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Impact of Conventional Stroke Risk Factors on Stroke in Women: An Update

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INTRODUCTION

Stroke is a disease that affects all populations, but women bear a greater disease burden compared with men. Due to increasing stroke risk with age and a longer life expectancy, women experience more strokes and more death from stroke over the lifetime.[1, 2] In addition, recent data show that age-adjusted stroke risk in women may not be declining to the same extent that it is in men, potentially resulting in similar age-adjusted stroke incidence rates between the sexes.[3] Finally, women have worse functional outcomes following stroke,[2] adding to the negative impact that stroke has on women.

Optimizing stroke prevention in women is critical to reducing the number of strokes, the personal and societal costs of long term disability from stroke, and stroke deaths. In 2014, guidelines published by the American Heart Association (AHA) and American Stroke

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Association (ASA) highlighted aspects of stroke prevention that should be tailored for women.[4] The objective of this paper is to summarize recent evidence on stroke risk factors in women and to identify possible sex differences in these risk factors. We aim to review current literature (2013 to present) to determine whether: 1) there are sex differences in the prevalence of key risk factors for ischemic stroke; 2) there is a sex difference in the strength of associations between key risk factors and ischemic stroke; and 3) there is evidence for disparities in treatment or control of stroke risk factors between women and men. We chose to focus on ischemic stroke because the risk factors and pathophysiology differ from those relevant to hemorrhagic stroke. Risk factors included in the current review include hypertension, atrial fibrillation, dyslipidemia, diabetes, migraine, and cognitive impairment.

METHODS

This paper was designed as a narrative review. Pubmed was searched using the following terms: women, sex differences, or gender differences and stroke or cerebrovascular accident and terms specific to each topic area. Only articles published since 2013 were included as this paper was intended to update evidence published in the 2014 AHA/ASA guidelines.[4] For each of the risk factors listed above, key articles were selected based on relevance to the topic of prevention of ischemic stroke in women and/or sex differences in stroke prevention.

HYPERTENSION

Hypertension remains the most prevalent modifiable risk factor for stroke globally among both sexes. In the US between 2011 and 2014, the prevalence of hypertension (systolic blood pressure [SBP] ≥140 mmHg and/or diastolic blood pressure [DBP] ≥90mmHg) among women aged ≥18 years was 28%.[5] However, the prevalence varies by age, sex and race/ethnicity. In the general population, women exhibit a lower prevalence of hypertension than men up to the sixth decade of life and a higher prevalence thereafter (women=66.5%; men=63.1%).[5] In the U.S., the age-adjusted prevalence of hypertension among black women exceeds that of both men and women of other racial/ethnic groups (non-Hispanic black, non-Hispanic white, non-Hispanic Asian and Hispanic).[5] Among cohorts of stroke patients, hypertension has been found to be more prevalent in women compared with men in many but not all studies,[6, 7] though this could potentially be explained by women being older at the time of first stroke with known sex differences in hypertension in those over 60 years old. Additionally, the prevalence of hypertension may be increasing over time, with trends varying by age, sex, race/ethnicity and geographic region.[3, 8] Moreover, among women, consideration of pregnancy related hypertension disorders, which may have long lasting effects on a woman's cardiovascular health, should be considered when examining stroke risk.[9]

Evidence from several large-scale studies, including a meta-analysis of 56 cohorts, suggests that hypertension influences risk of stroke similarly in men and women.[10–12] It is unclear, however, if these findings are consistent across age and racial/ethnic groups. For example, among an elderly Chinese population (≥65 years of age), the association between self-reported hypertension and risk of stroke was stronger among women (odd ratio [OR]=6.73, 95%CI: 2.14-21.15) than men (OR=3.18, 95%CI: 1.65-6.14), although the p-value for the

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sex interaction was not reported.[13] Moreover, in this same population, diabetes and hypertension exhibited a synergistic association with stroke risk, such that a history of both was associated with a significantly greater risk of stroke among women but not men. While discrepancies in these findings may be due to variation in the collection of hypertension status (clinically measured versus self-report), differences in the underlying age distribution of participants may also play a role in understanding how sex differences in stroke risk change over the life-course.

