Focused Updates in Cerebrovascular Disease

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

Tracy E. Madsen, MD, ScM; Virginia J. Howard, PhD; Monik Jiménez, ScD;
Kathryn M. Rexrode, MD, MPH; Maria Czarina Acelajado, MD; Dawn Kleindorfer, MD;
Seemant Chaturvedi, MD

Stroke is a disease that affects all populations, but women bear a greater disease burden compared with men. Because of 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 after 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 and American Stroke Association highlighted aspects of stroke prevention that should be tailored for women.[4] The objective of this article 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 (AF), dyslipidemia, diabetes mellitus, migraine, and cognitive impairment.

Methods

This article 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 because this article was intended to update evidence published in the 2014 American Heart Association/American Stroke Association 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 or sex differences in stroke prevention.

Hypertension

Hypertension remains the most prevalent modifiable risk factor for stroke globally among both sexes. In the United States between 2011 and 2014, the prevalence of hypertension (systolic blood pressure [SBP] ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg) 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 United States, 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 patients with stroke, hypertension has been found to be more prevalent in women compared with men in many but not all studies[6,7] although this could potentially be explained by women being older at the time of first stroke with known sex differences in hypertension in those >60 years old. In addition, 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, whether 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=6.73; 95% confidence interval [CI], 2.14–21.15) than men (odd ratio=3.18; 95% CI, 1.65–6.14) although the *P* value for the sex interaction was not reported.[13] Moreover, in this same population, diabetes mellitus 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. Although discrepancies in these findings may be because of 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 secondary stroke preventions are limited. One study of recurrent stroke risk between patients randomized to SBP 130 to 149 mm Hg and those with SBP <130 mm Hg showed no difference between SBP groups among women or men and a nonsignificant *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 diastolic blood pressure <90) among US adults was generally higher among women (56.3%) than men (50.6%); however, this varied with age such that control among women 60+ years (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

AF is a leading cause of cardiovascular disease and mortality. The risk of developing AF is 1.5× to 2× 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] 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 prestroke 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 (congestive heart failure, hypertension, age, diabetes, previous stroke/transient ischemic attack–vascular disease), 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 with men.[15] Catheter ablation, in some studies, has also been associated with more complications in women.[21]

Use of oral anticoagulant medications is the cornerstone of stroke prevention for patients with AF. A recent analysis of the PINNACLE registry (Practice Innovation and Clinical Excellence) from 2008 to 2014 found that women were less likely to receive oral anticoagulant treatment compared with men (56.7% versus 61.3%; *P*<0.001).[22] At all levels of the CHADS-VASc score, the lower rate of oral anticoagulant use in women persisted (adjusted risk ratio, 9%–33% lower). Other registries have found similar rates of oral anticoagulant 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 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] Because 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 Mellitus

The risk of abdominal adiposity associated with stroke seems 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 mellitus.[31] Among those with incident stroke, the prevalence of diabetes mellitus between women and men is similar (32.5% versus 32.7% from data in the Greater Cincinnati Northern Kentucky Stroke Study).[32] The excess risk, however, of stroke associated with diabetes mellitus 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 mellitus had a 27% higher risk of stroke than men with diabetes

mellitus.[33] Female sex may increase the risk of fatal stroke among those with diabetes mellitus. In the UK Prospective Diabetes Study,[34] women with diabetes mellitus had a 2-fold higher risk of fatal stroke than men with diabetes mellitus, and female sex remained a strong predictor of fatality even after adjustment for age, glucose control, and blood pressure. Diabetes mellitus in women may be classified as a stroke equivalent; among women with diabetes mellitus, risk of fatal stroke is similar to women with a prior history of stroke but no diabetes mellitus.[35] The 2014 American Heart Association/American Stroke Association Stroke Prevention Guidelines for Women[4] classify diabetes mellitus as a risk factor that is stronger in women than in men. Despite evidence that diabetes mellitus 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 mellitus 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 (LDL) cholesterol and nonhigh-density lipoprotein cholesterol, 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] although other data from the general population indicate similar rates of dyslipidemia by sex.[3] Furthermore, 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 577642 individuals (and ≈12000 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 with 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, nonhigh-density lipoprotein-total cholesterol, high-density lipoprotein, and triglycerides and stroke risk.

