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## Original Contributions

# Atrial Fibrillation as an Independent Risk Factor for Stroke: The Framingham Study

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The impact of nonrheumatic atrial fibrillation, hypertension, coronary heart disease, and cardiac failure on stroke incidence was examined in 5,070 participants in the Framingham Study after 34 years of follow-up. Compared with subjects free of these conditions, the age-adjusted incidence of stroke was more than doubled in the presence of coronary heart disease ( $p < 0.001$ ) and more than trebled in the presence of hypertension ( $p < 0.001$ ). There was a more than fourfold excess of stroke in subjects with cardiac failure ( $p < 0.001$ ) and a near fivefold excess when atrial fibrillation was present ( $p < 0.001$ ). In persons with coronary heart disease or cardiac failure, atrial fibrillation doubled the stroke risk in men and trebled the risk in women. With increasing age the effects of hypertension, coronary heart disease, and cardiac failure on the risk of stroke became progressively weaker ( $p < 0.05$ ). Advancing age, however, did not reduce the significant impact of atrial fibrillation. For persons aged 80–89 years, atrial fibrillation was the sole cardiovascular condition to exert an independent effect on stroke incidence ( $p < 0.001$ ). The attributable risk of stroke for all cardiovascular contributors decreased with age except for atrial fibrillation, for which the attributable risk increased significantly ( $p < 0.01$ ), rising from 1.5% for those aged 50–59 years to 23.5% for those aged 80–89 years. While these findings highlight the impact of each cardiovascular condition on the risk of stroke, the data suggest that the elderly are particularly vulnerable to stroke when atrial fibrillation is present. The powerful independent effect of atrial fibrillation reported here is in accord with the findings of recent randomized clinical trials in which >50% of stroke events were prevented by warfarin anticoagulation. (*Stroke* 1991;22:983–988)

**A**lthough hypertension is the strongest risk factor for stroke, age and the presence of other risk factors may modify or enhance the effect of increased blood pressure on stroke occurrence.<sup>1–4</sup> Impaired cardiac function, overt or occult, increases stroke incidence at all levels of blood pressure. In hypertensive persons coronary heart disease, cardiac failure, and particularly atrial fibrillation are associated with increased stroke risk.<sup>5–7</sup>

Atrial fibrillation, which is frequently associated with hypertension, coronary heart disease, and cardiac failure, becomes increasingly prevalent among persons aged >70 years.<sup>8</sup> It has been suggested that

atrial fibrillation is a risk “marker” for stroke and that the increased stroke incidence in persons with this arrhythmia is a result of age and associated cardiovascular abnormalities.<sup>9,10</sup> To help address this issue, we have extended our previous study and examined in detail the relative impacts of hypertension, coronary heart disease, cardiac failure, and atrial fibrillation on the incidence of stroke in the Framingham Study.<sup>8</sup> We took advantage of the 110 additional initial stroke events, and additional coronary heart disease and cardiac failure cases occurring during the 4 further years of follow-up, to enhance the analysis of the relative importance of each of the cardiovascular contributors to stroke with advancing age.

### Subjects and Methods

Since 1948, the Framingham Study has biennially followed 5,209 men and women for the development of cardiovascular disease. For this report, 5,070 men and women free of cardiovascular disease (including atrial fibrillation) at study enrollment were examined every 2 years during a 34-year follow-up period. Sampling procedures, response rates and follow-up, and methods of examination have been described elsewhere.<sup>11</sup>

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For stroke, surveillance was maintained by daily monitoring of all admissions to the only local hospital. If stroke was suspected, the patient was seen in the hospital by one of the study neurologists. Neurological symptoms or signs noted by a study physician at a biennial examination were followed up by a detailed evaluation in the neurology clinic. The circumstances surrounding every illness and the death of each subject were evaluated by review of all available medical information, including hospital and physician records and autopsy data. The clinical data were reviewed by a panel of physicians to determine if minimal criteria were met for the diagnosis of the disease under study and to determine the underlying cause of death. A neurologist participated in reviews of all suspected cases of stroke. Most subjects were admitted to a hospital by their personal physician when stroke or transient ischemic attack was suspected. Since 1981 a computed tomogram of the head was performed on 84% of stroke cases and was confirmatory in 54%. Cerebral arteriography was infrequently performed, except in subjects with subarachnoid hemorrhage or when carotid stenosis was suspected.

