Epidemiology of Stroke: Legacy of the Framingham Heart Study

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SUMMARY

In the present historical review, we highlight several papers outlining contributions of the Framingham Heart Study (FHS) over the span of nearly 7 decades to our understanding of the epidemiology of blood pressure (BP), atrial fibrillation, and genetic factors as they relate to cerebrovascular disease. In 1970, Framingham investigators led by William Kannel explored the epidemiological relations of BP and its various components to risk of ischemic stroke as well as hemorrhage, and they noted the greater impact of hypertension to risk of stroke compared with other cardiovascular outcomes. Framingham investigators changed the prevalent concepts in terms of the contribution of BP components to stroke risk; that is, they showed systolic pressure to be no less important a component for stroke risk than the diastolic or mean arterial pressures. In addition, they challenged the notion that hypertension was a normal consequence of increasing age, as connoted by the term essential hypertension. They also refuted the idea that BP elevation in the elderly population is innocuous by demonstrating that increased stroke risk persisted in advanced age in hypertensive persons. Thirty years later, the Framingham study attained long-term follow-up of an entire generation of participants with excellent retention to follow-up, thus providing an opportunity to study hypertension and risk of stroke in a general population sample. Framingham investigators examined the effect of various BP components over a 50-year follow-up in normotensive and untreated hypertensive individuals as regards stroke risk and showed the long-term importance of antecedent (midlife) hypertension in future stroke risk. Similarly, by calling attention to the importance of chronic nonvalvular atrial fibrillation as a contributor to stroke, particularly in the elderly population, FHS investigators confirmed the clinical observations of the founder of stroke neurology, C. Miller Fisher, MD, who had made the clinical and pathological association of atrial fibrillation to stroke. Lastly, in the dawn of the era of individualized preventive medicine, FHS is participating in the effort to further our understanding of the role of genetic factors to stroke incidence. The contributions of FHS have been many and have shaped our understanding of the relation of BP, atrial fibrillation, and other risk factors to stroke risk, thereby setting the stage for clinical trials that demonstrated how control of these risk contributors could prevent stroke and enable stroke prevention. FHS investigators are collaborating with other geneticists and epidemiologists internationally to elucidate the role of genetic factors and stroke susceptibility, which is likely to continue to shape the practice of preventive cardiovascular medicine.

The role of elevated blood pressure (BP) in causing cerebrovascular disease was first recognized in the 1920s. Keith et al. [1] recognized symptoms arising from organic lesions of the central nervous system in 29 of 81 patients in their description of the syndrome of malignant hypertension. Nonetheless, the relation of hypertension and cerebrovascular disease, particularly ischemic stroke, remained unclear for nearly 50 years. "Benign hypertension" was used to describe hypertensive individuals and in the elderly population even marked BP elevations were not considered pathological [2]. Subsequently, it was not until antihypertensive medications became available in the mid to late 1960s that treatment of extreme levels of diastolic hypertension was undertaken by Fries [3], who demonstrated their effectiveness in reducing cardiovascular disease, particularly stroke. Thus began the series of clinical trials of patients with lower and lower diastolic blood pressure (DBP) levels uniformly demonstrating the efficacy of BP reduction in stroke prevention. Based on epidemiological data provided by the Framingham Heart Study (FHS), the National High Blood Pressure Education Program was started in 1972 with the goal of educating healthcare professionals and the public on the adverse impact of hypertension [4]. The contribution of individual components of BP was first elucidated by Kannel et al. in 1970 [5] in their landmark JAMA publication, which was recognized in the first "Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure" in 1977, which used BP risk stratification cut points defined by the FHS. Contributions of the FHS undoubtedly influenced the understanding of the role of individual components of BP as they relate to stroke. The scientific community eventually embraced these concepts leading to evaluation and identification of effective therapies for individuals with much lower BP values, less focus on the DBP than the systolic blood pressure (SBP), and in hypertensive elderly people (above age 80 years) than previously was even considered.

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The Framingham study provided an exemplary model for the conduct of epidemiological studies, achieving the challenging task of close and comprehensive serial follow-up of 3 generations of participants, with remarkable participant retention at follow-up. The study began in 1948 with the enrollment of the original cohort, following participants prospectively over more than 5 decades. This has allowed for a more accurate understanding of the natural history of participants with and without hypertension, in terms of their risk of cerebrovascular disease, clinically evident in the form of overt stroke, and in subclinical stages. Since antihypertensive medication was not used in clinical practice until the early 1970s, FHS investigators were able to observe the impact of untreated BP levels, including elevated levels, on a number of outcomes including aspects of cognitive impairment [6].