Data on potential sex-specific blood pressure targets for primary and/or secondary stroke prevention are limited. One study of recurrent stroke risk between patients randomized to SBP 130-149 mmHg and those with SBP < 130 mmHg showed no difference between SBP groups among women or men and a non-significant p-value for the sex-by-treatment group interaction term.[14]

Regarding differences in treatment and control of hypertension between women and men, one study showed that hypertension control (SBP<140 and DB < 90) among U.S. adults was generally higher among women (56.3%) than men (50.6%); however, this varied with age such that control among women 60+ (50.8%) was lower than similarly aged men (54.6%; p-value for sex differences<0.05).[5] Control also varied by race/ethnicity.[5] Among all adults, non-Hispanic Asian women had the lowest prevalence of hypertension control (46.8%), followed closely by Hispanic (52.1%) and non-Hispanic black (52.3%) individuals compared with non-Hispanic white women (59.1%). Differences between racial/ethnic groups were significant between non-Hispanic white women and non-Hispanic black women and separately between non-Hispanic white and non-Hispanic Asian women ($p<0.05$).[5]

In summary, these findings highlight differences in the role of hypertension on risk of stroke in women compared with men, which are likely influenced by age and race/ethnicity. Future work should consider racial/ethnic and sex variability in the prevalence of hypertension and its association with stroke risk given stark racial/ethnic disparities in both stroke and hypertension.

ATRIAL FIBRILLATION

Atrial fibrillation (AF) is a leading cause of cardiovascular disease and mortality. The risk of developing AF is 1.5 to 2 times higher in men than in women,[15] but because women live longer and the prevalence of AF rises with age, the absolute number of women with AF is higher than men. AF is associated with an increased risk of stroke in men and women, and data show that female sex is an independent risk factor for death, stroke and cardiovascular disease attributable to AF. A large meta-analysis involving 30 studies (n=4,371,714) found that AF was associated with a higher risk of all-cause mortality in women and a significantly stronger risk of stroke, cardiovascular mortality and cardiac events.[16] The higher stroke risk persisted even after adjusting for the higher burden of hypertension and prior stroke in women.

Compared with men, women with AF also have greater risks of dependency and recurrence 36 months after a stroke after adjustment for stroke subtype, severity, and risk factors.[17]

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Moreover, not only do women with AF have a greater risk of stroke than men, the AF-related stroke is also more severe.[18] In one meta-analysis, the greater mortality after stroke in women was mostly attributable to their advanced age but greater stroke severity, greater pre-stroke functional limitations, and the presence of AF in women also contributed to the difference.[19] Current AF guidelines recommend the use of the CHA_2DS_2-VASc score, which factors in female sex in the risk calculation, for the prediction of stroke risk and guidance of anticoagulation therapy in individuals with AF.[20]

Regarding treatment, several sex-related disparities have been identified. Women have been found to less frequently undergo cardiac ablation procedures compared to men.[15] Catheter ablation, in some studies, has also been associated with more complications in women.[21]

Use of oral anticoagulant (OAC) medications is the cornerstone of stroke prevention for patients with AF. A recent analysis of the PINNACLE registry from 2008-2014 found that women were less likely to receive OAC treatment compared to men (56.7% vs. 61.3%, $p<0.001$).[22] At all levels of the CHADS-VASc score, the lower rate of OAC use in women persisted (adjusted risk ratio 9% to 33% lower). Other registries have found similar rates of OAC treatment by sex so further investigation of this disparity is needed.[23]

No major disparity has been found with regard to efficacy of Novel Oral Anticoagulant (NOAC) medications by sex.[24] However, in a population-based study from Quebec, women were more likely to be prescribed a lower dose of dabigatran (110 mg), even after adjustment for age and comorbidities.[25] Since the higher dose of dabigatran (150 mg) is superior to warfarin, this raises concerns that some women may be undertreated and not receiving maximal stroke prevention.

