# Cerebrovascular disease in women

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**Abstract**:  Cerebrovascular disease is a major cause of morbidity, mortality, and disability in women. The spectrum of disease differs between men and women, with women being particularly vulnerable to certain conditions, especially during specific periods of life such as pregnancy. There are several unique risk factors for cerebrovascular disease in women, and the influence of some traditional risk factors for stroke is stronger in women. Moreover, disparities persist in representation of women in clinical trials, acute intervention, and stroke outcomes. In this review, we aimed to explore the epidemiology, etiologies, and management of cerebrovascular disease in women, highlighting some of these differences and the growing need for sex-specific management guidelines and health policies.

## Introduction

Stroke is the second leading cause of mortality and of disability-adjusted life-years lost worldwide, affecting almost 14 million individuals annually, with an 8.9% increase in the global lifetime risk between 1990 and 2016.[1] A working group of the American Heart Association concluded that by 2030, almost 4% of United States (US) adults will have had a stroke.[2] It is estimated that stroke-related medical costs will increase from 36.7 billion USD in 2015 to a staggering 94.3 billion by 2035.[2,3] This increase is primarily driven by a growing and aging population, lower mortality rates from improved acute stroke care, and enhancements in stroke prevention strategies. There are about 7 million stroke survivors in the US, out of which 54.2% are women.[2] As women continue to increasingly outnumber and outlive men, a disproportionate increase in the burden of stroke in women is expected, leading to more disabled women and a substantive detrimental impact on society.[4,5] The spectrum of cerebrovascular disease in women is not limited to atherosclerosis, ischemic stroke (IS) and intracerebral hemorrhage (ICH), but also includes aneurysms, subarachnoid hemorrhage (SAH), and other neurovascular syndromes such as cerebral venous sinus thrombosis (CVST), and reversible cerebral vasoconstriction syndrome (RCVS), all of which lead to significant morbidity and mortality among women (Figure 1).

It has now been more than 3 decades since the landmark 1985 Task Force on Women's Health Issues which called for expanded consideration of women in clinical trials. Representation is still not equitable, but progress has been made, with increasing recruitment of women, and several female-exclusive trials and studies now being conducted across the world.[6] Tremendous insight has been gained over the last several years on cerebrovascular disease in women, leading to a greater focus on risk factors unique and more pertinent to women, such as pregnancy/eclampsia. Implementation of optimal screening and treatment based on these data will help equalize stroke outcomes between the sexes.

This review explores the etio-pathogenic factors contributing to cerebrovascular disease in women, some proposed mechanisms of disease that may be sex specific, and their impact on stroke outcome.

## Epidemiology

In the US, about 53.5% of the total stroke incidence is attributed to women.[2] The quality of epidemiological data for stroke in women is highly

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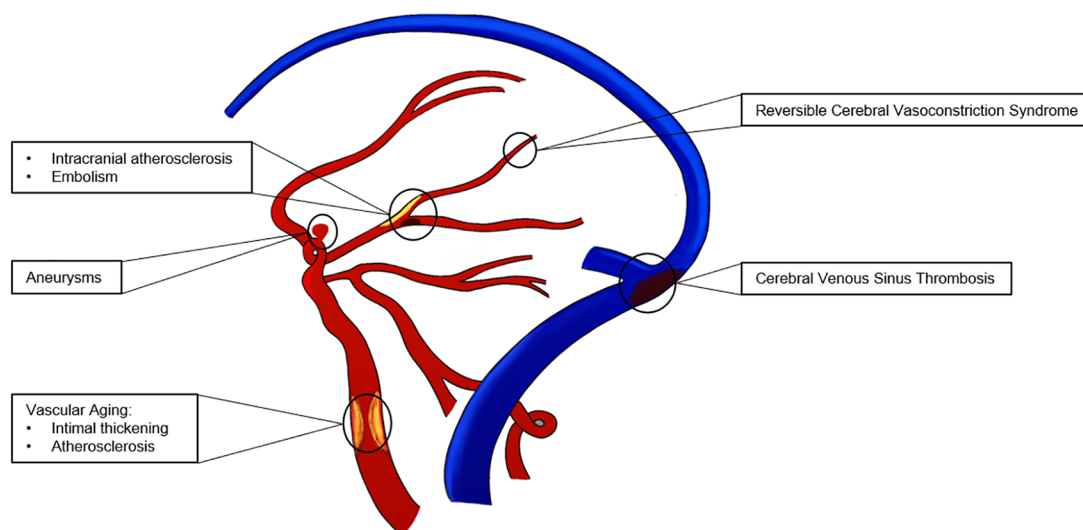Houston, Houston, TX, USA

**Figure 1.** Spectrum of cerebrovascular disease in women.

heterogeneous across different countries, owing to different societal roles for women, and other sociocultural factors (Table 1). Nevertheless, there were about 80.1 million prevalent cases of stroke globally in 2016, of which 41.1 million were in women.[1] Stroke accrues a significant degree of disability in survivors, and with the higher incidence in women, translates to almost 200,000 more disabled women after stroke than men in the US. Women also have a higher life expectancy than men, and as stroke occurs more frequently in the aged population, the lifetime risk in those aged 55–75 years is higher in women by about 3% compared with men. Data from the Framingham Heart Study also suggested that one in five women and one in six men who reach the age of 55 years free from stroke, will develop a stroke during the remainder of their lifetime.[5,7]

Epidemiological data have shown that 87% of cerebrovascular events in women are IS, 10% ICH, and about 3% are SAH. The incidence of both IS and ICH has been noted as higher in older women >80–85 years, compared with men.[8] Women also have a higher prevalence of intracerebral aneurysms and have a higher risk of aneurysm rupture.[9]

In women, stroke risk is higher in certain phases of life, especially the antenatal and postpartum periods. In the US, between 1994–1995 and 2006–2007, there was a 47% increase in antenatal stroke admissions and an 83% increase in postpartum stroke admissions. Stroke is responsible for approximately 7.4% of all maternal deaths in the US.[10] In Japan, stroke is the second leading cause of maternal mortality (16% of all maternal deaths).[11]

In the US, Black women have consistently been shown to have a higher incidence of stroke compared with their White counterparts.[2,12] Several studies, including the NOMAS (Northern Manhattan Stroke Study) and the ARIC study (Atherosclerosis Risk in Communities) have reported a nearly threefold greater risk of stroke among Black compared with White women.[13,14] Various socioeconomic factors may play a role, especially in younger Black women, who have been shown to carry a disproportionately high burden of stroke risk factors.

