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Sex differences in stroke co-morbidities

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Abstract

Males and females possess distinct biological differences that manifest in diverse risk profiles for acute and chronic diseases. A well-documented example of this is ischemic stroke. It has been demonstrated that older females have greater prevalence of, and worse outcome after, ischemic stroke than do males and younger females. Loss of estrogen after menopause is heavily implicated as a contributing factor for this phenomenon; however, there is mounting evidence to suggest that certain risk factors tend to occur more often in older females, such as hypertension and atrial fibrillation, while others more adversely affect females than they do males, such as diabetes and smoking. Sex-specific risk factors, such as oral contraceptive use and menopause, could also contribute to the discrepancy in stroke prevalence and outcome. Additionally, there is evidence to suggest that females tend to present with more nontraditional symptoms of acute stroke than do males, making it more difficult for clinicians to correctly identify the occurrence of a stroke, which may delay the administration of thrombolytic intervention. Finally, certain sociodemographic factors, such as the fact that females were more likely to live alone prior to stroke, may contribute to poorer recovery in females. This review will explore the various co-morbidities and sociodemographic factors that contribute to the greater prevalence of and poorer outcome after stroke in older females and will highlight the critical need for considering sex as a predisposing biological variable in stroke studies.

Keywords

Sex Differences; Ischemic stroke; Hypertension; Atrial Fibrillation; Metabolic Disease; rT-PA; Thrombectomy; Nontraditional Symptoms; Opioid Addiction; Intimate Partner Violence

Introduction

Premenopausal women have a much lower risk of stroke compared to young men. However, after menopause, this trend reverses, and the incidence of stroke in older women is twice that

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of older men. This change is often attributed to the loss of ovarian hormones that accompany the transition to menopause. However, biological sex has been shown to affect many conditions that are co-morbid with ischemic stroke. Beyond this, sociodemographic differences can limit women's access to adequate healthcare, and the lack of preclinical research that uses female animal models leave clinicians uninformed about sex differences in symptom presentation and treatment efficacy. This review aims to examine sex differences in ischemic stroke beyond menopause and will highlight physiological and sociological differences that may contribute to the increased risk of and poorer outcome after ischemic stroke in older women.

Hypertension

Hypertension is a significant risk factor for ischemic stroke. Hypertension is defined as blood pressure greater than 140/90 mmHg. For younger age groups, men are more likely than women to experience hypertension, but around the age of 65, this trend reverses. In individuals in the 65–74 age range, 66% of women were affected by hypertension compared to 64% of men, and in those over 75 years of age, 81% of women were affected by hypertension compared to 73% of men¹. In a meta-analysis of studies that examined the relationship between sex, blood pressure, and cardiovascular events, women experienced a lower absolute risk, but they also demonstrated a steeper correlation between systolic blood pressure and incidence of cardiovascular events². This analysis suggests that many cardiovascular events may be preventable in women by more aggressive efforts to lower blood pressure. In the United States, women were more likely to use antihypertensive medication than were men, despite the absence of sex disparity in the prescription of medication³. Despite women being more likely to adhere to medication regimens, fewer women achieve sustained blood pressure control compared to men (45% vs. 51%)⁴. Furthermore, women were less likely than men to be prescribed aspirin or beta-blockers as a measure of secondary prevention⁵.

Studies have reported various findings concerning sex differences in the efficacy of antihypertensive medication. A study by the INDIANA investigators, a meta-analysis performed using 20,802 women and 19,975 men, reported that the effect of antihypertensive medication on all major cardiovascular events showed no significant difference between men and women, but the most prominent benefit for the treatment in women was for stroke⁶. The Blood Pressure Lowering Treatment Trialists' Collaboration analyzed the effects of a variety of antihypertensive treatments on 103,268 men and 87,349 women and reported no significant difference in effect for any of the treatments⁷. Analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack trial demonstrated that women on lisinopril, a commonly prescribed ACE inhibitor, experienced a higher stroke incidence compared to men on lisinopril during the trial⁸. The difference was not sustained post-trial, but women continued to experience higher systolic blood pressure than men⁹. There are well-established sex differences in the renin-angiotensin system (RAS), which is the primary system that regulates hypertension. Males tend to have greater expression levels and physiological responses to the activation of the classical RAS (ANG II, AT₁, ACE), while females have greater expression and physiological response to activation of the non-classical RAS (ANG (1–7), AT₂, mas receptor, ACE2)¹⁰. However, despite differences in RAS