In terms of treatment disparities, some data have demonstrated that women are at increased risk of not receiving statins for hyperlipidemia or not reaching recommended cholesterol goals. In one prospective cohort study, among individuals with diabetes mellitus 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 (adjusted odds ratio, 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 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 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, although 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 (ie, high LDL, low high-density lipoprotein, 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 ≈3× more prevalent in women than men in both the general population and among patients with stroke.[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 2- to 3-fold compared with those without migraine.[47,50,51] In a prospective case–control study that included ≈1000 patients aged 55 to 70 years with ischemic stroke, the prevalence of migraine was higher among ischemic stroke subjects compared with controls (17% versus 4%; P<0.01).[48] In a large prospective cohort study of >115000 nurses (age, 25–42 years at enrollment), >17000 of whom had a history of migraine, the risk of stroke associated with migraine was 1.62 (odd ratio, 1.37–1.92).[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, endothelial dysfunction, inflammation, migrainous infarction secondary to cortical spreading depression, genetic risk factors, or cervical artery dissection.[51] Although 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 ≈600 patients, there was no significant association between migraine and cerebrovascular atherosclerotic burden measured with computed tomographic 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

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 mellitus	Similar women vs men	Higher in women	Data conflict on 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 antidementia drugs

BP indicates blood pressure; HbA1c, glycated hemoglobin; IS, ischemic stroke; LDL, low-density lipoprotein; and NOAC, novel oral anticoagulant.

to strokes of known pathogenesis, with an odds ratio of 1.68 (95% CI, 1.33–2.13), after adjusting for age, sex, and comorbidities. 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 patent foramen ovale, data from an in-hospital stroke cohort reported that patent foramen ovale was >6× more common in stroke patients with a migraine history compared with 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 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 US 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, United States, and Australia estimated the pooled relative risk (95% CI) per SD 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)

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 anticoagulants 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 mellitus	Determine contributors (ie, pathophysiology, treatment differences) to increased stroke risk among women with diabetes mellitus
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

HTN indicates hypertension; LDL, low-density lipoprotein; and LDL-C, low-density lipoprotein cholesterol.

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 2 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 disease, dementia, and cognitive impairment are 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] In addition, the magnitude of the effect of the apolipoprotein E-4 genotype on Alzheimer disease 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 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 mellitus, metabolic syndrome, AF, 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 AF and dyslipidemia. Unfortunately, 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 examines sex-specific risk estimates of stroke risk factors. In addition, 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.