## Mortality

Stroke is the third leading cause of death in women, and the fifth leading cause for men. In the US, 57.9% of deaths related to stroke in 2017 occurred in women.[2] Age-specific stroke mortality is higher for men than women for all age groups except in those ≥85 years. Similarly, women worldwide have lower stroke mortality than men except in the older age groups. However, women have fewer stroke disability-adjusted life-years than men. The overall age-adjusted IS death rate in women is slightly lower than men, but crosses over at age 65, with higher mortality in women. Women also have higher age-adjusted mortality

from SAH. For ICH, data are more variable, with most studies showing lower mortality in women.[1,2]

## Risk factors

In addition to traditional stroke risk factors, such as hypertension and diabetes, there are certain factors specific to women that increase stroke risk (Table 2). Even traditional factors may confer different risk between men and women (Table 3). Data on the role of endogenous sex hormones and risk of stroke are limited, with no definitive association between high or low estrogen levels and stroke.[15,16] As many female stroke patients are postmenopausal at the time of stroke, lifetime exposure to gonadal hormones may be more closely tied to risk.[17,18] Unfortunately, studies that have measured endogenous hormones at the time of stroke, or longitudinally over time, are limited, so investigators have largely relied upon historical reporting, such as age at menarche and menopause.[18,17] A few studies have found that higher endogenous estradiol levels may be linked to higher stroke risk and mortality in older postmenopausal women, especially in those with greater central adiposity, but larger studies are needed. Female-specific factors that increase stroke risk include pregnancy and its complications, such as hypertensive disorders of pregnancy (HDP), oophorectomy, preterm delivery and stillbirth. A recent systematic review and meta-analysis of 78 studies with >10 million participants revealed that any hypertensive disorder during pregnancy, including gestational hypertension, preeclampsia, or eclampsia, was associated with a greater risk of IS; late menopause (after 55 years of age) and gestational hypertension were associated with a greater risk of ICH; and oophorectomy, HDP, preterm delivery, and stillbirth were associated with an increased risk of any stroke.[19] Among general stroke risk factors, there are a few with a higher female preponderance or that have a greater impact on stroke risk in women in comparison with men. The most prominent is atrial fibrillation (AF), which is associated with double the risk of stroke in women compared with men, and results in more severe strokes.[20] Diabetes mellitus and metabolic syndrome also confer a higher risk of stroke in women. Reasons behind these differences are still unclear but may be related to social factors leading to undertreatment, differences in adherence, or differences in physiology.[21,22] Some of these risk factors are discussed in more detail below (Figure 2).

**Table 1.** Epidemiology.

| Stroke |
|---|
| Incidence |
|     53.5% of total stroke |
|     87% ischemic |
|     10% ICH |
| Prevalence |
|     ~52% of total stroke prevalence |
| By race |
|     White 2.5% |
|     Black 4.7% |
| Mortality |
|     Third leading cause of death in women |
|     60% of all stroke deaths |
|     Highest in Black women |
| **SAH** |
|     3% of total stroke incidence |
|     Higher incidence after 55 years |
|     Higher prevalence of Pcomm aneurysms |
|     Higher mortality than men RR 1.59; 1.54–1.62 |
|     Highest mortality in Asian Americans |
| **Cerebral venous sinus thrombosis** |
|     >70% cases women |
| Incidence |
|     Overall: 1.86/100,000 |
|     Women aged 31–50 years: 2.78/100,000 |
| Highest risk: third trimester and up to 4 weeks post-partum |

ICH, intracerebral hemorrhage; Pcomm, posterior communicating artery; RR, relative risk.

## Sex-specific risk factors

### Pregnancy

The peripartum period confers a high risk of stroke, with an estimated incidence of about 30 cases per 100,000 deliveries.[23] HDP are the

**Table 2.** Sex-specific risk factors.

Pregnancy

- 34 strokes/100,000 deliveries
- Highest third trimester, post-partum

Hypertensive disorders of pregnancy (preeclampsia, eclampsia, pregnancy-induced hypertension)

- Up to twice the risk of cerebrovascular disease
- Preeclampsia onset <32 weeks' gestation: 5× higher stroke risk compared with later
- Close evaluation post-partum and treatment of cardiovascular risk factors (HTN, smoking, obesity, HLD)

Menopause

- Inconsistent association between early menopause and stroke risk
- Framingham Heart Study: menopause before age 42: two-fold higher adjusted stroke risk
- Hysterectomy with bilateral oophorectomy before age 50: higher stroke risk in some studies

Hormone-replacement therapy (HRT)

- Nine RCTs negative for decreased stroke risk with HRT
- Trend towards higher stroke risk with HRT initiation later (⩾10 years) after menopause

Oral contraceptive (OC) use

- ~1.4–2-fold increase in IS risk
- No increase with progestin only formulations
- Certain gene polymorphisms, prothrombotic mutations may increase IS and ICH risk
- Obesity, hyperlipidemia, smoking may compound stroke risk with OC use
- Routine screening for prothrombotic mutations not useful
- Measurement of BP before initiation recommended

BP, blood pressure; HLD, hyperlipidemia; HTN, hypertension; ICH, intracerebral hemorrhage; IS, ischemic stroke; RCT, randomized-controlled trial.