DIABETES

The risk of abdominal adiposity associated with stroke appears to differ by sex, with a stronger risk of stroke in women than men.[26] Similarly, the relative risk of ischemic stroke associated with metabolic syndrome is higher in women than men.[27]

Diabetes mellitus is a potent risk factor for stroke in both men and women, with an overall 2-fold increased risk of ischemic stroke.[28] Among ischemic strokes, the risk of lacunar stroke may be particularly increased.[29, 30]

There are substantial sex differences in the cardiovascular consequences of diabetes.[31] Among those with incident stroke, the prevalence of diabetes between women and men is similar (32.5% vs. 32.7% from data in the Greater Cincinnati Northern Kentucky Stroke Study).[32] The excess risk, however, of stroke associated with diabetes is higher in women than men, independent of sex differences in other major cardiovascular risk factors. In a systematic review and meta-analysis from 64 cohort studies, women with diabetes had a 27% higher risk of stroke than men with diabetes.[33] Female sex may increase the risk of fatal stroke among those with diabetes. In the UK Prospective Diabetes Study,[34] women with diabetes had a 2-fold higher risk of fatal stroke than men with diabetes, and female sex remained a strong predictor of fatality even after adjustment for age, glucose control, and blood pressure. Diabetes in women may be classified as a stroke equivalent; among women

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with diabetes, risk of fatal stroke is similar to women with a prior history of stroke but no diabetes.[35] The 2014 AHA/ASA Stroke Prevention Guidelines for Women[4] classify diabetes as a risk factor that is stronger in women than in men. Despite evidence that diabetes carries more stroke risk for women than men, some data indicate that women are less likely than men to have their glycated hemoglobin controlled (defined by levels <7%),[36] while other data conflict, showing no sex difference in glycated hemoglobin levels.[37]

Recent data show a slower decline in stroke rates in women than men in recent years, with rates in women now equal to those in men.[3] The rising rates of diabetes and obesity, and their associated greater risk in women, have been postulated as one explanation for the slower decline in stroke rates in women than men in recent years.

DYSLIPIDEMIA

Dyslipidemia, particularly elevated low-density lipoprotein cholesterol (LDL) and non-high density lipoprotein cholesterol (non-HDL-C), increases risk of ischemic stroke,[38] but no guidelines have included sex-specific recommendations for the management of dyslipidemia for stroke prevention.

Some data show that among stroke cohorts, men have higher rates of reported dyslipidemia, [39] though other data from the general population indicate similar rates of dyslipidemia by sex.[3] Further, it is typically assumed that associations between dyslipidemia and stroke risk are similar by sex, but few studies have reported sex-specific estimates of stroke risk. A recent meta-analysis of 577,642 individuals (and almost 12,000 stroke cases) demonstrated a slightly higher risk in men: comparing the highest to lowest categories of total cholesterol, the relative risk for total stroke in women was 0.99 compared to 1.14 in men with a relative risk ratio (women:men) of 0.86 (0.76-0.97).[40] When only ischemic strokes were included, the relative risks were 1.27 for women and 1.50 for men with no significant sex difference.[40] It is unknown whether there are sex differences in the associations between LDL, Non-HDL-TC, HDL, and TG and stroke risk.

In terms of treatment disparities, some data have demonstrated that women are at increased risk of not receiving statins for hyperlipidemia and/or not reaching recommended cholesterol goals. In one prospective cohort study, among individuals with diabetes and a baseline LDL ≥ 100, white and black women were less likely to report statin use and less likely to have their LDL controlled than their male counterparts with white men having the highest percentage of statin use and controlled LDL.[41] This is consistent with data from the cardiology literature demonstrating that women are less likely to meet cholesterol goals.[42] Some data conflict, however. In a sample of individuals surveyed from the general population living in southern Ohio/ northern Kentucky, self-reported use of lipid lowering medications increased in both women and men between 1995 and 2011, but proportions in each time period did not differ by sex.[3] Finally, in a prospective cohort investigating the initiation of statins at discharge for incident ischemic stroke, men residing in the stroke belt were less likely than women to be discharged on a statin (aOR 0.69, 95%CI 0.5-0.96), but there was no sex difference in statin prescriptions among those not living in the stroke belt.[43] More research is needed to better understand reasons for disparities in the recommended use

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of statins for stroke prevention. Of note, a recent large meta-analysis of clinical trials comparing statins to control or high intensity statin therapy to low intensity statin therapy found that the effectiveness of statins, as defined by reducing LDL and total cholesterol and/or lowering risk of stroke events, was similar between women and men.[44] It should be noted, however, that across all 27 studies included, only 26% of the participants were women.

In conclusion, though some data indicate that the stroke risk associated with total cholesterol is slightly higher in men compared with women, more data are needed to determine the magnitude of increased ischemic stroke risk associated with other types of dyslipidemia (i.e. high LDL, low HDL, high triglycerides). It is also critical that future studies report sex-specific estimates of risk by stroke subtype.

