Burden of stroke in women

Gina Price Lundberg\textsuperscript{a,b,c,*}, and Annabelle Santos Volgman\textsuperscript{d,e}

\textsuperscript{a}Emory Women’s Heart Center
\textsuperscript{b}Emory University School of Medicine, Atlanta, GA
\textsuperscript{c}Emory Heart and Vascular Center East Cobb, 137 Johnson Ferry Road, Suite 1200, Marietta, GA 30068
\textsuperscript{d}Rush College of Medicine, Rush University Medical Center, Chicago, IL
\textsuperscript{e}Rush Heart Center for Women, Rush University Medical Center, Chicago, IL

**Abstract**

Stroke is the fifth cause of death in the United States and the first cause of disability. While reductions in stroke mortality have occurred, stroke remains a significant burden in women. In addition to traditional cardiovascular risk factors, there are specific risk factors in women that need to be addressed to further reduce deaths in women from stroke. Atrial fibrillation is common in women and needs proper evaluation for anticoagulation for risk reduction. Stroke in women remains a serious cause of preventable deaths, disability, and cost. Implementation of the new guidelines for stroke prevention in women is critical for reducing the burden of stroke in women.

**Keywords:** Stroke, Cardiovascular disease, Women, Prevention, Disability, Risk factors, Atrial fibrillation, Cost, Gender.

Introduction

Women have a higher burden of stroke than men do. Sex and gender differences have been found in the incidence and mortality of stroke. This article reviews these differences and current guidelines for the prevention of stroke in American women.

The CDC report on mortality data in 2013 revealed that the total stroke death rate dropped from the fourth leading cause of death to the fifth leading cause of death in the United States (US) [1]. Worldwide, stroke is the second leading cause of death, causing over 11% of total deaths. The recent American Heart Association (AHA) and the American Stroke Association (ASA) Statistical Update for 2015 showed that over the past ten years, the relative rate of stroke death declined about 35% and the actual number of stroke deaths declined 21% as seen in Fig. 1 [2]. But still in the US, every 40s someone has a stroke, and every 4 min someone dies from a stroke [2].

Despite the reduction in deaths from stroke, the long-term effects of stroke are still very concerning, especially for women. Table 1 shows that more women than men are dying from stroke as well as having new and recurrent strokes. Stroke is the fifth leading cause of death for men, but still the third leading cause of death for women [3]. In 2010, nearly 60% of stroke deaths occurred in women. More than half of all strokes occur in women, and there are 55,000 more stroke events in women than in men according to the AHA/ASA Statistical Update for 2015. Women tend to be an average of four years older than men at stroke onset with the age of 75 vs. 71 years [2].

Stroke is the leading cause of disability in the US as well as the leading preventable cause of disability. Over 6.5 million people are living after stroke with the majority of survivors, 3.8 million, being women [2]. Nearly half of stroke survivors have persistent residual deficits 6 months after their initial stroke, increasing the number of disabled women to 200,000.
more than men [4]. Because women are more likely to be living alone and widowed before a stroke, women are more often institutionalized after a stroke. Unfortunately, women tend to have worse recovery after a stroke as compared to men [5].

The AHA/ASA published the first ever Stroke Prevention Guidelines for Women in 2014 [6]. Similar guidelines for the prevention of heart disease in women were published 10 years earlier [7]. Guidelines specific to women are important since they address unique differences in women such as genetics, hormonal and reproductive factors, immunity, and coagulation factors. It is critically important to identify women at higher risk for stroke so proper preventive measures can be implemented.

### Awareness of stroke in women

Differences exist between genders with regard to awareness of stroke [8]. Although women are more aware of the signs and symptoms of stroke, they have a longer delay in getting to the hospital. In general, women have poor overall knowledge about CVD and stroke. The American Stroke Association has a campaign to promote awareness of stroke, especially in women, using the acronym FAST—face drooping, arm weakness, speech difficulty, and time to call 911.

A recent questionnaire survey of over 1000 women revealed that reproductive-aged women prefer to see their Obstetrician-Gynecologist annually for primary care [9]. Cardiovascular disease awareness is low among this patient population, and especially among young, nonwhite women. In addition, Obstetrician-Gynecologists do not appear to be providing education aimed at the prevention of CVD.

Similarly, another questionnaire survey showed that the rate of awareness of heart disease as the leading cause of death was lower among younger women (25–34 years of age) [10]. The younger women were also more likely than their older counterparts to state that their doctor did not discuss their heart disease risk. This may represent a missed opportunity, especially because women in the child-bearing years may present with novel risk factors for CVD (i.e., preeclampsia and gestational diabetes) that can identify at-risk women earlier in their life course when lifestyle and other preventive efforts may be implemented.