leading cause of both IS and ICH in pregnant and postpartum women.[24,25] Pregnant women with ICH have fewer traditional risk factors, comorbidities, and tend to have a better outcome than their non-pregnant counterparts.[26]

Pregnancy-related complications like gestational diabetes and HDP are associated with a higher risk for stroke and future cardiovascular disease (CVD), a risk that extends beyond childbearing age.[27,28] A 2012 study reported over 13-fold increased odds of an adverse cardiovascular event within 10 years of pregnancy in women with history of preeclampsia compared with women with uncomplicated pregnancies. The lifetime risk was reported to be 3.25-fold higher.[29]

Notably, despite no absolute contraindication to therapy, pregnant women with IS are less likely to receive thrombolysis with tissue plasminogen activator (tPA) therapy by almost 3.5%, per the 'Get with the guidelines' data.[30]

*Hypertensive disorders of pregnancy.* Preeclampsia/eclampsia and pregnancy-induced hypertension are the most significant HDP. Obesity, older age (>40 years), chronic hypertension, history of preeclampsia or gestational hypertension, diabetes

**Table 3.** Risk factors with a differential impact in women.

Migraine with aura

- Four times more likely than men to have migraines
- 2.5-fold higher odds of stroke
- Seven-fold higher odds with OC use, and ninefold higher with smoking
- Increased risk of TIA/non-disabling stroke

Obesity

- 61.8% age-adjusted prevalence of abdominal obesity in women
- Measurable increase in stroke risk with each unit increase in waist circumference

Metabolic syndrome (insulin resistance, abdominal adiposity dyslipidemia, hypertension)

- Trend to higher stroke risk in women

Atrial fibrillation (AF)

- Female sex independent predictor of stroke in AF
- Women make up ~60% AF patients >75 years age
- Higher stroke risk in women ≥75 years with AF than men, even after adjustment for comorbidities and warfarin treatment

Hypertension

- Hypertension: higher risk of first stroke with hypertension
- Older women with prehypertension: 93% increased stroke risk compared with normotensive women
- Age-adjusted prevalence of uncontrolled BP 55.9 ± 1.5% (NHANES)

BP, blood pressure; NHANES, National Health and Nutrition Examination Survey; OC, oral contraceptive; TIA, transient ischemic attack.

mellitus, renal disease, among other factors, increase the risk of hypertension during pregnancy.[31] Black women are notably more likely to develop HDP, including preeclampsia, as well as have a higher stroke risk in this setting compared with White females.[32,33] Although less common than preeclampsia during pregnancy, postpartum preeclampsia is more insidious, is associated with a high risk for strokes, and potentially more dangerous, because women may be unaware of its development, as they are not routinely monitored. Several studies and meta-analyses have noted an approximately twofold increase in the risk of cerebrovascular disease, in women with a history of preeclampsia.[34] In one such study, the mean age at stroke onset was ≤50 years, suggesting an earlier onset despite the premenopausal cardiovascular advantage seen in women.[35] Early-onset preeclampsia, before 32 weeks' gestation, can increase stroke risk up to fivefold compared with late-onset preeclampsia.[36] Preeclampsia and cerebrovascular disease share some common risk factors including endothelial dysfunction, high blood pressure (BP), dyslipidemia, which may explain this association. The most important prevention strategy is early detection, with frequent antenatal BP measurements. Tight BP control has been deemed safe in pregnancy and is crucial in preventing serious complications. Low-dose aspirin (ASA) and calcium supplementation can both lower the risk for preeclampsia and are recommended by the American Heart Association (AHA) in women with a history of hypertension, HDP, and in those with low dietary calcium intake.[3]

Although BP may normalize after delivery, vascular risk does not, and the same is true for gestational diabetes mellitus. It may be decades before women with a history of preeclampsia or gestational diabetes mellitus have formal cardiovascular
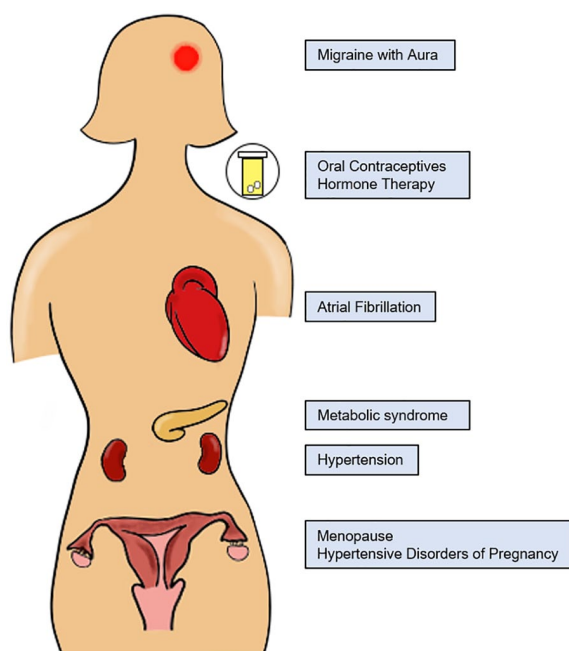
**Figure 2.** Stroke risk factors in women.

risk factor screening and treatment, highlighting the importance of regular follow up.