Sources of Funding

Disclosures

References

1. Centers for Disease Control and Prevention. Leading causes of death in females United States, 2014: all females, all ages. https://www.cdc.gov/women/lcod/2014/index.htm. Accessed November 1, 2017.
2. Reeves MJ, Bushnell CD, Howard G, Gargano JW, Duncan PW, Lynch G, et al. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. *Lancet Neurol*. 2008;7:915–926. doi: 10.1016/S1474-4422(08)70193-5.
3. Madsen TE, Khoury J, Alwell K, Moomaw CJ, Rademacher E, Flaherty ML, et al. Sex-specific stroke incidence over time in the Greater Cincinnati/Northern Kentucky Stroke Study. *Neurology*. 2017;89:990–996. doi: 10.1212/WNL.0000000000004325.
4. Bushnell C, McCullough LD, Awad IA, Chireau MV, Fedder WN, Furie KL, et al; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Epidemiology and Prevention; 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;45:1545–1588. doi: 10.1161/01.str.0000442009.06663.48.
5. Yoon SS, Carroll MD, Fryar CD. Hypertension prevalence and control among adults: United states, 2011–2014. *NCHS Data Brief*. 2015;220:1–8.
6. Koton S, Telman G, Kimiagar I, Tanne D; NASIS Investigators. Gender differences in characteristics, management and outcome at discharge and three months after stroke in a national acute stroke registry. *Int J Cardiol*. 2013;168:4081–4084. doi: 10.1016/j.ijcard.2013.07.019.
7. Gattringer T, Ferrari J, Knoflach M, Seyfang L, Horner S, Niederkorn K, et al. Sex-related differences of acute stroke unit care: results from the Austrian stroke unit registry. *Stroke*. 2014;45:1632–1638. doi: 10.1161/STROKEAHA.114.004897.
8. Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015. *JAMA*. 2017;317:165–182. doi: 10.1001/jama.2016.19043.
9. Appelman Y, van Rijn BB, Ten Haaf ME, Boersma E, Peters SA. Sex differences in cardiovascular risk factors and disease prevention. *Atherosclerosis*. 2015;241:211–218. doi: 10.1016/j.atherosclerosis.2015.01.027.
10. Peters SA, Huxley RR, Woodward M. Comparison of the sex-specific associations between systolic blood pressure and the risk of cardiovascular disease: a systematic review and meta-analysis of 124 cohort studies, including 1.2 million individuals. *Stroke*. 2013;44:2394–2401. doi: 10.1161/STROKEAHA.113.001624.
11. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. *Lancet*. 2014;383:1899–1911. doi: 10.1016/S0140-6736(14)60685-1.
12. Turin TC, Okamura T, Afzal AR, Rumana N, Watanabe M, Higashiyama A, et al. Hypertension and lifetime risk of stroke. *J Hypertens*. 2016;34:116–122. doi: 10.1097/HJH.0000000000000753.
13. Lai YJ, Chen HC, Chou P. Gender difference in the interaction effects of diabetes and hypertension on stroke among the elderly in the Shih-Pai Study, Taiwan. *PLoS One*. 2015;10:e0136634. doi: 10.1371/journal.pone.0136634.
14. Benavente OR, Coffey CS, Conwit R, Hart RG, McClure LA, Pearce LA, et al; SPS3 Study Group. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet*. 2013;382:507–515. doi: 10.1016/S0140-6736(13)60852-1.
15. Ko D, Rahman F, Schnabel RB, Yin X, Benjamin EJ, Christophersen IE. Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis. *Nat Rev Cardiol*. 2016;13:321–332. doi: 10.1038/nrcardio.2016.45.
16. Emdin CA, Wong CX, Hsiao AJ, Altman DG, Peters SA, Woodward M, et al. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. *BMJ*. 2016;532:h7013.
17. Hong Y, Yang X, Zhao W, Zhang X, Zhao J, Yang Y, et al. Sex differences in outcomes among stroke survivors with non-valvular atrial fibrillation in China. *Front Neurol*. 2017;8:166. doi: 10.3389/fneur.2017.00166.
18. Wagstaff AJ, Overvad TF, Lip GY, Lane DA. Is female sex a risk factor for stroke and thromboembolism in patients with atrial fibrillation? A systematic review and meta-analysis. *QJM*. 2014;107:955–967. doi: 10.1093/qjmed/hcu054.

19. Phan HT, Blizzard CL, Reeves MJ, Thrift AG, Cadilhac D, Sturm J, et al. Sex differences in long-term mortality After Stroke In The Instruct (International Stroke Outcomes Study): a meta-analysis of individual participant data. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003436.

20. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, et al; ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation*. 2014;130:2071–2104. doi: 10.1161/CIR.0000000000000040.

21. Piccini JP, Sinner MF, Greiner MA, Hammill BG, Fontes JD, Daubert JP, et al. Outcomes of medicare beneficiaries undergoing catheter ablation for atrial fibrillation. *Circulation*. 2012;126:2200–2207. doi: 10.1161/CIRCULATIONAHA.112.109330.

22. Thompson LE, Maddox TM, Lei L, Grunwald GK, Bradley SM, Peterson PN, et al. Sex differences in the use of oral anticoagulants for atrial fibrillation: a report from the national cardiovascular data registry (NCDR(R)) PINNACLE registry. *J Am Heart Assoc*. 2017;6:e005801.

23. Lip GY, Rushton-Smith SK, Goldhaber SZ, Fitzmaurice DA, Mantovani LG, Goto S, et al; GARFIELD-AF Investigators. Does sex affect anti-coagulant use for stroke prevention in nonvalvular atrial fibrillation? The prospective global anticoagulant registry in the FIELD-Atrial Fibrillation. *Circ Cardiovasc Qual Outcomes*. 2015;8(2 suppl 1):S12–S20. doi: 10.1161/CIRCOUTCOMES.114.001556.

24. Moseley A, Doukky R, Williams KA, Jaffer AK, Volgman AS. Indirect comparison of novel oral anticoagulants in women with nonvalvular atrial fibrillation. *J Womens Health (Larchmt)*. 2017;26:214–221. doi: 10.1089/jwh.2016.5892.