regulation, males and females are commonly prescribed the same ACE inhibitors to reduce blood pressure¹¹. Lisinopril has similar efficacy in acutely reducing blood pressure in both sexes¹²; however, in studies that examine longer term treatment with lisinopril, men experience a larger decrease in ambulatory blood pressure compared to women¹³. Analysis of the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) demonstrated that losartan treatment reduced total mortality and resulted in fewer overall cardiovascular events and strokes compared to atenolol treatment in women with hypertension¹⁴, indicating that losartan-based treatment may be a better option for women seeking to regulate blood pressure than other hypertension medications.

Gonadal hormones likely mediate many of the sex differences observed in hypertension. Chronic infusions of ANG II cause a greater increase in blood pressure in ovariectomized wild-type female mice¹⁵ and in intact female mice treated intracerebroventricularly with ICI-182780, a non-selective estrogen receptor antagonist¹⁶. Furthermore, the replacement of 17 β -estradiol in the ovariectomized mice attenuated the increase in blood pressure. These findings demonstrate that 17 β -estradiol is critically involved in protection against ANG II-dependent hypertension. In studies done in young Rag-1^{-/-} mice, which are deficient in mature B and T lymphocytes¹⁷, females were shown to be resistant to T-cell induced hypertension, while male mice were not¹⁰. This sex difference is likely due to ANG II activation of NADPH oxidase and ROS in the subfornical organ and upregulation of cytokine production in the kidneys, which acts as a signal that attracts T-cells to traffic into these organs. The T-cell infiltration results in an escalation of the inflammatory cascade, resulting in increased hypertension. Females are resistant to this T-cell induced hypertension because 17 β -estradiol inhibits the pro-inflammatory pathway¹⁰. 17 β -estradiol-mediated nitric oxide production is implicated in many of the protective vascular effects seen in females, while chronic testosterone exposure reduces nitric oxide bioavailability¹⁸. Finally, expression of endothelin-1 (ET-1), a potent vasoconstrictor, changes in response to sex hormones—male sex hormones increase ET-1 levels, while female sex hormones reduce ET-1 levels¹⁹. In aged females, ovarian hormone expression is reduced, resulting in the loss of 17 β -estradiol-mediated protection from hypertension.

Hypertension during pregnancy is correlated with higher risk of stroke postpartum. During pregnancy, women can experience preeclampsia, eclampsia, chronic hypertension, and gestational hypertension. Preeclampsia is characterized by elevated blood pressure and signs of damage to another organ system. Women with eclampsia experience the same symptoms as women with preeclampsia as well as seizures. In pregnant women, chronic hypertension is diagnosed when blood pressure greater than 140/90 mmHg either precedes the pregnancy or begins before the 20th week of pregnancy. Gestational hypertension is characterized by high blood pressure that appears after the 20th week of pregnancy²⁰. Women in their fifties who experienced preeclampsia 9 to 16 years earlier were more likely to be diagnosed with hypertension and metabolic syndrome than women who had not experience preeclampsia²¹. An analysis by Theilen et al revealed that women who experienced hypertension during pregnancy had increased overall mortality risk, with one of the greatest risks being stroke²². Antihypertensive medication used to treat mild to moderate hypertension was demonstrated to have negligible effect on preventing the development of preeclampsia²³, indicating that

traditional treatment for hypertension is ineffective. Hypertension in pregnancy poses a unique risk of stroke for women, for which there is limited effective medical intervention.