Atrial fibrillation was identified on biennial examination and sought on review of all interim hospitalizations. Onset was considered to be the time of first documentation on a hard-copy electrocardiogram tracing. Chronic atrial fibrillation was defined as the persistence of the rhythm disturbance from onset without the electrocardiographically documented interim appearance of regular sinus rhythm. When atrial fibrillation was documented for the first time on hospital admission for a stroke, which was not rare, the duration of the arrhythmia could not be determined. A normal rhythm had usually been documented 1 year before, on average, at the time of a prior biennial examination. Since stroke is not recognized as a precipitant of atrial fibrillation, the arrhythmia was assumed to have occurred during the interim.<sup>12</sup> Anticoagulants were seldom used in this

group, either at the time of the initial stroke or at stroke recurrence.

Since it was often difficult to distinguish between thrombotic and embolic infarctions, all strokes, including transient ischemic attacks, occurring in persons with nonrheumatic atrial fibrillation were counted as stroke events without making a judgment as to the probable stroke mechanism. Many of the events classified as transient ischemic attacks would probably now appear as infarcts on magnetic resonance imaging. However, unless the clinical episode persisted for 24 hours, Framingham Study criteria required that the event be classified as a transient ischemic attack. Stroke events resulting from hemorrhage accounted for only 11.6% of the total, and their exclusion would not appreciably influence the results of the analyses. Furthermore, with the exception of cerebral embolism (which increased in frequency with advancing age), the other stroke subtypes intracerebral hemorrhage, subarachnoid hemorrhage, brain infarction, and transient ischemic attack occurred in approximately equal proportions in persons the two major age groups 35–64 and 65–94 years old. Stroke occurrence in the presence of atrial fibrillation was studied without being influenced by the self-fulfilling criteria for stroke type, which for cerebral embolism includes a cardiac source of emboli, such as atrial fibrillation.

Coronary heart disease and cardiac failure are defined elsewhere.<sup>11</sup> The exclusion of subjects with rheumatic heart disease was based on clinical grounds.<sup>8</sup> Analyses relating atrial fibrillation to stroke were restricted to persons who were free of rheumatic heart disease. Hypertension was defined as the presence of at least one abnormal blood pressure reading at a biennial examination. Systolic blood pressures exceeding 160 mm Hg and diastolic readings exceeding 95 mm Hg were considered abnormal. The prevalences of hypertension, coronary heart disease, cardiac failure, and atrial fibrillation were determined by dividing the 34 years of follow-up

TABLE 1. Estimated Prevalence of Various Cardiovascular Conditions by Age

Cardiovascular condition	Age group			
	50–59 yr (20,520 person-bienniums)	60–69 yr (19,298 person-bienniums)	70–79 yr (8,994 person-bienniums)	80–89 yr (2,084 person-bienniums)
<b>Hypertension</b>				
Prevalence (rate/100)	38.2	51.7	63.1	71.6
Person-bienniums observed	7,846	9,974	5,676	1,492
<b>Coronary heart disease</b>				
Prevalence (rate/100)	6.6	14.1	20.6	27.7
Person-bienniums observed	1,346	2,718	1,856	578
<b>Cardiac failure</b>				
Prevalence (rate/100)	0.8	2.3	4.9	9.1
Person-bienniums observed	166	451	438	190
<b>Atrial fibrillation</b>				
Prevalence (rate/100)	0.5	1.8	4.8	8.8
Person-bienniums observed	109	351	429	184

Prevalence of each condition increased significantly with age ( $p < 0.001$ ).

