

# An Overview of Stroke and the Impact of Atrial Fibrillation

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Stroke is a very significant but preventable health problem that is estimated to account for 45.1 deaths in every 100,000 people in the United States.<sup>1</sup> According to the most recent statistical update from the American Heart Association (AHA), approximately 795,000 people in the United States experience a new or recurrent stroke each year, and 87% of these are ischemic in nature.<sup>2</sup> Additionally, about 610,000 of these strokes are first events, while the remaining 185,000 are recurrent attacks. The overall burden of stroke is quite large in terms of life-years lost and diminished quality of life, as well as the direct and indirect medical costs associated with providing care for stroke victims.<sup>2</sup> Despite considerable evidence that supports preventative measures to improve outcomes among patients at risk of stroke, many of these patients do not receive the recommended interventions. Stroke prevention can be significantly improved through greater, more effectively targeted implementation of proven risk reduction measures.

## Preventive Measures Have a Positive Effect

A recent analysis from the Centers for Disease Control and Prevention using data from 2007 shows that, despite a continuing, long-term downward trend among the top 3 causes of death in the United States, stroke continues to rank third, trailing behind only heart disease and cancer.<sup>3</sup> This downward trend is evident in an encouraging report on the recent progress toward meeting the 2010 Impact Goals for reduction of stroke, coronary heart disease (CHD), and cardiovascular risk.<sup>4</sup> As set forth in 2000, the stated 2010 Impact Goals were to achieve: (1) a 25% reduction in deaths due to stroke and CHD, and (2) a 25% reduction in risk factors, including the prevalence of smoking, uncontrolled hypertension, high blood cholesterol, and physical inactivity. The 2010 Impact Goals also included the ambitious target of zero growth in obesity and diabetes by 2010. By 2008, the estimated reductions included a 29.2% decrease in deaths due to stroke and a 30.7% decrease in deaths due to CHD. Similarly, reductions in risk factors included a 29.4% decrease in uncontrolled hypertension, a 24.5% decrease in high blood cholesterol, and a 15.8% decrease in smoking. Unfortunately, the reported prevalence of obesity and diabetes in 2008 increased rather than meeting the stated goal of zero growth.

## Abstract

As the third-leading cause of death in the United States, stroke has a very significant impact on patients and the total healthcare burden. Many factors that increase the risk of stroke are modifiable, and changes in these factors can provide effective avenues toward significantly reducing the incidence of stroke. Atrial fibrillation (AF) is one such risk factor; it is strongly associated with an elevation of stroke risk that can be greatly diminished using antithrombotic therapy. However, currently recommended prevention measures, particularly oral vitamin K antagonists, are underused due to difficulties associated with their use. There is an evident need for oral anticoagulant drugs with a wide therapeutic range, which do not require international normalized ratio monitoring and have a safe bleeding profile. By targeting patients with AF for stroke prevention treatment through greater use of long-term anticoagulation therapy, the burden of stroke can be substantially reduced.

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For author information and disclosures, see end of text.

### Stroke Prevention Can Be Improved

On the heels of this recent progress, the AHA established a new set of Impact Goals for 2020, which have been broadened to address morbidity and mortality due to all manifestations of stroke and cardiovascular disease (CVD).<sup>4</sup> Current efforts are aimed at improving the cardiovascular health of all Americans by 20%, while achieving a 20% reduction in deaths from CVD and stroke by 2020. The AHA notes that reaching this ambitious goal will depend on improved acute care processes and therapies, as well as greater efforts toward advocating, promoting, and implementing population-level programs to reduce nonfatal and fatal CVD and stroke. With respect to the latter statement, there are some populations that should receive more emphasis in such programs; characteristics like sex, age, and race should be considered, as well as cardiovascular risk factors like hypertension, hypercholesterolemia, and atrial fibrillation (AF).<sup>2</sup>