### Risk factors for stroke

The Prevention of Stroke Guidelines for Women focuses on risk factors unique to women. The risk factors common to

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**Table 1 – AHA/ASA Statistics Update 2015: gender-specific stroke statistics.**

<table>
<thead>
<tr>
<th>Gender group</th>
<th>Mortality, 2011: all ages</th>
<th>Prevalence, 2012: age ≥ 20 y</th>
<th>New and recurrent attacks, all ages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>76,597 (59.4%)*</td>
<td>3,600,000 (2.7%)</td>
<td>425,000 (53.5%)*</td>
</tr>
<tr>
<td>Males</td>
<td>52,335 (40.6%)*</td>
<td>3,000,000 (2.6%)</td>
<td>370,000 (46.5%)*</td>
</tr>
<tr>
<td>Total</td>
<td>128,932</td>
<td>6,600,000 (2.6%)</td>
<td>795,000</td>
</tr>
</tbody>
</table>

* These percentages represent the portion of total stroke incidence or mortality that applies to males vs. females.
both men and women are addressed in the Guidelines for the Primary Prevention of Stroke published in December 2014 [11]. Stroke risk factors that are specific to younger women are oral contraceptive use, pregnancy, preeclampsia, and gestational diabetes. Older women are affected by changes in hormonal status and in postmenopausal hormone use. Stroke risk factors that are more commonly seen in women are migraine headaches with aura, atrial fibrillation (AF), diabetes mellitus (DM), and hypertension (HTN). The risk factors for stroke that are common in both sexes are previous CVD, smoking, metabolic syndrome (MetS), age, physical inactivity, poor diet, and obesity. Table 2 highlights these risk factors for stroke.

Hypertension is the most common modifiable risk factor for stroke in both men and women. Overall, 77% of people who have a first stroke have blood pressure 140/90 mmHg or greater. The Women’s Health Initiative (WHI) showed that older women with high normal blood pressure (prehypertension) had a 93% increased risk of stroke compared to normotensive women [12]. A recent meta-analysis of large randomized controlled studies showed treatment of HTN in women aged 55 years or older has a 38% lower risk of fatal and nonfatal strokes [13].

Hypertension in pregnancy increases the risk for preeclampsia, eclampsia, and stroke during pregnancy. Fortunately, stroke is uncommon during pregnancy. There are 34 strokes per 100,000 deliveries [14]. Risk for stroke is higher in pregnant women than in age-matched non-pregnant women with the highest risk of stroke in the third trimester and postpartum. An increased risk of hypertension and stroke occurs in women with a history of preeclampsia for up to 30 years after delivery [15]. Therefore, it is essential that these women be followed long term for hypertension and other modifiable cardiovascular risks. Long-term health risks also include renal disease, DM, and CVD.

Migraine headache with aura has a prevalence of 4.4% and has a 2.5% increase in ischemic stroke risk [16]. This risk is higher in women who also take oral contraceptives. Increased frequency of migraine headache with aura is associated with increased risk of stroke. Women under the age of 55 years with migraine headache with aura have an increased risk of both ischemic stroke (IS) and intracerebral hemorrhage (ICH) [17]. Migraine and stroke has been associated for more than 40 years, but the pathobiology of this association has only recently been studied. The various mechanisms include vasospasm, endothelial injury, platelet aggregation and prothrombotic states, cortical spreading depression, carotid dissection, genetic variants, and traditional vascular risk factors [18].

Obesity is strongly related to stroke risk. Both body mass index (BMI) and waist circumference increase risk for stroke. By 2030, it is estimated that 86% of Americans will be overweight or obese (BMI ≥ 25 kg/m²) [19]. Abdominal obesity is common in postmenopausal women and associated with insulin resistance. Further, women with metabolic syndrome (MetS) are much more likely to have stroke [20]. MetS affects one-third of the American population [21]. MetS is three of the following constellation of risk factors: abdominal obesity, dyslipidemia (elevated triglycerides and/or low levels of high-density lipoprotein cholesterol), HTN, and insulin resistance/impaired fasting glucose. Lifestyle changes such as a healthy diet with caloric restriction and regular physical activity are essential for managing the risk factors associated with MetS.