An additional important contribution by investigators of the Framingham study as it relates to stroke prevention is the identification of nonvalvular atrial fibrillation (AF) as a strong predictor of risk of stroke. Follow-up for an extended period allowed for the evaluation of risk in persons at a wide age range, showing the strong and relative contributions of AF to stroke risk, particularly in the elderly population.

More recently, the FHS has contributed significantly to elucidation of the role of genetic factors in stroke risk. The careful ascertainment of stroke occurrence in the original and offspring cohorts of the FHS permitted clarification of the contribution of parental history of stroke, to stroke risk in the offspring, and provided evidence that genetic factors contribute substantially to stroke susceptibility. Advances in genetic methods have been incorporated in the FHS, allowing for the performance of genome-wide association studies in which single nucleotide polymorphisms distributed across the entire human genome can be assessed, without assuming a priori hypothesis. FHS investigators directed a collaborative effort to identify previously unknown gene variations in common forms of stroke, leading to the identification of novel genes implied in stroke risk.

In the present historical review, we highlight several selected FHS publications, over the course of nearly 7 decades, with regard to our understanding of the role of BP in general, its individual components in particular (systolic, diastolic, and pulse pressures), and AF as regards cerebrovascular disease. (More comprehensive treatment of this subject can be found elsewhere [7,8].) We also describe a unique contribution provided by the FHS, emphasizing the importance of antecedent BP measurements to stroke risk prediction compared with the use of current BP measurements and FHS contributions to the understanding of the role of genetic factors in stroke risk.

BP AND ITS RELATION TO CEREBROVASCULAR DISEASE

In 1970, Kannel et al. [9] reiterated hypertension as "the most common and potent precursor of atherothrombotic brain infarction," and they further suggested that "the key to the prevention of CVAs would therefore, appear to be early detection and control of hypertension." Forty-two years later, these statements remain true. In this report, Kannel et al. describe the relationship of BP and its components to stroke in 5,209 original cohort participants followed biennially over 14 years for the occurrence of stroke in general and ischemic stroke attributable to atherosclerotic brain infarction (ABI), that is, brain infarction in the absence of an obvious cardiac source of emboli, in particular. A casual BP, representing the mean of 2 measurements recorded by a physician was taken as the BP at the examination rather than the basal or resting pressure, which was the measure recommended at the time. Hypertension was arbitrarily defined as BP $\geq$160/95 mm Hg, normotension as BP $<$140/90 mm Hg, and borderline BP for measures within this range; stroke was defined according to conventional clinical criteria. The method of surveillance for occurrence of stroke included a brief neurological exam during the biennial examination, confirmation of cases by a neurologist in consultation, and examination of study participants admitted with a presumptive or confirmed diagnosis of stroke to the only local hospital in Framingham (since 1965). Surviving participants were followed regularly after the stroke and in cases of death; all pertinent information concerning circumstances of death was reviewed to determine if stroke was the cause of death. Further information was gathered by interview of participants regarding the occurrence of stroke in their spouse. The investigators tested the accuracy of their stroke detection methods in a random subset of 263 participants who underwent detailed neurological evaluation at the time of their biennial examination, and they uncovered no additional cases of stroke.

Retention of participants at follow-up was impressive with less than 2% lost to follow-up in 14 years. During this period, 135 participants developed strokes (65 men, 70 women), with 86 considered ABI (39 men, 47 women). ABI incidence increased with age in both men and women, with women reflecting increased incidence in the older age groups and men reflecting predominance at younger ages (Fig. 1). Another important observation in this study is the finding that the incidence of stroke in hypertensive individuals (with the BP cut points defined here) versus in normotensive participants was much higher than the incidence of coronary heart disease in hypertensive compared to normotensive participants (Fig. 2). FHS investigators also noted sex differences in stroke rates compared with coronary artery disease and peripheral arterial disease, where there is a male predominance and a closing gap between sexes with advancing age. Women had similar rates of coronary artery disease and ABI, whereas men had greater incidence of coronary artery disease than ABI. Risk of stroke was distinctly related to BP status at initial examination. Contrary to the prevailing notion, the relative risk of intracranial hemorrhage (intracerebral or subarachnoid hemorrhage) and ABI was not different in relation to BP level.