MIGRAINE

In the general population, migraine headache is approximately three times more prevalent in women than men in both the general population and among stroke patients.[45,46] Recent studies have confirmed previous reports of an association between migraine and stroke across diverse populations.[47–50] Across most studies, the increase in risk of ischemic stroke among patients with migraine with aura is two- to three-fold compared to those without migraine.[47, 50, 51] In a prospective case control study that included almost 1000 patients aged 55-70 with ischemic stroke, the prevalence of migraine was higher among ischemic stroke subjects compared with controls (17% vs. 4%, $p<0.01$).[48] In a large prospective cohort study of over 115,000 nurses (age 25-42 at enrollment), over 17,000 of whom had a history of migraine, the risk of stroke associated with migraine was 1.62 (OR 1.37 to 1.92).[51] Most data indicate that the risk is highest in women and those with migraine with aura.[52,53]

The mechanism by which migraine with aura leads to increased stroke risk is unknown but may be related to differences in the prevalence of other stroke risk factors, patent foramen ovale (PFO), endothelial dysfunction, inflammation, migranous infarction secondary to cortical spreading depression, genetic risk factors, or cervical artery dissection.[51] Though the pathophysiology remains elusive, recent data have advanced our knowledge of the mechanism by which migraine with aura may lead to ischemic stroke.[46, 49, 54] In a Dutch stroke registry of approximately 600 patients, there was no significant association between migraine and cerebrovascular atherosclerotic burden measured with CT angiography, suggesting that large vessel disease is not the mechanism. Other data from 1800 incident ischemic strokes and transient ischemic attacks from a prospective cohort study demonstrated that migraine was associated with cryptogenic strokes as opposed to strokes of known etiology, with an odds ratio of 1.68 (95%CI 1.33-2.13), after adjusting for age, sex, and co-morbidities. This association was stronger in those with fewer vascular risk factors, those on hormone replacement therapy, and those in older age groups, again suggesting a possible mechanistic role apart from atherosclerotic burden.[49] The association between migraine and cryptogenic stroke was slightly stronger in women than men.[49] Other recent data have confirmed previous reports that use of estrogen containing oral contraceptives amplify the risk of ischemic stroke associated with migraine with aura.[47] Finally, confirming prior reports of a potential role for PFO, data from an in-hospital stroke cohort reported that

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PFO was over 6 times more common in stroke patients with a migraine history compared to those without a history of migraine.[46]

There are several limitations to the current literature on migraine and stroke. Some studies of migraine and ischemic stroke are limited by self-report and/or retrospective recall of headache history,[46, 50] which may be prone to bias. Other studies combine patients with migraine with aura with those without aura, which may dilute the association between migraine with aura and stroke.[50, 54]

In summary, migraine, particularly migraine with aura, is a risk factor for ischemic stroke. This risk, is higher in women than men but persists across age groups. To translate such findings into stroke prevention strategies for women, more data are needed to discern the mechanism by which migraines lead to stroke. It is reasonable to continue to follow previous recommendations to avoid estrogen containing forms of contraception in women with migraine with aura and to encourage smoking cessation in those with migraine.[55] Future research directions include whether more aggressive treatment of migraines could reduce stroke risk or whether there are novel drug therapies that could alter vascular function and reduce migraine prevalence, migraine frequency, and stroke risk.

COGNITIVE IMPAIRMENT

Although cognitive impairment is not included as a stroke risk factor in current U.S. guidelines for primary prevention,[56] data from multiple prospective cohort studies support that cognitive impairment is strongly associated with an elevated risk of stroke. Two somewhat overlapping systematic reviews/meta-analyses found a strong association between cognitive impairment and subsequent incident stroke.[57, 58] One review with 12 long-term studies from Europe, U.S., and Australia estimated the pooled relative risk (95%CI) per standard deviation difference to be 1.07 (1.02,1.12) for memory, 1.14 (1.06,1.24) for global cognitive function, and 1.14 (1.06,1.24) for executive function/attention.[57] Additional cohort studies published since these meta-analyses demonstrating an association between cognitive function and stroke add to the evidence.[59–61] Although two of these studies had large sample sizes with more than half women (N=3926, 56% women)[60] (N=7205, 59% women)[61], the potential for interaction by sex was not examined.