Oral contraceptives (OC) are associated with strokes with the incidence 1.4–2.0 times higher in OC users compared to non-OC users [22]. The risk of stroke associated with OC use is lower than the risk associated with pregnancy [14]. However, stroke risk increases with age, smoking, obesity, HTN, diabetes, and other prothrombotic factors. Future research will determine the safety of low-dose OC, transdermal and vaginal rings in women who may be at risk for stroke based on age, lifestyle habits, ethnicity, and race.

Geography can also be considered a risk factor for stroke. The Southeast US is known as the “Stroke Belt.” The overall stroke risk is this area is approximately 20% higher than the remainder of the US [23]. The REGARDS study (Reasons for Geographic and Racial differences in Stroke) evaluated differences in HTN awareness, treatment, and control between the Stroke Belt and other regions of the US [24]. They found similar treatment and control rates between the two regions. There may be many other things that explain the geographic differences in the Stroke Belt, including lifestyle, cultural, dietary, and genetic differences. However, this difference is not due to hypertension management.

According to the 2015 AHA Heart Disease and Stroke Statistics, there are racial differences for stroke prevalence between white and black females. The prevalence for stroke in 2012 was 2.5% for white females and 4.7% for black females [2]. Black women have higher mortality rates from stroke in every age category compared to non-Hispanic white, American Indian, Asian, and Hispanic women. Interestingly,

### Table 2 – Gender differences in stroke risk factors.

<table>
<thead>
<tr>
<th>Risk factors specific to women</th>
<th>Risk factors that are stronger or more prevalent in women</th>
<th>Risk Factors with similar prevalence in men and women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes in hormonal status</td>
<td>Atrial fibrillation</td>
<td>Age</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>Depression</td>
<td>Diet</td>
</tr>
<tr>
<td>Oral contraceptive use</td>
<td>Diabetes mellitus</td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>Postmenopausal hormone use</td>
<td>Hypertension</td>
<td>Obesity</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>Migraine with aura</td>
<td>Physical inactivity</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Psychosocial stress</td>
<td>Prior cardiovascular disease</td>
</tr>
</tbody>
</table>

...continue
REGARDS found that blacks with HTN were more likely to be aware of HTN and more frequently received treatment for HTN compared to whites. However, whites had better HTN control compared to blacks. Black women and other minorities have lower overall knowledge about CVD and stroke according to surveys conducted by the AHA [25]. While deaths from cardiovascular disease (CVD) in general continue to decline in the US, stroke prevalence has actually increased for older adults, blacks, lower education groups and those living in the Southeastern US [2].

**Atrial fibrillation and stroke risk in women**

Epidemiologic data show that there are an estimated 2.2 million people in the United States with atrial fibrillation (AF) [26]. The median age was about 75 years. Although men have a higher prevalence of AF, the absolute number of women and men with AF is about equal. Women over the age of 75 years comprise 60% of the people with AF [26].

Framingham Heart Study found that AF was associated with a 1.5–1.9-fold mortality risk after adjustment for the preexisting CVD with which AF was related. Although this risk of mortality did not significantly vary by age, there was a significant interaction with AF and gender such that female advantage of longevity disappeared [27].

Strokes from AF cause the most severe disability than other causes of strokes [28]. Women with AF have been found to have a higher risk of stroke compared to men with AF [29,30]. In 1998, it was reported that stroke rates in patients with CVD were approximately 25% higher in women with AF ($P < 0.05$) but only 10% higher in men compared to those without CVD. Despite this, it was found that the adjusted total Medicare spending in 1 year was 8.6–22.6-fold greater in men, and 9.8–11.2-fold greater in women with AF ($P < 0.05$) [31].

Between 1992 and 2007, a continued, steady decline in ischemic stroke rates was seen in patients with AF with the increase use of warfarin (26.7% in 1992; 63.1% in 2007) as depicted in Fig. 2. However, there continues to be underuse of anticoagulation in appropriate patients with AF [32]. Most studies showed that $<70\%$ anticoagulation use in patients who met the criteria for anticoagulation using the CHADS2 score, a risk score for stroke for patients with AF that includes heart failure, age, history of HTN, diabetes mellitus, and prior stroke.

A review of 2004–2005 Medicare data of 119,764 patients with non-valvular AF showed that 41.5% of the patients did not receive anticoagulation. Ischemic stroke incidence was 27% lower in patients on warfarin than in patients not on warfarin ($P < 0.0001$) after multivariate adjustment. There was no increase in hemorrhagic stroke but a slightly elevated risk of a major bleed. Warfarin use was independently associated with lower total cost with an average cost saving of $9836 per patient per year [33].