*Oral contraceptives*

In the US, four out of five sexually active women have taken hormonal contraception.[37] Although the crude incidence of stroke associated with hormonal contraception is low at 21.4 per 100,000 person-years, multiple studies and meta-analysis have shown an almost 2.5-fold increased risk of IS in women who take oral contraceptives (OCs).[38] This is more notable in older women, increasing to about 64.4 per 100,000 person-years in women aged 45–49 years.[39] A meta-analysis of studies from 1980 to 2002 limited to low-dose combined OCs (second and third generation only) also showed 2.12-fold odds of having an IS.[40] Studies on progestin-only hormonal contraception have not shown any significant increase in stroke risk.[41]

Longitudinal data from a Danish study concluded that among the 10,000 women included in the study, and who were taking a 20 μg dose of desogestrel with ethinyl estradiol for 1 year, two women will have arterial thrombosis and 6.8 will have venous thrombosis.[38] Another Swedish study which included 49,259 women followed for

more than a decade, did not find any association between the use of OCs and incident stroke (ischemic and hemorrhagic), in the 285 cases of stroke that occurred during the study.[42]

Data on ICH and OC use are far less consistent, with some reports of a higher risk noted in developing countries. A study of Chinese women evaluated single-nucleotide polymorphisms (SNPs) and the association between OC use and stroke risk and found that women with rs10958409 GA/AA (located near *SOX17*, a transcription factor that modulates cardiovascular development and endothelial cell biology) or rs1333040 CT/TT genotypes (associated with risk of intracranial aneurysm) had an increased overall risk of stroke, with the rs1333040 SNP only increasing the risk for ICH.[43]

*Additive risk with other factors and OCs.* OC use may also augment stroke risk from traditional risk factors. 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, dyslipidemia, or prothrombotic mutations, may be at higher risk for stroke. The RATIO (Risk of Arterial Thrombosis in Relation to Oral Contraceptives) study showed that women who were obese or had a history of dyslipidemia were at an increased risk from OC use compared with women with these risk factors who did not use OCs.[44] They also found that women using OCs who were heterozygous for factor V Leiden and methyl tetrahydrofolate reductase (MTHFR 677TT) mutation were at an increased risk for IS. In addition, the presence of β2 glycoprotein-1 antibodies was associated with 2.3-fold increased odds of stroke in women taking OCs, but no association was found with anticardiolipin or antiprothrombin antibodies.[45]

Questions about screening for the presence of these risk factors and other inherited thrombophilia before prescribing OCs has been raised often, but given the low prevalence of these, its yield may be low and is currently not recommended routinely. Selective screening based on prior personal or family history of venous thromboembolism (VTE) is proposed to be more cost-effective. In addition, there are some data to show that OCs may marginally increase BP, and so BP monitoring may be beneficial, especially when initiating OCs.[3]

## Age at menarche

In the Million Women Study from the United Kingdom, a U-shaped relationship between age at menarche and cerebrovascular disease was observed. Women who experienced menarche at age ⩽10 years and at ⩾17 years of age, were at higher risk of having a stroke compared with those who had menarche at age 13.[46] Some studies have shown an association between early menarche and increased cardiovascular risk but not all. As many of the studies rely on self-reported data, and many other confounding factors (i.e. obesity) may influence stroke risk,[47] the link between age of menarche and 'exposure years' to gonadal hormones remains unclear.

## Menopause and postmenopausal hormonal therapy

Menopause is associated with a decrease in estrogen and an increase in the risk of cardiovascular and cerebrovascular disease, a risk that is clearly also linked to aging. According to a meta-analysis of over 300,000 women, early onset of menopause (<45 years), increases relative risk of coronary artery disease, stroke, and all-cause mortality.[48]

The hypothesized vasoprotective role of estrogen did not translate into direct clinical benefit in women who were treated with hormonal therapy (HT) after menopause. In fact, results from multiple randomized controlled trials (RCTs) of stroke prevention suggested an almost 30% increase in stroke risk with HT despite some protection against CVD noted in observational studies.[3] After 3 years of HT, the risk of stroke increases from 6 to 6–12 per 1000 treated women. After 7 years, it increases from 24 to 25–40 per 1000 women.[49] However, the timing of initiation of HT has differed between observational studies and RCTs, with early initiation at the start of menopause in observational studies which showed benefit, and late enrollment of women in RCTs, up to a decade or more after menopause, showing increased risk. It has since been hypothesized that HT may have beneficial vasoprotective effects, decreasing stroke risk, only when started early after menopause.[50] Estrogen has also been hypothesized to have a beneficial effect in slowing atherogenesis but an adverse role later in the disease course.[51]

In the ELITE (Vascular Effects of Early *versus* Late Postmenopausal Treatment with Estradiol) trial, HT initiated within 6 years after menopause led to a significantly lower increase in carotid intima-media thickness (CIMT) after 5 years follow up than did initiation of HT 10 years or later after menopause, independent of progesterone treatment.[52] Most recently, the results of the Kronos Early Estrogen Prevention Study of women 42–58 years of age, within 36 months of their final menstrual period and randomized to receive different formulations of HT, did not show any effect of HT on progression of CIMT. No adverse cardiac events, venous thrombosis, or adverse increase in systolic BP were noted.[53] At this point, it remains unclear if HT could be beneficial or harmful, and current guidelines recommend limiting their use for short periods during the menopausal transition, primarily for menopausal symptoms.

## Risk factors with a differential impact in women

### Hypertension

Hypertension is the most common modifiable risk factor for stroke in both men and women and has the highest population-attributable risk.[54] Multiple analyses have shown that intensive BP control is the most beneficial for stroke risk reduction.[55,56] Studies have shown that postmenopausal women are more likely to have hypertension than men, and have a higher risk of first stroke with hypertension. About 75% of women >60 years of age become hypertensive.[3] Hypertensive women are more likely than men to be treated for their hypertension but less likely to achieve BP control. Differences in vascular physiology, arterial stiffness, and vascular compliance may possibly contribute to this discrepancy.[57,58] Adherence to therapy and sex differences in the effects of specific antihypertensive agents may also contribute but remain relatively unexplored.

