to their overall risk to guide prevention and treatment recommendations. The goal of such scores is to accurately classify individuals as high or low risk so that high-risk individuals receive appropriate interventions to reduce risk.

Although there are several general cardiovascular risk scores,<sup>438,439</sup> there are fewer stroke-specific scores. Risk prediction models that are specific to women have not been developed. Furthermore, whether risk factors differ by age and racial/ethnic group has not been established. The Framingham stroke risk calculator does take sex into account.<sup>440</sup> The number of points assigned to particular conditions differs by sex, with diabetes mellitus, systolic BP, and AF garnering a higher number of points in women than men, whereas women with existing CVD receive fewer points than do men (Table 16). Moreover, the 10-year probability



**Table 16. Risk Factors and Points Included in the Framingham Stroke Risk Score for 10-Year Stroke Risk Prediction in Women\***

Predictors	0	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10
Age, y	54–56	57–59	60–62	63–64	65–67	68–70	71–73	74–76	77–78	79–81	82–84
SBP (untreated), mm Hg		95–106	107–118	119–130	131–143	144–155	156–167	168–180	181–192	193–204	205–216
SBP (treated), mm Hg		95–106	107–113	114–119	120–125	126–131	132–139	140–148	149–160	161–204	204–216
Diabetes mellitus	No			Yes							
Cigarette smoking	No			Yes							
Prior CVD†	No		Yes								
AF	No						Yes				
LVH on ECG	No				Yes	Yes					

AF indicates atrial fibrillation; CVD, cardiovascular disease; ECG, electrocardiogram; LVH, left ventricular hypertrophy; and SBP, systolic blood pressure.

\*Available at <http://www.framinghamheartstudy.org/risk-functions/stroke/stroke.php>.

†CVD is defined as any of the following: history of myocardial infarction, angina pectoris, coronary insufficiency, intermittent claudication, or congestive heart failure.

of stroke from the Framingham Stroke Risk Score (FSRS) is lower for women than for men with the same score (Table 17); however, few other widely validated stroke prediction scores for the general population are available. Data in minorities and women are limited.

The FSRS was derived in a predominantly white, middle- to older-aged population in a single community. The FSRS was applied to the Cardiovascular Health Study (CHS) population of men and women >65 years of age, and it was found that the FSRS model predicted stroke less effectively in elderly women than men. A CHS stroke risk model and applet were created that improved discrimination in women (area under the receiver operating characteristic curve of 0.73 for FSRS in women compared with 0.77 for the CHS model in men;  $P=0.044$ ).<sup>441</sup> Additional variables included in the CHS score included time to walk 15 feet (functional status) and creatinine. When the FSRS was used to evaluate risk in a group of elderly French men and women (aged 65–84 years at baseline), it overestimated the risk substantially (by a factor of 4.4 in women and 3.7 in men), which led to a recalibrated stroke score for that population.<sup>442</sup> Therefore, comparative data are needed on how well risk scores perform in women versus men and in different racial and ethnic populations.

Several stroke risk scores were developed exclusively for use in men,<sup>443,444</sup> but woman-specific models are needed to more accurately reflect risk across the lifespan. Specific risk factors are unique to or more common in women that have not been included in traditional risk assessment (Table 3). Prospective research is needed for these woman-specific risk factors, including pregnancy-related risk factors and hormonal exposure (OCs and postmenopausal HT), as well as changes in hormone status across the lifespan (menarche, menopause, and oophorectomy). For example, preeclampsia clearly increases risk of stroke in the peripartum period and has been listed as a risk factor for CVD in women in the 2011 AHA “Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women”<sup>721</sup>; however, relatively limited data on long-term risk of stroke among women with a history of preeclampsia are available.<sup>180</sup> In addition, several less traditional risk factors, including psychosocial stress and depression, were important in the INTERSTROKE study<sup>92</sup> and

other observational studies<sup>398,399</sup> but are not included in traditional risk scores.<sup>440,445</sup> Women have higher rates of depression, and thus, these factors may be of greater impact for women.<sup>446</sup> Additionally, there are potential differences in the risk of stroke among older individuals with AF, with higher rates in women despite warfarin therapy, as discussed above.<sup>372</sup> Whether biomarkers, in addition to lipid measures, additionally contribute to risk stratification in women is unclear. C-reactive protein, an inflammatory marker that is also included in the Reynolds Cardiovascular Risk Score,<sup>439,447</sup> was found to improve prediction of risk of IS, particularly cardioembolic stroke, in older women in the WHI.<sup>448</sup> Lipoprotein-associated phospholipase A<sub>2</sub> was associated with improvement in the prediction of large-artery strokes.<sup>448</sup> Additional evaluation of other biomarkers for risk prediction will be of continued interest.

### Woman-Specific Risk Score: Summary and Gaps

Consideration of the risk factors that are unique to women and are more prevalent or differentially increase risk, compared with men, may improve the accuracy of stroke risk assessment compared with current risk scores. This is especially true for younger women of reproductive age. Prospective data on the long-term stroke risk of women with a history of preeclampsia

**Table 17. Ten-Year Stroke Probability in Women According to Framingham Stroke Risk Score**

Points	10-y Probability, %	Points	10-y Probability, %	Points	10-y Probability, %
1	1	11	8	21	43
2	1	12	9	22	50
3	2	13	11	23	57
4	2	14	13	24	64
5	2	15	16	25	71
6	3	16	19	26	78
7	4	17	23	27	84
8	4	18	27		
9	5	19	32		
10	6	20	37		

and other pregnancy-related complications are also needed.<sup>449</sup> Further development of stroke risk prediction models in women could be achieved by use of data from large, diverse longitudinal studies including the WHI, WHS, Nurses' Health Study, ARIC study, Multi-Ethnic Study of Atherosclerosis (MESA), and Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. Sex-specific and race- and ethnic-specific analyses need to be conducted explicitly to determine whether current and future risk scores perform equally well in white, black, and Latina women.

### Conclusions and Summary

In this guideline, we have summarized the current evidence and provided summaries and gaps for prevention focused on the risk factors that are either unique to or more common in women than men. Some of the recommendations in this guideline were formerly associated with other prevention guidelines but have been assimilated because of the focus on women. In addition, we have summarized the data that support the development of woman-specific stroke risk profiles,

which might more accurately reflect a woman's future risk of stroke than some of the currently available stroke risk profiles.

Prevention efforts for women would be enhanced if future epidemiological studies provided more detail on stroke subtype, 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, including childbearing ages, because of women's increased risk of stroke with age; the risks of stroke associated with pregnancy, gestational hypertension, and hormonal contraception; and the onset of stroke 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. There is a need for recognition of women's unique sex-specific stroke risk factors, and a risk score that includes these factors would thereby identify women at risk. Until sex-specific risk is better understood, prevention and management of stroke and cardiovascular risk factors remains essentially the same for men and women.



# Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION

## Disclosures

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Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

\*Modest.

†Significant.



# Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
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\*Modest.

†Significant.

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## **Guidelines for the Prevention of Stroke in Women: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association**

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*Stroke*. published online February 6, 2014;

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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