A review of the Atrial Fibrillation Follow-up in Rhythm Management (AFFIRM) data showed that women had a higher risk of stroke than men did even when they were anticoagulated with warfarin. Women spent more time outside or below the therapeutic range. However, even in women who had good anticoagulation control, defined as high time in therapeutic range ($\geq 66\%$), still had more ischemic strokes compared to men ($P = 0.009$) [28].

Novel anticoagulants were approved for stroke prevention in non-valvular AF starting in November 2010. A meta-analysis evaluating gender differences in residual risk of strokes and major bleeding in patients treated with warfarin or a novel anticoagulant was recently published. Compared to men, women with AF taking warfarin had a significantly greater residual risk of stroke and systemic embolism compared with men (odds ratio = 1.279, 95% confidence interval: 1.111–1.473, $Z = -3.428$, $P = 0.001$). However the gender

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**Fig. 2** Decreasing stroke rate with increasing warfarin use.
difference was not seen in patients receiving novel anticoagulant agents (odds ratio = 1.146, 95% confidence interval: 0.97–1.354, P = 0.109). The disadvantage of women with AF compared to men disappeared with the use of novel anticoagulants [34].

Not only was decreased ischemic strokes seen with the novel anticoagulants such as dabigatran [35] and apixaban [36], intracranial hemorrhage was also decreased with the use of dabigatran, rivaroxaban [37], and apixaban compared to warfarin. Mortality benefit was also found in both genders with the use of apixaban [34].

Recent guidelines reflect the higher risk of stroke burden in women and older patients with AF by recommending assessment of a patient’s risk of stroke by using the CHA2DS2-VASC instead of the CHADS2 scoring algorithm. Female sex was considered an independent risk factor for stroke in atrial fibrillation. The presence of atherosclerosis and younger age of ≥65 were added as risk factors. The new guidelines recommend that for patients with non-valvular AF with prior stroke, transient ischemic attack, or a CHA2DS2-VASC score of 2 or greater, oral anticoagulants should be considered. Oral anticoagulants were warfarin (INR 2.0–3.0), dabigatran, rivaroxaban, or apixaban. In addition, if the patient is unable to maintain a therapeutic INR level with warfarin, a direct thrombin or factor Xa inhibitor (dabigatran, rivaroxaban, or apixaban) is recommended [38].

Types of strokes

Ischemic stroke is more common in women after the age of 65 years. Overall, 87% of all strokes are IS and 10% are ICH. Nearly 3% of all strokes are subarachnoid hemorrhages (SAH) [2]. Women have higher rates of SAH than men do, especially after the age of 55 years. Central venous thrombosis (CVT) is the rarest type of stroke accounting for less than 1% of all strokes. It is more common in women and has a lower overall mortality and better functional outcome than other types of stroke. Headache is the primary manifestation of CVT and is due to thrombus formation in the cerebral venous sinuses. CVT is associated with increased clotting abnormalities, which include hormones, contraceptives, and pregnancy. Guidelines for the diagnosis and management of CVT were published by the ASA/AHA in 2011 [39].

Treatments for stroke

Acute management of stroke is limited by time of presentation. Presenting to the emergency department (ED) as soon as possible after stroke onset is critical for proper evaluation and treatment. The treatment window for acute reperfusion therapy has been prolonged from the original 3-h time limit to the new recommended 4.5-h limit after symptom onset [40]. The AHA/ASA has set a goal for the ED arrival to treatment time of 1 h. Most Stroke Centers have protocols to determine IS from ICH or SAH. Patients with hemorrhagic strokes or with high risk of bleeding must not receive thrombolytic therapy. Unfortunately, tissue plasminogen activator (tPA) is only given to about 7% of patients due to delayed presentation [41]. Women are less likely than men to be aware of the (previous 3 h) time limit from stroke onset to hospital presentation to receive tPA treatment [42].

Medical therapy should be aimed at controlling hypertension, diabetes, renal dysfunction, and even fever during acute stroke. However, particular of aspirin, antiplatelet therapy, and even hypertension control vary by studies and institutions. General medical care is aimed at not only treating acute stroke but also at preventing complications, improving outcomes, and preventing recurrent strokes. In 2013, the AHA/ASA published guidelines for the management of acute ischemic stroke and should be referred to for further medical treatment recommendations [43].

Poststroke

An estimated 6.6 million people in the US over the age of 20 years have had a stroke according to the AHA/ASA Statistical Update for 2015. Projections for 2030 indicate that stroke prevalence will increase by 20.5% from 2012. This increase is predicted to be especially significant among elderly women due to an increase in the aging population in general.