### Migraine with aura

Women are four times more likely to have migraines than men.[59] Migraine with aura is associated with an up to 2.5-fold increase in IS, especially in those <55 years of age.[60] Data from the Women's Health Study showed that migraine with aura accounted for 4 additional IS cases per 10, 000 women per year, with higher risk with increasing migraine frequency, and if the aura did not include nausea and vomiting.[61–63] It is also associated with a higher risk of transient ischemic

attack (TIA) and non-disabling stroke.[64] In women with migraine with aura, the risk increases to nine-fold in those using OCs and smoking cigarettes. This increased risk was not observed in women who did not smoke, suggesting a possibly synergistic effect of smoking and OC use in women who have migraine with aura.[65,66] Current consensus from headache and stroke experts does not preclude the use of OCs in women who suffer from migraine with aura, although caution is warranted.[3] Screening for all traditional stroke risk factors is recommended.

### Metabolic syndrome, obesity, and lifestyle factors

Metabolic syndrome is a combination of cardiometabolic risk factors that includes insulin resistance, abdominal adiposity, dyslipidemia, and hypertension. Studies suggest that metabolic syndrome may account for a higher percentage of stroke events in women than men, 30% *versus* 4%.[67] An analysis of data from the National Health and Nutrition Examination Survey (NHANES) from 1988 to 2012 revealed that the prevalence of metabolic syndrome among women increased from 25.0% during 1988–1994 to 34.9% during 2007–2012. During the entire study period, the largest increase in the prevalence of metabolic syndrome was observed among non-Hispanic Black men (55%), then non-Hispanic White women (44%), and non-Hispanic Black women (41%), while the smallest increase was observed among Mexican American women (2%). Strikingly, the prevalence of metabolic syndrome increased from about 10% among those aged 18–29 years for all racial/ethnic groups to almost 70% among women aged 70 or older in 2007–2012. The component with the most significant increase during the study period was the prevalence of elevated waist circumference (>88 cm in women and >102 cm in men), from 23.6% in 1988–1994 to 42.6% in 2007–2012 in men, and from 38.2% to 60.9% in women.[68]

Studies have revealed an almost linear increase in stroke risk with increasing body mass index. Obesity affects stroke risk almost equally 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.[69–72] However, abdominal obesity has a stronger correlation with insulin resistance, diabetes, and

CVD, impacting women more, given its higher prevalence.[68,73] Studies in women have shown about a 2% relative increase in total stroke risk with each single-unit increase in waist circumference.[74] The biological pathways by which abdominal adiposity contributes to increased stroke risk are not fully understood, but endothelial dysfunction, platelet and immune system activation, increased very-low-density lipoprotein production, and an overactive endocannabinoid system may all have roles to play.[75]

### Atrial fibrillation

AF increases IS risk by 4–5-fold in both sexes, and is associated with higher morbidity and mortality.[54] This risk increases with age, with an attributable risk of about 1.5% in those aged 50–59 years, to almost 25% among persons aged ≥80 years.[54,76] About 60% of AF patients >75 years of age are women.[77] Given current population dynamics and increasing prevalence of AF with age, there will be an increasing number of women with AF as the population ages. In Get With The Guidelines-Stroke, a third of hospital admissions for stroke were for stroke patients ≥80 years of age, and AF was identified in ~5% more women than men.[78]

Stroke risk with AF can be stratified using the CHA2DS2-VASc score, and female sex is an independent predictor of stroke risk.[79] Several large studies of non-valvular AF have confirmed a higher stroke risk in women ≥75 years with AF compared with men, even in those taking warfarin.[80,81] However, more recently, warfarin use was associated with a greater stroke reduction in women by about 20%.[82]

Despite this, studies have shown that women are significantly less likely than men to use any oral anticoagulant at all levels of thromboembolic risk.[83,84] Higher rates of bleeding in women taking warfarin, provider bias, concerns about frailty and higher fall risk, and older age at the time of stroke may all be potential reasons for this discrepancy. No sex differences in safety or efficacy have been reported in the multiple RCTs of novel oral anticoagulants (NOACs) in AF and stroke prevention.[50] However, women represented <40% of the secondary prevention subgroups in most of these trials,[85] being as low as <20% in some.[86] It is also important to be mindful of dose adjustments with some NOACs like apixaban in patients aged ≥80 years, weight ≤60 kg and serum creatinine ≥1.5 mg/dl (two out

of three), which may be more likely in women. In women with contraindications for anticoagulation, left atrial appendage closure with the use of a Watchman device is a viable option. Data are emerging on its safety in both sexes and there may be a greater improvement of mobility, self-care, and resumption of usual activities in female patients compared with men, presumably from discontinuation of anticoagulation.[87] Low-dose edoxaban may be a safe option for stroke prevention in elderly women who otherwise may not have been candidates for oral anticoagulation.[88]

### Age over 80 years

Elderly women represent an especially vulnerable cohort of the population with more severe strokes, poorer outcomes, higher rates of institutionalization and more limited access to healthcare.[50] Analysis of multiple studies in stroke have shown that they are also less likely to have optimal BP control after stroke and to receive anticoagulation for AF to prevent subsequent strokes.[89,90]

### Social factors

In women, social factors such as education, gender roles, social support, integration into society, and education, have an influence on stroke risk and outcomes, as they directly influence access to preventative health care as well as acute treatment. In particular, perceived psychosocial stress associated with family relationships, living situation, finances, and stressful life events, was associated with an increased risk of stroke in both men and women, but with a greater increase in women.[50]

### Vascular aging

Age-related changes in vascular function generally include endothelial dysfunction and arterial stiffness, accompanied by increasing systolic BP and pulse pressure.[91] This progresses at a faster rate in women than men after the sixth decade of life. Postmenopausal women have stiffer arteries than their male counterparts, which is consistent with higher rates of hypertension in women than men after the age of 65.[92]

CIMT, coronary artery calcification, and carotid atherosclerotic plaques all increase in prevalence with advancing age.[93,94] Women are less likely than men to have severe, flow-limiting plaques.[95]