The prevalence and incidence of Alzheimer's disease (AD), dementia, and cognitive impairment is generally higher in women than men, but similar to stroke epidemiology, a contributing factor may be that women live longer than men.[62, 63] Research on human brain morphology has been conducted, however, showing that brain development and adult brain structure, function, and biochemistry differ by sex.[64, 65] Men have higher brain volume and percentage of white matter than women, yet women have higher percentage of gray matter.[65] Additionally, the magnitude of the effect of the apolipoprotein E-4 genotype on AD risk is larger in women than men.[63, 66] Other risk factors for cognitive impairment that differ by sex include change in sex hormones and education/occupational history.[66] Finally, some data indicate that women with dementia are less likely to be treated cholinesterase inhibitors.[67] These differences affirm that beyond adjustment for traditional vascular risk factors, studies

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of cognitive impairment and incident stroke should report results by sex and consider *a priori* a test for interaction by sex.

CONCLUSIONS

In conclusion, recent evidence indicates that risk factors including diabetes, metabolic syndrome, atrial fibrillation, and migraine carry greater ischemic stroke risk for women compared with men, while the association between dyslipidemia and stroke may be slightly higher among men. The topic of hypertension is complex, and sex differences in the association between hypertension and ischemic stroke vary by age and race/ethnicity. Evidence also suggests that treatment disparities continue with regard to key stroke risk factors including atrial fibrillation and dyslipidemia. Unfortunately, very little sex-specific data exist on the association between cognitive impairment with stroke risk. Table 1 highlights differences in risk factor prevalence, association with stroke risk, and treatment disparities between women and men.

Moving forward, it is imperative that future research examine sex-specific risk estimates of stroke risk factors. Additionally, contributors to treatment disparities leading to suboptimal stroke prevention in women need to be addressed. Table 2 highlights additional research directions. Greater attention to sex-specific risks and treatment strategies has the potential to improve the effectiveness of stroke prevention in women and ultimately reduce stroke-related death and disability.

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Table 1

Sex Differences in Risk Factor Prevalence, Associations, and Treatment Disparities, Women Compared with Men

Risk Factor	Prevalence	Association with IS	Treatment Disparity
Hypertension	Lower in women (vs. men) in younger age groups, higher in older age groups	Similar in women (vs. men) in younger age groups, higher in older age groups	In younger age groups, women more likely to have BP controlled; in older age groups, women less likely to have BP controlled.
Dyslipidemia	Data conflict; either similar between sexes or lower in women	Lower in women	Women less likely to be on statins and have LDL controlled.
Atrial Fibrillation	Higher in women	Higher in women	Women less likely to be prescribed oral anticoagulants, less likely to have cardiac ablation, and receive lower doses of NOACs.
Migraine	Higher in women	Higher in women.	Unknown if migraine treatment reduces stroke risk.
Diabetes	Similar women vs. men	Higher in women	Data conflict regarding sex differences in meeting HbA1c goal
Cognitive Impairment	Higher in women	Unknown whether there is a sex difference	Women less likely to be treated with anti-dementia drugs

IS: Ischemic stroke. BP: blood pressure. NOAC: novel oral anticoagulant. HbA1c: glycated hemoglobin

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Table 2

Future research directions

Risk Factor	Future Research Priorities
Hypertension	• Consider racial/ethnic and sex variability in the prevalence of hypertension and its association with stroke risk • Stratify by age in studies of association between HTN and stroke
Dyslipidemia	• Report sex-specific associations between LDL, non-HDL-C, and triglycerides and stroke • Investigate interventions to increase statin use and control of dyslipidemia in women
Atrial Fibrillation	• Determine contributors to decreased use of anti-coagulants in women • Assess reasons for lower use of cardiac ablation procedures in women
Migraine with aura	• Determine pathophysiologic link with stroke • Investigate interventions to decrease migraine frequency/ prevalence and stroke risk
Diabetes	• Determine contributors (i.e. pathophysiology, treatment differences) to increased stroke risk among women with diabetes
Cognitive Impairment	• Report sex-specific association with stroke and consider *a priori* tests for interaction by sex. • Investigate differences in care for women vs. men with dementia