25. Avgil Tsadok M, Jackevicius CA, Rahme E, Humphries KH, Pilote L. Sex differences in dabigatran use, safety, and effective-ness in a population-based cohort of patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2015;8:593–599. doi: 10.1161/CIRCOUTCOMES.114.001398.

26. Rodríguez-Campello A, Jiménez-Conde J, Ois Á, Cuadrado-Godia E, Giralt-Steinhauer E, Vivanco RM, et al. Sex-related differences in abdominal obesity impact on ischemic stroke risk. *Eur J Neurol*. 2017;24:397–403. doi: 10.1111/ene.13216.

27. Li X, Li X, Lin H, Fu X, Lin W, Li M, et al. Metabolic syndrome and stroke: a meta-analysis of prospective cohort studies. *J Clin Neurosci*. 2017;40:34–38. doi: 10.1016/j.jocn.2017.01.018.

28. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet*. 2010;375:2215–2222. doi: 10.1016/S0140-6736(10)60484-9.

29. Iso H, Rexrode K, Hennekens CH, Manson JE. Application of computer tomography-oriented criteria for stroke subtype classification in a pro-spective study. *Ann Epidemiol*. 2000;10:81–87.

30. Ohira T, Shahar E, Chambless LE, Rosamond WD, Mosley TH Jr, Folsom AR. Risk factors for ischemic stroke subtypes: the Atherosclerosis Risk in Communities study. *Stroke*. 2006;37:2493–2498. doi: 10.1161/01.STR.0000239694.19359.88.

31. Regensteiner JG, Golden S, Huebschmann AG, Barrett-Connor E, Chang AY, Chyun D, et al; American Heart Association Diabetes Committee of the Council on Lifestyle and Cardiometabolic Health, Council on Epidemiology and Prevention, Council on Functional Genomics and Translational Biology, and Council on Hypertension. Sex differences in the cardiovascular consequences of diabetes mellitus: a scientific state-ment from the American Heart Association. *Circulation*. 2015;132:2424–2447. doi: 10.1161/CIR.0000000000000343.

32. Madsen TE, Khoury JC, Alwell KA, Moomaw CJ, Demel SL, Flaherty ML, et al. Sex differences in cardiovascular risk profiles of ischemic stroke patients with diabetes in the Greater Cincinnati/Northern Kentucky Stroke Study [published online ahead of print May 18, 2017]. *J Diabetes*. http://onlinelibrary.wiley.com/wol1/doi/10.1111/1753-0407.12567/full. doi: 10.1111/1753-0407.12567.

33. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. *Lancet*. 2014;383:1973–1980. doi: 10.1016/S0140-6736(14)60040-4.

34. Stevens RJ, Coleman RL, Adler AI, Stratton IM, Matthews DR, Holman RR. Risk factors for myocardial infarction case fatality and stroke case fatality in type 2 diabetes: UKPDS 66. *Diabetes Care*. 2004;27:201–207.

35. Ho JE, Paultre F, Mosca L; Women's Pooling Project. Is diabetes mel-litus a cardiovascular disease risk equivalent for fatal stroke in women? Data from the Women's Pooling Project. *Stroke*. 2003;34:2812–2816. doi: 10.1161/01.STR.0000102901.41780.5C.

36. Franzini L, Ardigò D, Cavalot F, Miccoli R, Rivellese AA, Trovati M, et al. Women show worse control of type 2 diabetes and cardiovascular disease risk factors than men: results from the MIND.IT Study Group of the Italian Society of Diabetology. *Nutr Metab Cardiovasc Dis*. 2013;23:235–241. doi: 10.1016/j.numecd.2011.12.003.

37. Wong ND, Zhao Y, Patel R, Patao C, Malik S, Bertoni AG, et al. Cardiovascular risk factor targets and cardiovascular disease event risk in diabetes: a pooling project of the Atherosclerosis Risk in Communities Study, Multi-Ethnic Study of Atherosclerosis, and Jackson Heart Study. *Diabetes Care*. 2016;39:668–676. doi: 10.2337/dc15-2439.