In women, the prevalence of typical obstructive coronary disease is low prior to menopause and then increases dramatically after age 50, affecting up to 79% of women age 75 or older. Women are more likely to have microvascular and/or endothelial dysfunction, and are overall more likely to suffer angina and acute coronary syndromes in the presence of non-obstructive coronary artery disease.[92]

## Stroke management

Women have better awareness for stroke symptoms but are less likely to call an ambulance and more likely to have an unknown time of symptom onset, even when adjusted for age and socioeconomic status.[96]

Women also have a longer delay to treatment, and less frequently receive acute stroke evaluation than men.[97,98] This may have to do more with societal factors, as it is more apparent in low-income countries where cultural factors and belief systems differ significantly; women with stroke in low-income countries have a lower tendency to be admitted to hospitals.[99]

The percentage of women included in clinical trials is not representative of the actual demographics of stroke, despite several national and international acts and resolutions passed to encourage equality.[3,50] Women may also face more barriers to participating in clinical trials owing to less independence and access. In additon, they have higher disability at baseline, with older age at onset of stroke and more comorbidities, which may limit their eligibility for inclusion.[50] More recently, women constituted only 40% of the total participants in trials evaluating NOACs despite a higher prevalence of AF and cardioembolism in women (Table 4).[100]

### Thrombolysis and mechanical thrombectomy

Prior studies have shown that women have a longer time from symptom onset to hospital arrival, more delays in thrombolytic treatment, and receive appropriate diagnostic evaluation and thrombolytic treatment for stroke less frequently than men.[101,102] In a study spanning over a decade (1997–2006), men were more likely than women to receive intravenous tPA, angioplasty/stents, carotid endarterectomy, or cardiac reperfusion. However, toward the end of the study period, sex differences in the use of intravenous (IV) tPA

**Table 4.** Management.

| |
|---|
| Under-represented in stroke prevention and treatment trials |
| Less likely to undergo CEA for symptomatic carotid stenosis after adjusting for age, degree of stenosis |
| Time to CEA also longer in women |
| May derive more benefit from aspirin in the primary prevention of IS |
| Higher odds of poor functional outcomes after intravenous thrombolysis |
| Similar benefit from EVT as men |
| May have more disability adjusted life years after EVT than men |
| Less likely to receive anticoagulation for secondary stroke prevention in the setting of AF |
| No differential benefit of NOACs |

AF, atrial fibrillation; CEA, carotid endarterectomy; EVT, endovascular thrombectomy; IS, ischemic stroke; NOAC, novel oral anticoagulant.

were no longer present.[103] Reasons for these differences are unclear, although they might be due in part to sex-related differences in clinical presentation, timing of presentation, differences in patients' knowledge of stroke and response to symptoms, and physician perception of patients. Many of these gaps in care are closing, possibly due to increased education efforts for both patients and providers.

Overall, evidence that thrombolytic therapy may have increased efficacy in women compared with men has largely been surmised from the absence of sex differences in 90-day functional outcomes after thrombolysis despite more severe strokes, older age, and higher prevalence of AF and hypertension in women, perhaps due to a greater tendency for recanalization of small cardioembolic clots.[104–106] A small study of 100 patients found higher rates of recanalization after tPA for anterior circulation strokes among women than men despite comparable age, BP, symptom-to-needle time, and stroke etiology.[107] In addition, neurological improvement within 72 h of treatment occurred significantly more frequently in women. Data from the Safe Implementation of Treatments in Stroke- International Stroke Thrombolysis Register (SITS-ISTR) which included 45,079 patients (42.8% women), also suggested greater benefit of thrombolysis in women, and a higher mortality and rate of symptomatic ICH in men.[108] On the other hand, an analysis of data from multiple European registries revealed that women had 1.15-fold odds of poor functional outcome after IV thrombolysis compared with men, independent of age.[109] A more recent pooled analysis of thrombolysis outcomes from Asian stroke registries also found that women were more likely to have a cardioembolic stroke, more severe neurological deficits after stroke, and a worse functional outcome after thrombolysis, especially in in women aged >70 years.[110] The retrospective nature of these studies, potentially unaccounted confounders, lower tPA dose, as well as ethnic differences in the cohorts studied may be responsible for these conflicting results. Further investigation is needed for a more definitive conclusion of whether thrombolytic therapy has sex-specific effects, whether this holds for 'newer' thrombolytic agents like tenecteplase, and the potential mechanisms of these differences.

Endovascular thrombectomy (EVT) for acute stroke management is now standard of care in patients with large-vessel occlusions presenting in a variety of time windows with appropriate imaging characteristics. A recent analysis of data from three early EVT trials, Solitaire FR With the Intention for Thrombectomy (SWIFT), Solitaire FR Thrombectomy for Acute Revascularization (STAR), and Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) to assess sex differences in thrombectomy outcomes, found no difference in the rates of reperfusion, time to reperfusion, or adjusted rates of functional independence. However, after adjusting for age at presentation and stroke severity, females had

more years of optimal life (disability-adjusted life-years) after EVT.[111] Another analysis of data from seven RCTs on EVT within the Highly Effective Reperfusion Using Multiple Endovascular Devices collaboration also concluded that sex did not influence outcomes after EVT.[112] Older women have a higher likelihood of functional dependence and higher modified Rankin Scale (mRS) scores at baseline which may have precluded them from inclusion in some of these studies.[113,114]

*Outcomes*

The overall impact of cerebrovascular disease is higher in women than in men. Women are institutionalized more often after stroke and have poorer recovery from stroke. Women consistently have greater long-term mortality after stroke than men, regardless of study location and time period, and controlling for pre-stroke function and stroke severity.[2,115,116]

A pooled analysis of five international RCTs investigating differences in pre- and post-stroke treatments and outcomes, including the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage trials (INTERACT-1 and INTERACT-2), the Enhanced Control of Hypertension and Thrombolysis Stroke study (ENCHANTED), the Head Position in Acute Stroke Trial (HeadPoST), and the Scandinavian Candesartan Acute Stroke Trial (SCAST), showed that women had higher odds of surviving than men after stroke (ischemic and hemorrhagic combined). This study also found that women lived with greater disability after IS, although there were no differences in disability after ICH or when both stroke types were combined. Women had poorer health-related quality of life after IS.[117]