### Attention to Gender Differences May Be an Important Avenue Toward Improving Stroke Prevention

Data derived from the Framingham Heart Study cohort demonstrate some important characteristics regarding the impact of age and sex on stroke incidence (Figure 1).<sup>5</sup> At the first occurrence of a stroke, women were significantly older than men (average age, 75.1 years vs 71.1 years, respectively;  $P < .001$ ). Furthermore, stroke incidence was higher in women than men older than 85 years of age, but lower in women of all other age groups. Overall, women had a higher lifetime risk of stroke than men. One very interesting observation from the Framingham cohort was that women who reached menopause before the age of 42 years had twice the stroke risk of all other women across different age groups.<sup>6</sup> No differences in stroke subtype, stroke severity, or case fatality rates were observed between sexes.<sup>5</sup>

Differences between sexes were also observed following a stroke. Three to 6 months after a stroke, women reported significantly greater disability ( $P < .01$ ) and were 3.5 times more likely to be institutionalized ( $P < .01$ ).<sup>5</sup> An examination of specific activities of daily living revealed disparities in impairment among women and men: being able to dress themselves (59% vs 37%, respectively), grooming (57% vs 34%), and moving from the bed to a chair (59% vs 35%).

In addition to disabilities, sex-related differences have been observed in stroke mortality. In 2006, the overall rate of death due to stroke was 43.6 per 100,000 people; however, examination of specific populations showed that death rates due to stroke were 41.7 for white males, 67.1 for black

males, 41.1 for white females, and 57.0 for black females.<sup>2</sup> In contrast, death rates due to stroke among other races were 35.9 for Hispanic or Latino males and 32.3 for females, 39.8 for Asian or Pacific Islander males and 34.9 for females, and 25.8 for American Indian/Alaska native males and 30.9 for females. These data suggest that racial background and sex should be considered in the development of more targeted stroke prevention strategies.

### Racial Disparities in the Risk of Stroke and Mortality Should Have a Role in Improved Prevention Strategies

The risk of a first stroke in black patients is almost twice that of white patients<sup>2</sup>; however, compared with other stroke risk factors (eg, hypertension or type 2 diabetes), AF is not likely to have an important role in this disparity of risk, given that it has a lower prevalence in black patients compared with white patients.<sup>7</sup> AF is consistently found more often in white patients than in black patients across all age groups in those older than 50 years of age. The Anticoagulation and Risk factors In Atrial fibrillation (ATRIA) study found rates of 1.8% white versus 1.3% black ( $P = .001$ ) among patients aged 60 to 69 years; 5.2% white versus 4.4% black ( $P = .003$ ) for patients aged 70 to 79 years; and 9.9% white versus 7.7% black ( $P = .001$ ) for patients 80 years and older. Overall, black patients appeared to be less likely than white patients to have AF, but those black patients who do have AF are likely to have a higher risk of stroke, given the higher rate of hypertension among blacks.<sup>8</sup> The risk of a first stroke is also elevated in Hispanics relative to whites.<sup>2</sup> In a comparison of racial backgrounds using pooled data from multiple studies by the National Heart, Lung, and Blood Institute, the age-adjusted incidence of a first ischemic stroke per 100,000 people was 88 in white patients, 191 in black patients, and 149 in Hispanic patients. This racial disparity in stroke incidence has not changed over time, and community socioeconomic status appears to explain 39% of the excess stroke risk in black patients. Racial differences have also been documented in stroke recurrence. In people aged 40 to 69 years, 5-year stroke recurrence was reported in 15% of white men and 17% of white women compared with 10% of black men and 27% of black women. Further examination of older patients (aged  $\geq 70$  years) found stroke recurrence in 23% of white men and 27% of white women compared with 16% of black men and 32% of black women. Therefore, age, sex, and race should alert clinicians to particular patients who have a greater need for evaluation of risk of first stroke or recurrent stroke, and may require prophylactic measures.

### AF Is a Powerful but Modifiable Risk Factor for Stroke

As demonstrated in **Figure 2**, data from the Framingham Heart Study cohort point to AF as a significant factor in determining the risk of stroke.<sup>9</sup> AF increases the risk of stroke, independent of other cardiovascular abnormalities that are often associated with elevated risk of stroke.