Atrial Fibrillation

Atrial fibrillation, defined by an irregular and often extremely fast heart rate, is the most common type of arrhythmia in both sexes worldwide²⁴. While men experience a greater incidence of atrial fibrillation²⁵, women with atrial fibrillation are more likely to experience more severe symptoms²⁶, and were more associated with an increased risk of stroke²⁷. The risk of developing atrial fibrillation increases with age, and since women tend to live longer than men, there are more women with atrial fibrillation than there are men²⁸. In a Swedish study that examined 100,802 men and women with atrial fibrillation the risk of stroke in women (6.2%) with atrial fibrillation is significantly greater than the risk of stroke in men (4.2%) with atrial fibrillation per year²⁹. A Canadian study involving patients with atrial fibrillation also revealed an overall higher incidence of stroke in women compared to men, with the difference primarily being between men and women over 75 years of age, even after adjusting for comorbid conditions and warfarin treatment³⁰.

Anti-coagulation medication, such as warfarin, is fundamental to stroke prevention in patients with atrial fibrillation. However, women with atrial fibrillation are less likely to receive anti-coagulation medications compared to men (56.7% vs. 61.3%)³¹, due to the potential for excessive gynecological bleeding. This is concerning considering that female sex is correlated with a 4.6-fold greater risk of stroke³², as well as more severe strokes, a higher risk for embolism, and long-term mortality in those with atrial fibrillation³¹. Furthermore, warfarin treatment may be more effective in women with atrial fibrillation than in men with atrial fibrillation, evidenced by the fact that women experience higher risk for stroke and peripheral embolism in untreated groups yet both sexes showed similar risk in groups treated with warfarin³³. These data indicate that atrial fibrillation should be considered to be a greater risk factor for stroke in women and that women may experience augmented benefits from anticoagulation therapy. Clopidogrel, commercially known as Plavix, given with aspirin to high risk patients 24 hours post-stroke has recently been shown to reduce subsequent strokes by 2% though there is a slight increased risk (0.2%) of moderate to severe extracranial bleeding^{34,35}. These exciting new developments in anticoagulant medication will hopefully serve to prevent recurrent strokes and improve stroke treatment guidelines.

Metabolic Disease

Dyslipidemia

Dyslipidemia is characterized by increased levels of low density lipoprotein (LDL), triglycerides, or reduced levels of high density lipoprotein (HDL). This lipid dysregulation is a major risk factor for ischemic stroke, specifically, elevated levels of LDL and decreased levels of HDL³⁶. In patients with untreated dyslipidemia, men tend to have a higher risk of stroke than women. When treated with a statin, men and women experience equal risk reduction, but women benefitted less from mortality reduction than did men³⁷. More women than men with dyslipidemia were excluded from rt-PA, and this correlation was persistent

even after adjusting for age. Females that were excluded tended to be older, had a higher NIH Stroke Scale rating, and greater mean risk of mortality³⁸. These data suggest that traditional treatment for dyslipidemia is less effective in women than in men, which leaves women with more adverse lipid profiles and a greater risk for cardiovascular complications.

Diabetes

Diabetes is a major metabolic risk factor for adverse cardiac events such as stroke, and evidence suggests that the risk may be even greater in women. Diagnostic criteria for diabetes include a fasting plasma glucose level of 126mg/dL or a 2 hour plasma glucose level of 200 mg/dL or greater during a 75g oral glucose tolerance test. One meta-analysis reported that women with diabetes experience a 27% greater relative risk for stroke compared to men with diabetes³⁹. In individuals with type 2 diabetes, the chance of having a myocardial infarction or stroke is increased 2- to 3- fold with a significant difference between the sexes. The population included 7198 women and 5907 men and excluded those who had a previous stroke. The independent effect of type 2 diabetes on stroke was an increased risk of 1.5- to 2-fold in men and 1.5- to 6.5-fold in women. The sex difference was only observed in the age group 55 to 64 years⁴⁰. In a study of rural and urban communities in Japan, type 2 diabetes was associated with a 2-fold higher risk of stroke in men and a 2.5-fold higher risk of stroke in women. The observed insults were primarily lacunar strokes. The increased risk of ischemic stroke associated with diabetes was primarily seen in those without hypertension and with central obesity. These subjects tended to have higher glucose levels compared to other diabetic patients, suggesting that they had more severe diabetes⁴¹. Not only does diabetes likely increase the risk of stroke for women, diabetes is also associated with increased mortality after stroke, and evidence suggests that the relative risk for women is even greater. Diabetes is associated with a nearly 50% higher mortality rate after stroke in women compared to men⁴².