38. Glasser SP, Mosher A, Howard G, Banach M. What is the association of lipid levels and incident stroke? *Int J Cardiol*. 2016;220:890–894. doi: 10.1016/j.ijcard.2016.06.091.

39. Renoux C, Coulombe J, Li L, Ganesh A, Silver L, Rothwell PM; Oxford Vascular Study. Confounding by pre-morbid functional status in studies of apparent sex differences in severity and outcome of stroke. *Stroke*. 2017;48:2731–2738. doi: 10.1161/STROKEAHA.117.018187.

40. Peters SA, Singhateh Y, Mackay D, Huxley RR, Woodward M. Total cho-lesterol as a risk factor for coronary heart disease and stroke in women com-pared with men: a systematic review and meta-analysis. *Atherosclerosis*. 2016;248:123–131. doi: 10.1016/j.atherosclerosis.2016.03.016.

41. Gamboa CM, Colantonio LD, Brown TM, Carson AP, Safford MM. Race-sex differences in statin use and low-density lipoprotein choles-terol control among people with diabetes mellitus in the reasons for geographic and racial differences in stroke study. *J Am Heart Assoc*. 2017;6:e004264.

42. Spinler SA, Cziraky MJ, Willey VJ, Tang F, Maddox TM, Thomas T, et al; NCDR. Frequency of attainment of low-density lipoprotein cho-lesterol and non-high-density lipoprotein cholesterol goals in cardiovas-cular clinical practice (from the National Cardiovascular Data Registry PINNACLE Registry). *Am J Cardiol*. 2015;116:547–553. doi: 10.1016/j.amjcard.2015.05.011.

43. Albright KC, Howard VJ, Howard G, Muntner P, Bittner V, Safford MM, et al. Age and sex disparities in discharge statin prescribing in the stroke belt: evidence from the reasons for geographic and racial differences in stroke study. *J Am Heart Assoc*. 2017;6:e005523.

44. Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B, et al; Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of LDL-lowering therapy among men and women: meta-anal-ysis of individual data from 174,000 participants in 27 randomised trials. *Lancet*. 2015;385:1397–1405. doi: 10.1016/S0140-6736(14)61368-4.

45. Vetvik KG, MacGregor EA. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. *Lancet Neurol*. 2017;16:76–87. doi: 10.1016/S1474-4422(16)30293-9.

46. Lantz M, Kostulas K, Waldenlind E, Sjöstrand C. Prevalence of migraine headache in an in-patient stroke population. *Acta Neurol Scand*. 2015;131:290–297. doi: 10.1111/ane.12341.

47. Champaloux SW, Tepper NK, Monsour M, Curtis KM, Whiteman MK, Marchbanks PA, et al. Use of combined hormonal contraceptives among women with migraines and risk of ischemic stroke. *Am J Obstet Gynecol*. 2017;216:489.e1–e489.e7. doi: 10.1016/j.ajog.2016.12.019.

48. Li H, Yu Y. Association between ischemic stroke and migraine in elderly Chinese: a case-control study. *BMC Geriatr*. 2013;13:126. doi: 10.1186/1471-2318-13-126.

49. Li L, Schulz UG, Kuker W, Rothwell PM; Oxford Vascular Study. Age-specific association of migraine with cryptogenic TIA and stroke: population-based study. *Neurology*. 2015;85:1444–1451. doi: 10.1212/WNL.0000000000002059.

50. Rambarat CA, Elgendy IY, Johnson BD, Reis SE, Thompson DV, Sharaf BL, et al. Migraine headache and long-term cardiovascular outcomes: an extended follow-up of the women's ischemia syn-drome evaluation. *Am J Med*. 2017;130:738–743. doi: 10.1016/j.amjmed.2016.12.028.

51. Kurth T, Winter AC, Eliassen AH, Dushkes R, Mukamal KJ, Rimm EB, et al. Migraine and risk of cardiovascular disease in women: prospective cohort study. *BMJ*. 2016;353:i2610.

52. Abanoz Y, Gülen Abanoz Y, Gündüz A, Uludüz D, İnce B, Yavuz B, et al. Migraine as a risk factor for young patients with ischemic stroke: a case-control study. *Neurol Sci*. 2017;38:611–617. doi: 10.1007/s10072-017-2810-3.