Another analysis pooled data from 11 international population-based studies in stroke, in 4852 survivors of stroke at 1 year (10 studies) and 2226 survivors at 5 years (7 studies), and confirmed the prior finding that women experience a lower quality of life after stroke than men. Among stroke survivors, women had more severe strokes, were older at stroke onset, and had a greater likelihood of dependency before their stroke than men.[118] In another study of 1370 patients who had a stroke, with a median age 65 years, women had significantly lower quality of life at 3 and 12 months after stroke, even after adjusting for important

sociodemographic variables, stroke severity, and disability.[119] The cause of these differences needs further investigation; however, they may be in part due to advanced age, more severe strokes, higher pre-stroke dependency, and increased post-stroke depression in women.[120]

## Aspirin for prevention of stroke in women

A meta-analysis of 13 total trials on ASA for primary prevention of CVD, including three recently published trials involving over 160,000 patients, showed three patient subgroups: non-smokers, patients treated with statins, and males, had the greatest risk reduction of major adverse cardiac events (MACE). ASA reduced MACE in men but not in women.[121] Only one RCT has specifically evaluated ASA for primary prevention of CVD in women *versus* placebo in 39,876 initially asymptomatic women 45 years of age, who were followed for 10 years for a first major vascular event [non-fatal myocardial infarction (MI), non-fatal stroke, or cardiovascular death], and found a 17% reduction in risk of stroke.[122]

Data from previous meta-analyses have also detected a more pronounced effect of ASA for prevention of MACE or MI in men and for IS in women. This is at the cost of an increased risk of major bleeding events.[123,124] ASA is recommended for secondary stroke prevention in both men and women by the AHA. For primary prevention, low-dose ASA may be reasonable in patients with diabetes mellitus and in women with a high CVD risk.[3,54]

## Carotid disease

Women have more stable carotid plaque, with more smooth-muscle infiltration and fewer thin, fibrous caps and lipid-rich necrotic cores.[125] The period of increased recurrent stroke risk after having a stroke in the setting of carotid stenosis is also shorter in women.[126]

Carotid endarterectomy (CEA) for symptomatic carotid stenosis >70% is recommended based on the results from two major trials, the North American Symptomatic Carotid Artery Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial.[127] Combined analysis from these trials showed that the 30-day risk of perioperative stroke or death after CEA was higher in women compared with men (8.7% *versus* 6.8%). However, the risk

of perioperative stroke or death with surgery was lower in women.[128] Pooled analyses from NASCET and the Aspirin and Carotid Endarterectomy Study showed an increased 30-day risk of death in women.[129] Overall, women seem to derive less benefit from CEA in subgroup analyses of large trials comparing CEA with medical management, driven by increased risk of perioperative events.[129]

Various studies have also compared CEA and carotid artery stenting (CAS) in women with inconsistent results, with some showing worse short-term outcomes with CAS in women, and increased perioperative morbidity, stroke, and mortality.[130] Overall, trials examining CAS *versus* CEA were not powered to detect a difference between men and women, and thus outcomes have not been adequately investigated. Available evidence suggest that CAS and CEA provide similar long-term outcomes for patients, but the peri-procedural risk of stroke and death may be higher with CAS in women.[131] With improved risk factor control, medical management may be the preferred option, especially for older women with higher (>6%) peri-procedural morbidity and mortality.[130]

## Cerebral venous thrombosis

CVST is a form of cerebrovascular disease in which there is thrombosis of one or more cerebral venous sinuses, which may lead to cerebral ischemia, hemorrhage, edema, and seizures. CVST most commonly presents with a headache; however, in elderly (≥65 years) patients, mental status changes are more common.[132] Its incidence is estimated to be up to 1.32–1.57/100,000 person-years.[133] It comprises approximately 1% of all strokes but has a female preponderance, with up to three quarters of cases seen in females, potentially related to the use of hormonal contraception.[134] In women aged 31–50 years, CVST incidence may be as high as 2.78/100,000 person-years.[135] Inherited and acquired thrombophilia, including protein C and S deficiency, factor V Leiden mutation, cancer-associated hypercoagulability (more common in the elderly) and autoimmune conditions are well recognized risk factors; however, pregnancy and OC use are female-specific risk factors.[136,137] Females with underlying prothrombotic conditions have a much higher risk of developing CVST with OC use.[138] With pregnancy, most cases occur in the third trimester or during puerperium, and

incidence is estimated at 1 in 2500 to 1 in 10,000 deliveries in Western countries.[139,140]

Currently, CVST is not a contraindication for future pregnancies, but preventative anticoagulation with low-molecular-weight heparin should be considered during pregnancy and the postpartum period.

CVST is associated with more favorable functional outcomes and a lower mortality rate than most stroke subtypes; however, it can remain a disabling condition owing to neuropsychiatric complications, the need for chronic anticoagulation, and an overall negative impact on quality of life.[137] Women who have a CVST in the peripartum period or from hormonal contraception have a much better prognosis than other women and men, without any significant differences in recanalization rates.[135] It is unclear as of now if this is due to inherent differences in the characteristics of the thrombus, or influenced by the etiology of the thrombosis.