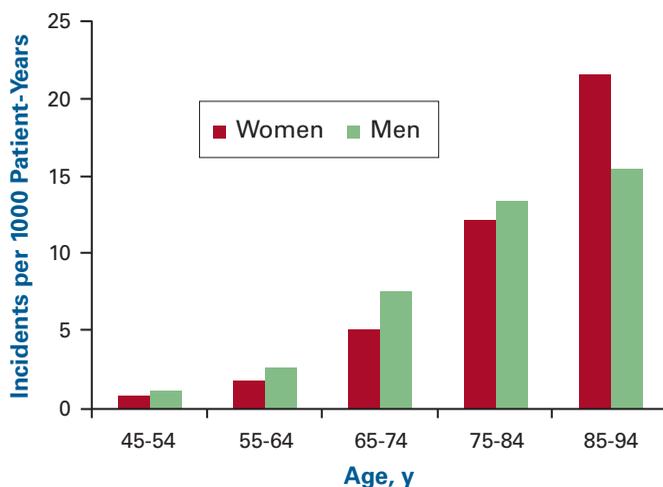
Across all age groups, AF independently increases risk of stroke by approximately 5-fold. AF is responsible for 15% to 20% of all strokes, and it is projected that AF will affect up to 12 million Americans by 2050.<sup>10</sup> The risk of stroke in AF increases with age. In people older than 80 years of age, AF is the direct cause of 1 in every 4 strokes.<sup>11</sup> Recurrent strokes are common among AF patients and recurrent strokes are often more severe than the first occurrence.<sup>12</sup> Greater stroke severity predicts longer hospital stays, a higher degree of disability, and admission to nursing homes. The cost of care for severe strokes can run twice as high as that associated with mild strokes. Therefore, targeted prevention of stroke due to AF could significantly lower the total economic burden of healthcare in the United States.

The mortality rate from AF, either as the primary or underlying cause of death, has increased over the past 20 years.<sup>10,13</sup> In addition to advancing age, risk factors for AF include high blood pressure, heart failure, diabetes, hyperthyroidism, and heart disease.<sup>10</sup> In a community-based study, AF was diagnosed in 18% of patients who were undergoing treatment for acute stroke.<sup>14</sup> In this population, AF increased sharply with age: from 2% in patients less than 50 years old, to 15% in patients who were in their 70s, to 28% in those in their 80s, and up to 40% in patients at least 90 years of age. Compared with those without AF, patients with AF had a higher mortality rate (odds ratio, 1.7; 95% confidence interval [CI], 1.2-2.5). Among stroke survivors, the average hospital stay for patients with AF was 50 days, compared with 40 days for patients without AF ( $P < .001$ ). Patients with AF in this study population also had worse neurological and functional outcomes.

### How Does AF Affect the Risk of Stroke?

AF is commonly encountered in daily practice. It is characterized by rapid, irregular impulses, and no regular contraction of the atria. The left atrial appendage is particularly affected in many patients with AF. However, the mechanism underlying thrombogenesis in AF is multifactorial and is not only related to abnormalities in flow stasis in the poorly contracting left atrium.<sup>15</sup> There is also evidence for abnormal

■ **Figure 1.** Stroke Incidence by Gender and Age (in 10-Year Intervals) Over 56 Years of Follow-Up<sup>5</sup>



Adapted from Petrea RE, Beiser AS, Seshadri S, Kelly-Hayes M, Kase CS, Wolf PA. *Stroke*. 2009;40:1032-1037.

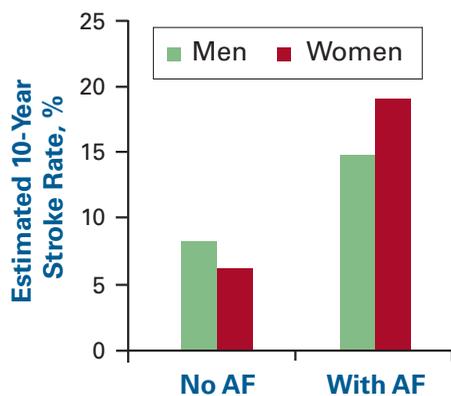
changes in vessel walls, such as endothelial damage and dysfunction, as well as abnormalities in blood constituents leading to coagulation cascade activation, inflammation, and growth factor changes. Some patients with AF experience palpitations, sensing the irregularity of the heart rhythm, but they may also experience shortness of breath, dizziness, or fatigue. Other patients may experience no symptoms.