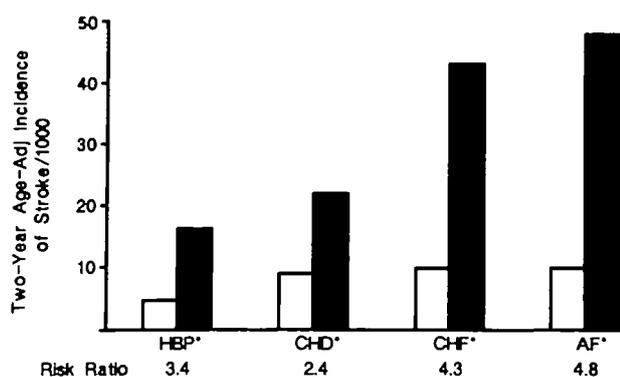


FIGURE 1. Bar graph of 2-year age-adjusted incidence of stroke according to presence (filled bars) and absence (open bars) of cardiovascular condition. HBP, hypertension; CHD, coronary heart disease; CHF, cardiac failure; AF, atrial fibrillation. \* $p < 0.001$  different from unity.

into 17 bienniums of experience. Prevalence rates were calculated for 10-year age groups by pooling bienniums of experience and counting the number of cardiovascular conditions. Tests of the association between age and each cardiovascular condition were also performed.<sup>13</sup>

To estimate the 2-year incidence of stroke, the 34 years of follow-up were again divided into 17 bienniums of experience. Subjects free of stroke and transient ischemic attacks at the beginning of each biennium were then followed up for 2 years. Incidence rates were calculated by combining all bienniums of experience and noting the number of occurrences of stroke or transient ischemic attacks. Two-year rates were calculated for first stroke events among subjects with and without each of the cardiovascular abnormalities hypertension, coronary heart disease, cardiac failure, and atrial fibrillation. This cross-sectional pooling method yields estimates of relations that are very close to those obtained by time-dependent Cox regression analysis.<sup>14</sup>

To describe the changing effects of cardiovascular risk factors on the incidence of stroke with advancing age, the relative risk of stroke associated with each condition was estimated within 10-year age groups. The estimated relative risk approximates the ratio of the probability of stroke in the presence of each cardiovascular condition compared with its absence. Each estimate of relative risk associated with a

specific cardiovascular condition was adjusted for the confounding effects of the other conditions based on logistic regression models for survival data analysis.<sup>13</sup> Statistical tests of the effect of age on changes in the relative risk were also performed. All tests of significance were two-sided.

To estimate the percentage of strokes that could be attributed to a specific cardiovascular condition, the attributable risk of stroke was calculated by 10-year age groups.<sup>15</sup> Attributable risks represent the percentage of strokes that could be eliminated from a population if the cardiovascular condition were removed. The attributable risk is a function of the prevalence of a cardiovascular condition and the relative risk of stroke in the presence of the condition versus its absence. The attributable risk increases if either the prevalence or the relative risk increases.

The effect of age on changes in the attributable risk of stroke was also examined for each cardiovascular condition. Age effects were evaluated by testing for a linear trend with advancing age after adjusting for differences in the variance of the attributable risk estimates.<sup>16</sup>

### Results

After 34 years of follow-up, a substantial number of cardiovascular events occurred among the Framingham Study participants. Among persons between the ages of 50 and 89 years, there were 572 initial strokes, 122 of which were transient ischemic attacks only. There were 256 instances of atherothrombotic brain infarction, 114 persons had stroke from cerebral embolism, 27 had intracerebral and 39 had subarachnoid hemorrhage, and 14 strokes were attributed to other miscellaneous causes. Hypertension was observed in 1,706 individuals. There were 1,328 initial coronary events and 495 instances of cardiac failure; atrial fibrillation occurred in 311 subjects.

The prevalence of each of these cardiovascular conditions increased significantly with advancing age (Table 1). The 2-year age-adjusted incidence of stroke was significantly increased in the presence of each cardiovascular condition compared with its absence (Figure 1). Hypertensive individuals experienced a more than threefold excess of stroke ( $p < 0.001$ ). In addition, the incidence of stroke in the presence of coronary heart disease was more than

TABLE 2. Estimated Relative Risk of Stroke for Persons With Given Cardiovascular Condition Compared to Those Without Condition by Age

Cardiovascular condition	Age group			
	50–59 yr	60–69 yr	70–79 yr	80–89 yr
Hypertension*	3.5†	3.2†	2.5†	1.7
Coronary heart disease‡	2.9†	2.0†	1.7§	0.7
Cardiac failure‡	3.9§	2.4†	2.2†	1.7
Atrial fibrillation	4.0†	2.6†	3.3†	4.5†

Each relative risk is adjusted for the other stroke risk factors.