## Subarachnoid hemorrhage

Aneurysmal subarachnoid hemorrhage (aSAH) is a major cause of morbidity and mortality worldwide in both sexes. Mortality rates for ruptured cerebral aneurysms continue to average near 50%, with 20% of survivors incurring severe disability.[141] Patients who survive the initial insult of aneurysm rupture are at risk for delayed cerebral ischemia (DCI), involving clinical deterioration, cerebral infarction and contributing to poor outcome. In women, the internal carotid artery is the most frequent site for ruptured aneurysm; however, aneurysms in the posterior communicating artery are more prevalent, overall.[142]

The incidence of intracranial aneurysms is disproportionally higher in women, and evidence also suggests that radiographic vasospasm and DCI after aSAH occur more frequently in women.[143] Some studies have found this risk to be stratified by age, with older women >55 years having a higher risk of clinical deterioration compared with age-matched men.[9] A large study using pooled data from 10 studies with 6713 patients reported a greater risk of DCI in women, but no difference in the risk of cerebral infarction or outcomes.[144] A more recent study of 994 patients identified female sex as an independent predictor of symptomatic vasospasm and reported that women appeared to

be at greatest risk for DCI and unfavorable outcome at age 55–74 years.[145] Mortality rates of female SAH patients are higher in some studies, and women also have multiple aneurysms more frequently than men.[9,146]

According to prospective cohort studies, smoking is the most important lifestyle risk factor for aSAH. A recent study found a multiplicative and additive effect modification between sex and cigarette smoking, with women seemingly much more vulnerable to its deleterious effects, which may account for some of the sex differences seen in aSAH.[147] Outcomes after aneurysm repair surgery have been similar in men and women.[9]

It has been hypothesized that postmenopausal women have a higher rate of aSAH due to the loss of estrogen, which plays a role in vascular modeling and inflammation.[148] Premenopausal women, especially those without a history of smoking or hypertension, are at a reduced risk for aSAH compared with age-matched postmenopausal women. A study of Japanese women after their first occurrence of aSAH found that an earlier age at menarche and nulliparity were associated with an increased risk of aSAH.[149] In addition, HT was associated with a reduced risk for SAH in some studies, but not all. In preclinical studies, estrogens have been shown to attenuate cerebral vasospasm by inducing nitric oxide expression. However, groups with the highest estrogen levels also had a higher rate of radiographic vasospasm, suggesting a more complex interaction.[12,150] Change in estrogen levels may be more important than the absolute levels.

The reported frequency of aSAH in pregnant women ranges from 8 to 31/100,000 deliveries, and it is estimated to cause up to 1 in 10 of all maternal deaths. It may also be higher in pregnant African American women. Repeated childbirths are associated with an increased risk of aSAH, possibly through pregnancy-induced hypertension and vascular tension during delivery, which weakens vessels and may lead to aneurysm formation.[151]

### Reversible cerebral vasoconstriction syndrome

RCVS is characterized by recurrent severe headaches and reversible narrowing of multiple medium-sized cerebral arteries.[152,153] IS, ICH, and convexity SAH are the major complications.

RCVS has a striking female preponderance, seen almost four times more commonly in women than in men in most reported case series.[154,155] Common triggers include vasoactive prescription and illicit drugs, but pregnancy is a well-known risk factor. This postpartum angiopathy usually occurs within 2 weeks post-delivery.[152,154,156] OCs and HT may also increase risk. Furthermore, women are shown to have a more severe clinical syndrome than men, with more severe focal deficits, higher frequency of clinical and radiological worsening, more widespread vasoconstriction, and a longer hospitalization.[154] Female hormones have been postulated to play a role in triggering this disease; however, there are no discernible differences in the clinical course and outcomes between various female subgroups regardless of pregnancy, menopause, or hysterectomy status.[154] The combined case fatality is reported to be less than 1%.[152] Long-term outcomes are usually favorable; however, some patients may have residual deficits from stroke.[152,155,157]

## Preclinical studies

### Sex hormones and IS

Pre-clinical studies have also consistently demonstrated that stroke severity varies with sex and age.[158] Young female animals have smaller infarcts after an induced stroke compared with males, but this effect is lost in ovariectomized females.[159] As female rodents age, stroke damage increases and surpasses that of males in mid-life (at approximately 12 months) coincident with reproductive senescence.[160] Aged female animals have a more detrimental immune response in the brain compared with age-matched males at early timepoints after stroke (i.e. 24 h); however, at later timepoints, male mice had higher mortality, profound peripheral changes in gut permeability and ongoing inflammation compared with females, despite equivalent infarct size.[161] Future research in this area is needed, as the majority of studies have examined only young male mice, or only relatively short endpoints.

### Sex chromosomes

The influence of sex chromosomes on stroke outcomes is being increasingly recognized. Using a four-core genotype (FCG) mouse model, it has been demonstrated that the sex chromosome complement contributes to the pathology of pain,

addiction behavior, and inflammation.[162,163] In these mice, *Sry*, the testes determining gene, is deleted from the Y chromosome and inserted on an autosome, giving an XY male (XYM) genotype. This is crossed with a wild-type female giving rise to FCG mice with different gonadal and chromosomal complements. Among young gonadally intact FCG mice subjected to middle-cerebral artery occlusion, animals that had ovaries had smaller strokes.[163] A subsequent study of gonadectomized mice, in which both ovaries and testes were removed, discovered that all mice, regardless of chromosome compliment (XX or XY) had equivalent infarct damage, implying that ischemic sensitivity is mediated primarily by the effects of circulating gonadal hormones in young animals. Interestingly, in aged FCG mice (18–20 months of age), after gonadal senescence, mice with two X chromosomes had larger strokes than those that were XY. These results suggest that there is a detrimental effect of the second X chromosome that is only evident after reproductive senescence and imply a complex interaction between aging, ischemia, and genetics.[164] Ongoing studies are examining candidate genes on the X chromosome that may be responsible for these effects.

## Conclusion

Cerebrovascular disease differentially impacts women, with several unique risk factors and management considerations. Equitable representation of women in clinical trials, improved screening during periods of increased risk, recognition of sex-specific risk factors, and implementation of specific up-to-date guidelines for cerebrovascular disease management in women are necessary to reduce stroke incidence and improve outcomes.

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