Atrial fibrillation (AF) in the presence of mitral stenosis, a consequence of rheumatic heart disease, was long recognized as the basis for cerebral infarction. Although it had long been acknowledged that atrial stasis resulting from mitral stenosis, often in the presence of AF, predisposed to thrombus formation, investigators questioned whether the AF played a role in the occurrence of systemic embolism, including stroke. As examples, in 1951, the esteemed Boston cardiologists Harris and Levine concluded, “...one wonders whether AF has much importance in influencing thrombus formation in mitral stenosis.”1

In his memoirs, Fisher2 recounts the events in 1949 soon after his arrival as a graduate fellow in neuropathology at the Boston City Hospital. He stated,

One day, three months after I’d arrived, I had the opportunity to examine the cerebral arteries before slicing three brains that had large hemorrhagic infarcts. The basal vessels were empty of thrombus ... People were signing out these cases as cerebral artery thrombosis—but pathologically there was no thrombus. Afterward, I looked up the records on these three cases and they had all been in AF and the general autopsy had shown infarcts in the spleen and kidneys. I speculated that they might be cases of embolism from the heart. The hemorrhagic change was from reperfusion of blocked vessels.

This experience led Fisher to conclude AF was indeed frequently associated with stroke attributed to cerebral thrombosis, and the hemorrhagic infarction in such cases was related to lysis of cerebral emboli and reperfusion of the infarct.

At about the same time, beginning in 1946, Wright and Foley3 at the New York Hospital-Cornell Medical Center showed that anticoagulation could prevent strokes originating from fibrillating atria in patients with mitral stenosis. This work was later extended to those with nonvalvular AF and was discussed by Wright at the First Princeton Conference.4 However, the evidence for a pathogenetic role for AF, in the absence of mitral stenosis, was mixed and contradictory. This issue remained unsettled and in dispute for more than 20 years. Reflecting current thinking among cardiologists, in the 3rd edition (1966) of the classic cardiology text, Diseases of the Heart, C.K. Friedberg averred, emboli rarely arise in the fibrillating heart without rheumatic heart disease. Thus persisted the common notion, based on the clinical impression that in the absence of valvular heart disease, AF, a frequent occurrence in the elderly, was generally a benign condition.

Evidence to the contrary accumulated slowly on the pathological, clinical, and epidemiological studies. A detailed exposition of the accumulating evidence is chronicled in the proceedings of a symposium on atrial fibrillation held in Kiruna, Sweden, in June 1981.5 Fisher reviews the status of the field at that time, reviewing the generally primitive, somewhat conflicting, and generally inconclusive clinical and pathological case–control studies, suggesting AF in the absence of rheumatic heart disease was a source of thrombus and the basis for systemic embolism, including cerebral infarction.

Sufficient evidence led Fisher to respond to an editorial on electric conversion of AF. He wrote a Letter to the Editor in The Lancet in June 1972. He outlined, with extraordinary brevity, the key features of stroke in patients with AF and suggested prevention with anticoagulation (Figure 1).6

The key points are: AF is not rare in patients >60 years of age; these patients were in relatively good health; they sustained a severe stroke as the initial event; and most had nonrheumatic heart disease.

To the accumulating pathological evidence and clinical experience, data from prospective epidemiological study of stroke in patients with AF became available. After 24 years of follow-up in the Framingham Heart Study, 345 documented strokes had occurred, 27 in subjects with chronic AF: 7 with rheumatic heart disease, and 20 with nonrheumatic AF. In patients with AF associated with rheumatic heart disease, the incidence of stroke was increased 17.6-fold, and in those with AF in the absence of valvular disease, there was a 5.6-fold increased stroke incidence.7 The authors noted that the stroke events in 19 of the 20 chronic fibrillators had the clinical features commonly associated with embolic strokes: abrupt onset; maximal deficit at onset; absence of antecedent transient ischemic attacks; and whether recovery ensued a rapid reversal of the neurological signs. Pathological support for embolism was found in 6 of the 12 who died. With
increased with age, more than doubling in successive decades in these Framingham Study participants. Prevalence of AF was sufficient data to clarify the independent contribution of AF to the increased stroke incidence and for the increasing incidence; it had been suggested that these cardiovascular diseases rather than the chronic AF accounted for the increased stroke incidence and for the increasing incidence with advancing age. It was possible, using 34 years of follow-up, that 572 stroke events had occurred providing sufficient data to clarify the independent contribution of AF in these Framingham Study participants. Prevalence of AF increased with age, more than doubling in successive decades from 0.5% at 50 to 59 years of age, to 1.8% at 60 to 69 years of age, to 4.8% at 70 to 79 years of age, and 8.8% at 80 to 89 years of age. The age-adjusted incidence of stroke was increased in the presence of hypertension, coronary heart disease, congestive heart failure, and AF (Figure 2). Incidence of stroke was greatest in patients with AF even after the effects of the other associated cardiac conditions were taken into account. In addition, the attributable risk of stroke within each decade of age was calculated to estimate the percentage of stroke events that could be eliminated if the specific cardiac malady was removed (Table). In addition, the proportion of stroke events occurring with these conditions was also computed. Attributable risk of stroke increased significantly with age (Figure 2). 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), attributable risk with AF of 23.5% approached that from hypertension. A key step in relating nonrheumatic AF was taken by demonstrating warfarin anticoagulation could prevent stroke in a clinical trial. Prevention by warfarin anticoagulation was accomplished in a series of 5 randomized clinical trials, which clearly established the effectiveness of warfarin therapy. Overall, a 68% reduction in risk occurred, and most of these trials had to be stopped early as the preventive effectiveness became apparent. For example, in the Boston Area Anti-coagulation Trial in AF (BAATAF), there were 2 strokes in the 212 patients randomized to low-dose warfarin therapy when compared with 13 strokes in the 208 controls after an average follow-up of 2.2 years, representing an 86% relative risk reduction, with an incidence rate in the warfarin group of 0.41 per year versus 3.0 per year in the control group, with virtually no excess in major bleeding.

Despite this remarkable trial outcome and incontrovertible evidence that warfarin prevented stroke in nonrheumatic AF presumably by preventing the formation of left atrial clots in the presence of stasis, an accompanying editorial expressed reservations and entertained alternative conclusions. However, as a possible example of the durability of a disproved but previously favored hypothesis, the authors seemed reluctant to attribute the remarkable outcome of the trial to the obvious. Emboli arising from aortic arch atheromata, left ventricular thrombi, mitral valve abnormalities, and cerebrovascular atherosclerosis were alternative stroke mechanisms and sites mentioned. Concern was also expressed about falls in elderly patients and the increased risk with warfarin, an obvious worry in this age group with anticoagulants and despite an absence of these events in the BATAAF trial subjects. Two decades later, it is clear that warfarin (and more recently an array of other anticoagulant agents) prevents stroke in patients with AF. This is clearly the single most powerful stroke prevention measure available and continues to increase in importance as the population ages and with the improved survival of patients with coronary heart disease and congestive heart failure, which form the cardiac substrate for AF. Although it was fascinating to read about the early 1949 neuropathological observations in the autobiography of Fisher mentioned above, as a testimony to Fisher’s wisdom and modesty, and in response to an interviewer’s question, “But your work on hemorrhagic infarction and heart embolism was...
never published,” he replied, “No, Raymond Adams and I reworked the paper several times, but the editor must have had a different theory. Anyway, at that time, I got side tracked to the internal carotid artery in the neck.”

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None.

References

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