More recently, the REduction of Atherothrombosis for Continued Health (REACH) Registry has followed stroke incidence in a cohort of patients who either had or did not have AF, but who also had established atherothrombosis or  $\geq 3$  atherothrombotic risk factors.<sup>16</sup> Among the patients with AF, 6.7% experienced cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke within a year. The annual incidence of nonfatal stroke was higher in AF than in non-AF patients, with rates of 2.4% and 1.6%, respectively ( $P < .0001$ ). After adjustment for age, sex, smoking, diabetes, hypertension, and hypercholesterolemia, the presence of AF at baseline was associated with higher rates of adverse cardiovascular outcomes (combined cardiovascular death/MI/stroke) at a 1-year follow-up. Mortality rates were substantially higher in patients with AF. All-cause mortality was 4.3% in AF and 2.3% in non-AF subjects, while cardiovascular mortality was 3.2% in AF and 1.4% in non-AF subjects ( $P < .0001$ ).

### Equivalent Influences of Paroxysmal and Permanent AF on Stroke Risk

A comparison of patients having either paroxysmal

**Figure 2.** Estimated 10-Year Stroke Risk Increases Substantially With Atrial Fibrillation<sup>9</sup>



Risk was estimated for a 55-year-old adult who smokes, has diabetes, and has a blood pressure measurement between 138 and 148 mm Hg. Adapted from Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. *Stroke*. 1991;22:312-318.

(n = 855) or permanent (n = 1126) AF recently tracked the incidence of stroke over 3.6 years and found a similar frequency of ischemic stroke associated with each group of patients with AF, specifically 26 events/1000 patient-years for paroxysmal AF versus 29 events/1000 patient-years for permanent AF.<sup>17</sup> The multivariable-adjusted hazard ratio for risk of ischemic stroke in paroxysmal versus permanent AF was 1.07 (95% CI, 0.71-1.61). These findings are similar to those of a previous meta-analysis that examined 5 randomized studies of stroke prevention in patients with AF.<sup>18</sup> Of the 3706 patients in that analysis, 462 had paroxysmal AF at the time of randomization, and the analysis showed no discernible effect on the stroke rate by the type of AF, either constant or paroxysmal, or the length of time the patient was in AF, supporting the findings of previous studies. Some drawbacks associated with this analysis include the fact that the number of patients with paroxysmal AF who subsequently reverted to constant AF was not known, and the definition of paroxysmal AF was changed in the Stroke Prevention in Atrial Fibrillation (SPAF) study from documented normal sinus rhythm within 12 months to documented normal sinus rhythm within 2 months. Despite the uncertainty in the underlying evidence, it seems reasonable to treat patients with paroxysmal AF in a manner similar to those with persistent AF, basing use of anticoagulants on the presence of risk factors for stroke. However, this approach is not being taken as

demonstrated in the recent study by Friberg et al, which observed that patients with paroxysmal AF did not receive protective anticoagulant treatment as often as patients with permanent AF.<sup>17</sup> This observation represents another important area for improving implementation of stroke prevention measures.

Since AF is associated with a higher risk of stroke, it seems a reasonable prediction that restoring normal sinus rhythm should diminish the risk of stroke; however, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial compared rate- versus rhythm-control strategies in patients with persistent or paroxysmal AF and found no difference in mortality or stroke rate.<sup>19</sup> Long-term oral anticoagulation therefore seems appropriate for most patients with AF who have risk factors for thromboembolism, regardless of treatment strategy and whether AF is documented at any given time.<sup>20</sup>

### Conclusion

AF is a modifiable risk factor for stroke. Appropriate prophylactic measures can substantially reduce the incidence or recurrence of stroke. The AHA recommends aggressive treatment of AF, which includes reducing stroke risk with anticoagulant and antiplatelet medications. Stroke risk is further reduced by controlling hypertension and diabetes and treating patients with statins to reduce levels of low-density lipoprotein cholesterol.<sup>21,22</sup> Many patients with AF are not currently receiving stroke prophylaxis. Implementation of guideline recommendations, in conjunction with concomitant improvements in other modifiable risk factors, can have a major impact on reaching the goal of improving the cardiovascular health of all Americans by 20% in 2020, while achieving a 20% reduction in deaths from CVD and stroke.

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**Authorship Information:** Concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; and supervision.

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