Women with type 2 diabetes may experience a more pronounced immune response to type 2 diabetes than do men. Heat shock proteins (HSPs) are proteins that respond to stress and reactive oxygen species activity, and their main purpose is to regulate cell function and maintain homeostasis⁴³. HSP70 is a well-studied heat shock protein that is strongly indicative of pro-inflammatory markers. Women with long-standing type 2 diabetes have higher serum levels of HSP70 before treatment when compared to men, indicating a greater degree of inflammation in women. Furthermore, while levels of HSP70 are reduced after glucose level-modulating treatment in men, women do not experience a decrease of HSP70 after treatment⁴⁴, indicating that their elevated degree of inflammation is not alleviated by diabetic treatment. Chronic inflammation increases risk for ischemic stroke⁴⁵, so this elevated basal inflammation in women with diabetes may augment their risk for stroke.

Obesity

Obesity affects more women than men in the United States⁴⁶. Abdominal obesity has been shown to be associated with increased risk of stroke⁴⁷. Menopause is associated with the accumulation of more visceral adipose tissue. This change in adipose tissue distribution is likely due to the changes in sex hormones that are associated with menopause⁴⁸. Women that were deficient in ovarian hormones had significantly higher lipoprotein lipase activity than

did pre-menopausal women⁴⁸. Furthermore, obesity is correlated with higher risk of developing diabetes. HbA1c (glycated hemoglobin) tests are a commonly used metric to determine blood glucose levels over 2–3 months, and a higher BMI increases the risk of developing abnormally high HbA1c levels that may lead to the development of diabetes⁴⁹. In those diagnosed with diabetes, women tend to have higher BMI compared to that of men despite similar levels of HbA1c^{50,51}, indicating that women may be experiencing a greater level of metabolic damage before they are clinically considered diabetic.

Effect of Gonadal Hormones vs. Sex Chromosomes

While gonadal hormones are often considered to be solely responsible for sex differences in neurological disease, sex chromosomes may contribute to metabolic disturbances such as dyslipidemia and obesity, resulting in increased risk of diabetes and stroke. Sex differences in lipid metabolism are likely regulated by a combination of sex chromosome differences and the effects of gonadal hormones. The evidence for regulation by gonadal hormones is demonstrated by the fact the premenopausal women usually have higher HDL levels and lower LDL levels than do men yet after menopause their lipid profiles tend to reflect that of men⁵⁴. However, genetic mutations in the Y chromosome have been shown to be associated with lipoprotein profiles in males both in humans^{55,56} and in animal models⁵⁷. The Four Core Genotypes (FCG) mouse is a unique model that possesses mutations in the sex chromosome complement to allow the role of sex chromosomes to be studied independently of gonadal hormones. In these models, the *Sry* (sex-determining region Y) gene is relocated from the Y chromosome to an autosome, which allows the generation of XX mice with either ovaries or testes and XY mice with either ovaries or testes^{52,53}. Using this model, the X chromosome has been correlated with increased HDL cholesterol levels⁵⁸ and increased body weight^{59,60}. Moreover, aged mice with two X chromosomes experience larger strokes regardless of gonadal hormone expression, which may be due to higher activation of microglia and expression of inflammatory cytokines such as IL-1 β and TNF- α in these animals⁶¹. However, in younger mice, gonadal hormones expression seems to better correlate with stroke outcome than sex chromosome composition⁶². These data indicate that the effects of both sex chromosome composition and gonadal hormones should be considered when studying sex differences especially when examining cardiovascular risk factors.