53. Peng KP, Chen YT, Fuh JL, Tang CH, Wang SJ. Migraine and incidence of ischemic stroke: a nationwide population-based study. *Cephalalgia*. 2017;37:327–335. doi: 10.1177/0333102416642602.

54. Van Os HJA, Mulder IA, Broersen A, Algra A, van der Schaaf IC, Kappelle LJ, et al. Migraine and cerebrovascular atherosclerosis in patients with ischemic stroke. *Stroke*. 2017;48:1973–1975.

55. Frieden TR, Jaffe HW, Cono J, Richards CL, Iademarco MF. U.S. Medical eligibility criteria for contraceptiive use, 2016. *MMWR Recomm Rep*. 2016;65:55–80.

56. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, et al; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; Council on Hypertension. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:3754–3832. doi: 10.1161/STR.0000000000000046.

57. Rostamian S, Mahinrad S, Stijnen T, Sabayan B, de Craen AJ. Cognitive impairment and risk of stroke: a systematic review and meta-analysis of prospective cohort studies. *Stroke*. 2014;45:1342–1348. doi: 10.1161/STROKEAHA.114.004658.

58. Lee M, Saver JL, Hong KS, Wu YL, Liu HC, Rao NM, et al. Cognitive impairment and risk of future stroke: a systematic review and meta-analysis. *CMAJ*. 2014;186:E536–E546. doi: 10.1503/cmaj.140147.

59. Oveisgharan S, Hachinski V. Executive dysfunction is a strong stroke predictor. *J Neurol Sci*. 2015;349:161–167. doi: 10.1016/j.jns.2015.01.010.

60. Rostamian S, van Buchem MA, Westendorp RG, Jukema JW, Mooijaart SP, Sabayan B, et al. Executive function, but not memory, associates with incident coronary heart disease and stroke. *Neurology*. 2015;85:783–789. doi: 10.1212/WNL.0000000000001895.

61. Rajan KB, Schneider JA, Aggarwal NT, Wilson RS, Everson-Rose SA, Evans DA. Racial differences in cognitive function and risk of incident stroke. *J Stroke Cerebrovasc Dis*. 2015;24:2854–2859. doi: 10.1016/j.jstrokecerebrovasdis.2015.08.020.

62. Au B, Dale-McGrath S, Tierney MC. Sex differences in the prevalence and incidence of mild cognitive impairment: a meta-analysis. *Ageing Res Rev*. 2017;35:176–199. doi: 10.1016/j.arr.2016.09.005.

63. Mazure CM, Swendsen J. Sex differences in Alzheimer's disease and other dementias. *Lancet Neurol*. 2016;15:451–452. doi: 10.1016/S1474-4422(16)00067-3.

64. Ruigrok AN, Salimi-Khorshidi G, Lai MC, Baron-Cohen S, Lombardo MV, Tait RJ, et al. A meta-analysis of sex differences in human brain structure. *Neurosci Biobehav Rev*. 2014;39:34–50. doi: 10.1016/j.neubiorev.2013.12.004.

65. Cosgrove KP, Mazure CM, Staley JK. Evolving knowledge of sex differences in brain structure, function, and chemistry. *Biol Psychiatry*. 2007;62:847–855. doi: 10.1016/j.biopsych.2007.03.001.

66. Li R, Singh M. Sex differences in cognitive impairment and Alzheimer's disease. *Front Neuroendocrinol*. 2014;35:385–403. doi: 10.1016/j.yfrne.2014.01.002.

67. Cooper C, Lodwick R, Walters K, Raine R, Manthorpe J, Iliffe S, et al. Observational cohort study: deprivation and access to anti-dementia drugs in the UK. *Age Ageing*. 2016;45:148–154. doi: 10.1093/ageing/afv154.

American Heart Association | American Stroke Association

Stroke
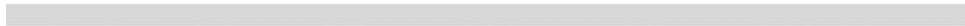
Stroke

American
Heart
Association

American
Stroke
Association®

Impact of Conventional Stroke Risk Factors on Stroke in Women: An Update
Tracy E. Madsen, Virginia J. Howard, Monik Jiménez, Kathryn M. Rexrode, Maria Czarina
Acelajado, Dawn Kleindorfer and Seemant Chaturvedi

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/early/2018/02/07/STROKEAHA.117.018418.citation