\* $†p < 0.05$  and  $0.001$ , respectively, significant decline in estimated relative risk of stroke with advancing age.

†§ $p < 0.001$  and  $0.01$ , respectively, significant excess of stroke in those with cardiovascular condition.

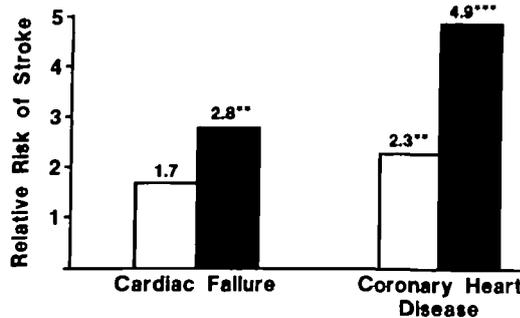


FIGURE 2. Bar graph of estimated age-adjusted relative risk of stroke for men (open bars) and women (filled bars) with atrial fibrillation compared with those without atrial fibrillation in presence of cardiac failure or coronary heart disease. \*\* $p < 0.01$ , \*\*\* $p < 0.001$  significant excess of strokes.

doubled ( $p < 0.001$ ). There was a more than fourfold excess of stroke in subjects with cardiac failure ( $p < 0.001$ ), and a near fivefold excess was observed in the presence of atrial fibrillation ( $p < 0.001$ ).

For each cardiovascular condition, the excess risk of stroke was significantly elevated in the three youngest 10-year age groups (Table 2). All relative risk estimates were adjusted for the other cardiovascular conditions. In the oldest 10-year age group, the excess risk of stroke was significant only in the presence of atrial fibrillation ( $p < 0.001$ ). In addition, significant inverse trends in the excess risk of stroke with advancing age were seen in those with hypertension, coronary heart disease, and cardiac failure ( $p < 0.05$ ).

Since cardiac conditions often coexist and may be present at a subclinical level, the excess risk of stroke associated with atrial fibrillation was also examined in the presence of overt coronary heart disease and cardiac failure (Figure 2). In men with overt coronary heart disease, those with atrial fibrillation had more than double the excess risk of stroke ( $p < 0.01$ ). There

was a near fivefold excess in women ( $p < 0.001$ ). In the presence of clinically evident cardiac failure, atrial fibrillation was associated with a twofold excess risk of stroke for either sex. The excess risk in women was statistically significant ( $p < 0.01$ ).

To estimate the percentage of strokes that could be attributed to a cardiovascular condition, attributable risks were computed for each 10-year age group. The attributable risk of stroke from atrial fibrillation increased significantly with age (Table 3). In contrast, the attributable risk of stroke resulting from the other cardiovascular conditions was not affected by age. In the oldest age group (80–89 years), the attributable risk of stroke from atrial fibrillation (23.5%) approached that from hypertension (33.4%).

### Discussion

Epidemiological studies have generally confirmed that cardiovascular abnormalities, including coronary heart disease, cardiac failure, and atrial fibrillation, increase the risk of stroke,<sup>1–7,17–19</sup> although some investigators have failed to observe an effect involving atrial fibrillation.<sup>9,20,21</sup> The current report may help to explain this discrepancy. The absence of a significant relation between atrial fibrillation and stroke incidence in other community studies may in part be explained by the substantially younger ages of their cohorts. A similar disparity exists between reports of a fourfold increased risk of stroke in lone atrial fibrillation in the Framingham Study<sup>22</sup> and no association between stroke and this same condition in Rochester, Minn.<sup>23</sup> These differences may also be related to the younger age range of the Rochester, Minn., sample.<sup>9,20,21</sup>

Cardiac impairments such as coronary heart disease, cardiac failure, and atrial fibrillation all reduce cardiac output, and together with hypertension these cardiac diseases reduce cerebral blood flow by as much as 30%.<sup>24–26</sup> It has been argued that a signifi-

TABLE 3. Attributable Risk of Stroke for Hypertension, Coronary Heart Disease, Cardiac Failure, and Atrial Fibrillation by Age