Age

Age is intimately tied to the expression of ovarian hormones and, therefore, regulation of blood pressure, distribution of adipose tissue, and other related risk factors. Hypertension has been shown to be associated with menopause, with a lower age at the onset of menopause correlating with higher systolic and diastolic blood pressure. Besides the loss of endogenous estrogen, the increase in blood pressure is thought to be due to increased stiffness of arterial walls, diminished endothelial nitric oxide production, and increased expression of angiotensin II receptors⁶³. Higher rates of obesity⁶⁴, depression, and anxiety⁶⁵ in post-menopausal women may also contribute to increased incidence of hypertension. In younger women, oral contraceptive use is associated with hypertension, and this risk increases in combination with increasing age, duration of oral contraceptive use,

tobacco use, and obesity⁶⁶. Ethinyl estradiol is more associated with increased blood pressure than newer estradiol/progesterone combination oral contraception⁶⁶. Generally, women tend to experience a longer lifespan than do men, and increased age is correlated with increased risk of ischemic stroke, leaving older women particularly vulnerable to adverse cardiovascular events.

Treatment

rt-PA Treatment

Beyond co-morbidities, which leave older women at greater risk for ischemic stroke, women are also less likely to receive thrombolytic treatment for stroke. The only FDA-approved treatment for ischemic stroke is recombinant tissue plasminogen activator (rt-PA), a drug designed to eliminate clots obstructing blood flow to the brain, which can only be administered within three to four hours of symptom onset. Due partially to the time-sensitive nature of the drug, very few (5.9%–7.0%) of patients admitted to the hospital with acute ischemic stroke receive rt-PA^{67,68}. Furthermore, a 2017 study showed that women are less likely to receive rt-PA at both primary stroke centers (6.8% vs 7.5%, $p<0.001$) and non-primary stroke centers (2.3% vs 2.8%) regardless of stroke presentation⁶⁹. This study corroborates previous evidence that suggests that women are consistently less likely to receive thrombolysis treatment even after adjusting for age, socioeconomic class, location, and hospital^{70–73}. While differences in intravenous rt-PA treatment in some studies may be explained by the fact that women tend to arrive at the hospital outside of the treatment window more often than men, more aggressive forms of thrombolytic therapy, such as intra-arterial rt-PA administration, were significantly less likely to be used for women even after adjusting for time of arrival⁷². Despite women being less likely to receive rt-PA treatment, evidence suggests that they may receive more benefit from rt-PA treatment in the acute phase of ischemic stroke, with women in placebo-treated groups exhibiting significantly worse functional outcomes than men in placebo-treated groups and women in rt-PA-treated groups exhibiting similar functional outcomes to men in rt-PA-treated groups⁷⁴.

Mechanical Thrombectomy—Females consistently demonstrate worse outcome than males after mechanical thrombectomy, a common treatment option for large vessel occlusion. In a particular study of patients with large vessel occlusion (LVO) treated with mechanical thrombectomy, females were less likely to be independent at 90 days post-stroke and had overall worse functional outcome, even when adjusting for factors such as age, stroke severity, and baseline functional status⁷⁵. This may be attributable to disparities in vessel size between men and women⁷⁶. Meta-analysis of the results of the MR CLEAN trial, a multicenter randomized-controlled trial of intra-arterial treatment (IAT) with stent thrombectomy showed that women experience poorer outcome than men after IAT⁷⁷. In men, mortality in the intervention group was lower than mortality in the control group; however, in women, mortality was higher in the intervention group than in the control group⁷⁷. In men, IAT reduced infarct size; however, in women, there was no significant difference in infarct size in response to treatment⁷⁷. Women in the intervention group also experienced more adverse outcomes than did controls, including recurrent stroke⁷⁷. This analysis demonstrates that IAT in men produce a favorable outcome after acute ischemic stroke,

while IAT in women may do more harm than good. While the results of this meta-analysis do not conclusively demonstrate that women should not receive IAT, they do highlight the necessity of including sex as a biological variable in planned future studies.