Post-stroke disability was evaluated in 892 stroke survivors, 57% of which were women [44]. Stroke survivors were compared to both age-matched and sociodemographic non-stroke controls. Not surprising, compared to controls, stroke survivors were much more likely to have someone perform household duties and need assistance with showering and bathing and dressing. They also had lower cognitive capacity, poor performance on word recall, and more aphasia/dysarthria. Of interest, stroke survivors were 40% more likely to have restricted participation in activities they valued, 84% more likely to restrict visiting with family and friends, 32% more likely to restricted attendance at religious services, and 59% less likely to participate in enjoyable events. These participation restrictions add to isolation and disability in ways that have not previously been appreciated.

Cost/economic impact

According to the 2015 Statistical Update from AHA/ASA, the total direct and indirect cost of stroke in 2011 was $33 billion. Indirect costs account for $16 billion and are attributed to lost productivity and mortality costs. Direct cost including hospital inpatient, hospital emergency department visits, home care, and medications, account for $17.5 billion. Direct health expenditures for stroke is low compared to other leading diagnoses such as heart disease and cancer. However, the total dollars for health care costs for CVD show stroke is more costly than congestive heart failure (CHF) but half as costly as coronary heart disease (CHD).

A recent study from Australia looked at cost for ten years after stroke [45]. Based on their data, which was reported in US dollars, they estimated the lifetime cost of care at over $68,000 for a patient after an IS and nearly $55,000 for a patient after ICH. These costs are likely to be much higher in the US for multiple reasons. The AHA/ASA 2015 Statistical Update reports total direct medical stroke-related costs are
projected to triple from 2012 to 2030 to an estimated cost of over $184 billion. Fig. 3 shows that stroke costs remain on a slow rise for adults 18–64 years of age but are skyrocketing for adults 65–79 years of age and adults over 80 years of age.

**Improved outcomes/preventable deaths**

Stroke rates and stroke mortality rates have dropped from 1988 to 2008 in Medicare patients over the age of 65 years. Both IS and ICH strokes rates dropped during this time period. Incident strokes in this population dropped 40% in the last two decades [46]. Over the past 10 years, the death rate from stroke has dropped 35% and stroke death rate has dropped 21%. Despite this promising drop, the number of people living after stroke went up with over 85 million Americans living with after stroke or with some form of CVD.

Treatment of stroke with tPA has only contributed a small amount to the drop in stroke mortality. Only 7–15% of patients receive tPA due to the three-hour duration from onset to presentation restriction. The number of approved Stroke Centers has risen across the country to over 1000, but the number of patients presenting in this time window has not increased. The drop in stroke mortality is most likely from prevention strategies and increased use of antihypertensive medications and statins. Since aspirin is over the counter, the contribution for aspirin use is harder to document.

Stroke incidence has decreased in women who follow healthy lifestyle behaviors [47]. Recommendations include a healthy diet, such as Mediterranean or DASH (Dietary Approaches to Stop Hypertension); weight control to a BMI < 25 kg/m²; physical activity most days of the week; abstinence from smoking; and moderate alcohol consumption.

**Summary**

Stroke in women remains a serious cause of preventable deaths, disability, and cost. While there is good news for mortality reduction in the US from CVD and stroke, intentional efforts are needed to reduce stroke in women. Women need education on gender-specific risk and attention from primary care providers, especially obstetricians/gynecologists, to improve awareness and reduce morbidity and mortality. All physicians and providers who care for women should follow the new 2014 Prevention of Stroke Guidelines in Women.

Atrial fibrillation remains undertreated in women, and anticoagulation needs to be implemented in all appropriate women. The incorporation of female sex as an additional risk factor in the CHA2DS2-VASC score may help decrease strokes in women with AF. As clinicians become more familiar with the ease of use and more comfortable with the risks and benefits of novel anticoagulants, we may see improved stroke and mortality outcomes in women as well as men with AF.

We recommend a comprehensive approach to women’s cardiovascular health addressing all the risk factors that are specific to women. We need to be deliberate in addressing stroke risk as part of the overall CVD risk reduction plan in women. Specifically, these include the following: (1) careful follow-up of pregnancy-related HTN, (2) increased attention to pre-hypertensive women to reduce their blood pressure through lifestyle changes, (3) emphasize the importance of a healthy weight, and (4) more intensive efforts to educate and increase awareness about stroke prevention, especially in the geographic regions with the highest incidence of strokes. We hope recent announcements by the AHA to allocate $15 million to study CVD in women may help not only decrease heart disease but also significantly decrease strokes in women.

**References**