Cardiovascular condition	Age group			
	50–59 year (92 stroke events)	60–69 yr (213 stroke events)	70–79 yr (192 stroke events)	80–89 yr (75 stroke events)
<b>Hypertension</b>				
Attributable risk (%)	48.8	53.2	48.6	33.4
Events occurring with condition (%)	72.8	80.3	83.9	84.0
<b>Coronary heart disease</b>				
Attributable risk (%)	11.1	12.4	12.6	0.0
Events occurring with condition (%)	25.0	32.9	38.0	28.0
<b>Cardiac failure</b>				
Attributable risk (%)	2.3	3.1	5.6	6.0
Events occurring with condition (%)	9.8	11.7	18.2	18.7
<b>Atrial fibrillation</b>				
Attributable risk (%)*	1.5	2.8	9.9	23.5
Events occurring with condition (%)	6.5	8.5	18.8	30.7

\*Significant increase with age ( $p < 0.01$ ).

cant proportion of the strokes occurring in patients with chronic atrial fibrillation are a consequence of the complications due to coronary heart disease, cardiac failure, and hypertension.<sup>9,10,27</sup> In a recent comprehensive study, 154 consecutive anterior-circulation stroke patients with atrial fibrillation were evaluated for alternative mechanisms for the stroke with carotid angiography or noninvasive carotid testing and lacunar infarction was excluded by computed tomography.<sup>28</sup> In 76% of these cases atrial fibrillation was the sole stroke mechanism identified.

These Framingham Study data indicate that atrial fibrillation exerts a significant impact on the risk of stroke that is independent of the often-associated cardiovascular abnormalities. Furthermore, other cardiovascular abnormalities have decreasing influence with advancing age, whereas the impact of atrial fibrillation increases into the ninth decade of life. Although atrial fibrillation increases stroke incidence in the absence of overt coronary heart disease or cardiac failure, these cardiac conditions may be present in subclinical form. However, atrial fibrillation increases stroke risk in the presence of overt coronary heart disease, cardiac failure, and hypertension, further strengthening the argument of an independent and significant role of atrial fibrillation in stroke occurrence. In the presence of rheumatic heart disease with mitral stenosis<sup>29,30</sup> or hypertrophic cardiomyopathy,<sup>31</sup> the presence of atrial fibrillation is known to increase the risk of stroke. In the Boston Area Anticoagulation Trial of warfarin and placebo in atrial fibrillation, the sole statistically significant clinical characteristic of the stroke group of atrial fibrillation patients compared with patients who remained free of stroke was the presence of mitral annulus calcification on echocardiography.<sup>32</sup> Mitral annulus calcification and an enlarged left atrium may promote stasis and atrial clot formation. Both these conditions increase with advancing age and with the duration and presence of atrial fibrillation and are associated with atrial fibrillation. The impact of a number of risk factors for coronary heart disease may diminish with advancing age although the mechanism is unknown.<sup>33</sup> Risk factors for coronary heart disease (cigarette smoking, the total cholesterol concentration, and the ratio of total to high density lipoprotein cholesterol concentrations) have reduced impact on incidence in the elderly. Perhaps this phenomenon helps to explain the diminishing effect of hypertension and cardiac contributors to stroke with advancing age while atrial fibrillation, a direct precipitant of the disease, retains its power in the elderly.

Recent reports of a dramatic and highly significant reduction in the incidence of stroke in randomized clinical trials by warfarin anticoagulation<sup>32,34,35</sup> and by aspirin<sup>35</sup> support the contention that the prevention of atrial thrombi in persons with atrial fibrillation is the key to stroke prevention. Since many of the clinical trial participants had coronary heart disease, hypertension, and cardiac failure and since warfarin exerts no beneficial effect on these cardiac impair-

ments, it is difficult to explain the 80% reduction in stroke incidence in the warfarin group in any other way.<sup>29</sup> Although these findings are encouraging, the use of these drugs carries some hazard, particularly in those most likely to benefit (i.e., elderly persons in the eighth and ninth decades of life). Identification of high-risk subgroups by means of echocardiography or other imaging studies has been unsuccessful to date but might permit drug treatment to be given to those at the greatest risk of stroke. Ideally, prevention of the predisposing cardiovascular diseases, particularly atrial fibrillation, will yield major dividends in preventing stroke in the elderly.

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KEY WORDS • atrial fibrillation • cerebrovascular disorders • risk factors