Nontraditional Symptoms

There is some evidence to support sex differences in the presentation of acute ischemic stroke. Men are more likely to report traditional stroke symptoms such as hemiparesis (men 24%, women 15%) and imbalance (men 20%, women 15%)⁷⁸, whereas women are more likely to report nontraditional stroke symptoms than men (men 43.9%, women 51.8%) with the most common nontraditional symptom reported being mental status change⁷⁹. Some studies have found significant sex differences in acute stroke presentation, with women being significantly more likely to present with coma, paralysis, aphasia, swallowing problems, urinary incontinence⁸⁰, vision problems and dysphagia⁸¹, while others demonstrate a much more modest difference. Lisabeth et al. reported that there is a trend toward women reporting more nonneurological symptoms, but prevalence of these symptoms is low in both genders. A borderline association between gender and diplopia was also reported, with women being more likely to report this symptom than men. Furthermore, women are more likely to have a later time of arrival than men (five hours after onset of symptoms compared to four hours), likely placing more women outside of the treatment window for tPA. One meta-analysis done by the Registry of the Canadian Stroke Network reported that women were more likely to present with headaches and were less likely to exhibit symptoms related to the brain stem or cerebellum⁸². Other studies report that women were less likely to be conscious upon admission at a hospital³¹, which may indicate the presence of more severe strokes or greater duration of symptoms. The presence of more nontraditional symptoms in women than in men could affect the length of time it takes to be diagnosed or to seek treatment, leading to missed treatment opportunities⁷⁹. Recognizing these nontraditional symptoms of acute stroke presentation is critical in order to make progress in women's cardiovascular health.

Sociocultural Differences

Lifestyle and Socioeconomic Status

Lifestyle differences could account for some sex differences in stroke incidence and outcome. Prior to stroke, women are more likely to live alone in their homes or in institutions³¹, likely due to the fact that women tend to have stroke at older ages and generally outlive their partners. Women are also more likely to be disabled before a stroke⁸⁰, which may put them at a disadvantage with respect to recovery. Furthermore, women are more likely to have depression pre-stroke, which has been shown to significantly affect recovery⁸³. After stroke, women were less likely to be discharged to their homes⁸⁴ and out-of-hospital death was more common among women, which may be correlated to a higher overall incidence of stroke⁸⁵. Post-stroke depression, reported to be associated with impairment in activities of daily living (ADL)^{86,87} and a 70% increased risk of all-cause mortality up to 10 years after a stroke^{83,88}, is also more commonly reported in women than in men⁸⁹. Lack of a social support system and greater levels of pre-stroke disability is likely

correlated with higher levels of depression and worse functional outcome after ischemic stroke.

Socioeconomic status also undoubtedly plays a role in stroke risk and outcomes. Socioeconomic status is a broad term that is based on a composite measure of the individuals income, education, employment and social status^{90,91}. People who are considered to be of lower socioeconomic status tend to report worse health outcomes and ischemic stroke is no exception. Lower socioeconomic status is associated with many of the major risk factors for stroke such as hypertension, diabetes, and obesity (especially among women)^{92,93}. This contrast is extremely stark in developing countries. Women in lower income countries were more likely to be affected by hypertension than women in higher income countries, and women in both lower and higher income countries were more likely to be using antihypertensive medication than men in lower and higher income countries³. Those in lower income groups tend to report increased levels of physical inactivity, diabetes, systolic blood pressure, and reported higher intake of blood-pressure lowering medications⁹⁴. In a study of older Dutch women, lower socioeconomic status was associated with increased incidence of stroke, diabetes, and obesity⁹⁵. Understanding how socioeconomic class correlates with stroke risk is critical in order to alleviate the massive health inequality experienced by those of lower status.

Opioid Addiction

In the United States, opioid abuse has dramatically risen in recent years, which has led to a significant increase in opioid-related deaths. A common method of taking opioids is intravenous injection, which can lead to infective endocarditis, an infection of the inner surface of the heart, that may result in stroke. Infective endocarditis is estimated to occur anywhere between 2–5% of those who inject drugs and is the cause of 5–20% of hospital admissions and 5–10% of the overall death rate for intravenous drug users⁹⁶. According to a study by Omran *et al.*, hospitalization for stroke correlated with infective endocarditis and opioid use rose from 2.4 to 18.8 per 10 million United States residents per year, with the majority of this increase occurring between 2008 and 2015⁹⁷. While men still account for the majority of these cases (65.8% of hospitalizations), women demonstrated the sharpest increase between 2008 and 2015 compared to any other demographic in the study besides individuals under the age of 45⁹⁷. These results emphasize the devastating neurological consequences of the opioid epidemic and indicate that stroke associated with infective endocarditis and opioid use is becoming a more salient concern for women.

Intimate Partner Violence

Intimate partner violence is a major cause for concern for women in the United States. The CDC estimates that approximately 1.5 million women experience intimate partner violence⁹⁸, and many of these instances of violence include strangulation. Strangulation involves the compression of the neck with the hands or other implements, resulting in the restriction of blood or oxygen flow to the brain. An increased number of strangulation events have been correlated with increased numbers of injuries to the neck and throat and is associated with higher incidence of neurological disorders⁹⁹. Specifically, strangulation victims can experience carotid artery dissections, which may result in a lesion forming around the

damaged area. The lesion potentially could lead to the occlusion of the artery, resulting in delayed cerebral infarction¹⁰⁰. Due to the disturbingly high incidence of intimate partner violence against women and the susceptibility of the carotid artery to injury, strangulation should be considered to be a major risk factor for stroke in women.

Conclusions

Despite the many physical and institutional disadvantages older women experience in regards to cardiovascular health, they possess one extremely significant advantage—longevity. Women live approximately five years longer than men on average. The resiliency of women in the face of these obstacles is truly astounding and warrants more investigation. It is tempting to attribute this to the protective effects of estrogen, but women in first world countries live approximately one-third of their lives in an estrogen-deficient state. These results highlight the need to better understand how current treatment options affect both sexes and provide validation for the need for more sex-based medicine. Considering sex as a biological variable is necessary to make progress in women's healthcare. Equality is not only the responsibility of legislators and activists; equality must be achieved at the benchtop and at the bedside in order to provide the best care for all people.

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Table 1:

Summary of Physiological Risk Factors for Stroke

Risk Factor	Occurs more often in	Higher Risk For Stroke in	References
Hypertension	Older women	Women	Benjamin <i>et al.</i> , Boggia <i>et al.</i> , Mills <i>et al.</i> , Gu <i>et al.</i> , Keyhani <i>et al.</i> , Gueyffier <i>et al.</i> , Turnbull <i>et al.</i> , Yamal <i>et al.</i> , Oparil <i>et al.</i> , Sandberg <i>et al.</i> , Sullivan <i>et al.</i> , Sáenz-Campos <i>et al.</i> , Falconnet <i>et al.</i> , Os <i>et al.</i> , Xue <i>et al.</i> (1&2), Blanco-Rivero <i>et al.</i> , Tostes <i>et al.</i> , Ahmad <i>et al.</i> , Bokslag <i>et al.</i> , Theilen <i>et al.</i> , Abalos <i>et al.</i> ,
Atrial Fibrillation	Men	Women	Ko <i>et al.</i> , Chugh <i>et al.</i> , Ball <i>et al.</i> , Bushnell <i>et al.</i> , Piccini <i>et al.</i> , Fribery <i>et al.</i> (1&2), Tsadok <i>et al.</i> , Glader <i>et al.</i> , Fang <i>et al.</i> , Hao <i>et al.</i> , Tan <i>et al.</i>
Dyslipidemia	Men	Men (when untreated)	Tziomalos <i>et al.</i> , Dale <i>et al.</i> , Blum <i>et al.</i>
Diabetes	Men	Women	Peters <i>et al.</i> , Almdal <i>et al.</i> , Iso <i>et al.</i> , Prospective Studies Collaboration and Asia Pacific Cohort Studies Collaboration, Asea <i>et al.</i> , Nakhjavani <i>et al.</i>
Obesity	Women	Equal Risk	Hales <i>et al.</i> , Chen <i>et al.</i> , Tchernof <i>et al.</i> , Logue <i>et al.</i> , Paul <i>et al.</i>