Control of hypertension whether labile or fixed, systolic or diastolic, and at any age or in either sex, appears to be central to the prevention of atherothrombotic brain infarction (ABI). Prospectively, hypertension proved to be the most common and potent precursor of ABIs. Its contribution was direct and could not be attributed to factors related both to stroke and hypertension. Asymptomatic, casual hypertension was associated with a risk of ABI about 4 times that of normotensive individuals. The probability of occurrence of an ABI was predicted no better with both blood pressure measurements or the mean arterial pressure than with systolic alone. Since there was no diminishing impact of systolic blood pressure with advancing age, the concept that systolic elevations are, even in the aged, innocuous is premature. When normotensive and hypertensive individuals were compared in each sex, women did not tolerate hypertension better than men.

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Commentary by William B. Kannel, MD, MPH, and Phillip A. Wolf, MD

In 1970, publication of this article, based on the Framingham Study, provided insights about elevated blood pressure (BP) and stroke risk. Today, in nearly all respects, these findings have been confirmed.

Prospective population epidemiological cardiovascular research in Framingham has played an important role in the prevention of cardiovascular disease (CVD) including stroke. In 1961, Framingham Study investigators developed the risk factor concept indicating that multiple interrelated factors promote the development of coronary heart disease. To date, no single essential factor has been identified—CVD is most appropriately viewed as the product of multiple influences. This concept has had clinical, public health, preventive, and therapeutic applications. The risk factor has become a crucial feature of epidemiological investigation, and elevated BP has emerged as a prominent one—particularly for stroke.

For hypertension and risk factors in general, Framingham research established the importance of distinguishing between usual (average) and optimal risk factor levels as normal and acceptable. The study determined population CVD morbidity and mortality attributable to hypertension, and recently the lifetime risk of developing hypertension and its associated vascular consequences. In particular, the lifetime risk of developing a stroke was shown to be 1 in 6, with hypertension being a powerful contributor to this hazard. The Framingham Study also provided insights on mechanisms of hypertension-induced CVD. Furthermore, Framingham data documented a strong link between BP and CVD development and stimulated the search for antihypertensive medications and many clinical trials to determine their efficacy in CVD risk reduction.

These developments required reevaluation of prevalent clinical misconceptions about hypertensive vascular disease such as “compensatory” left ventricular hypertrophy in hypertension, innocuous orthostatic proteinuria, and the role of obesity. The Framingham Study dispelled the concepts of benign essential hypertension, the dominance of diastolic BP as a cardiovascular hazard, and the benign nature of a rise in systolic BP with age. Reduction of isolated systolic hypertension was thought to be not only fruitless but also intolerable and dangerous. The prime importance of diastolic BP was convincingly refuted by the Framingham Study in 1971 and again in 1980, demonstrating that the effect of systolic BP was actually greater than the diastolic BP component and that even isolated systolic BP elevations are dangerous.©2008 American Medical Association. All rights reserved.

Author Affiliations: Boston University School of Medicine, Framingham Heart Study, Framingham, Massachusetts.

Corresponding Author: William B. Kannel, MD, MPH, Boston University School of Medicine, Framingham Heart Study, 73 Mt Wayte Ave, Framingham, MA 01702-5827 (billkannel@yahoo.com).
Influenced by Framingham Study findings, the focus has shifted to systolic BP and, recently, to pulse pressure.\textsuperscript{6,7} Increased pulse pressure in advanced age was considered an innocuous manifestation of increased vascular rigidity. However, assessment of the effect of BP components by the Framingham Study indicated that increments of pulse pressure at any systolic BP were associated with increased coronary heart disease incidence. With increasing age, the adverse cardiovascular consequences of elevated BP shifts in importance from diastolic to systolic and finally to pulse pressure.\textsuperscript{7}

Women were thought to tolerate elevated BP well, and it was commonly held that there were age-related critical cardiovascular risk thresholds for BP so that “normal” BP levels in both sexes should be designated at higher levels in elderly individuals. However, Framingham Study data refuted this assertion indicating that while the hypertensive risk ratios for all major atherosclerotic CVD events are greater for those younger than 65 years, the absolute incidence of disease in hypertensive individuals was greater in elderly persons. Systolic BPs previously regarded as normal for elderly persons (a BP level calculated by adding the individual’s age plus 100 [70-year-old denotes 170 mm Hg]) were shown to impose substantial excess cardiovascular risk. Also, while the absolute incidence of CVD in elderly hypertensive individuals is lower in women, risk ratios in women are similar to those in men. Thus, neither elderly participants nor women were found to tolerate hypertension well.\textsuperscript{5,6}

Because of the concept of benign essential hypertension and lack of effective and tolerable means for lowering BP, emphasis had been placed on diagnosing and treating underlying causes of secondary hypertension. As a result of population research, routine testing to identify specific underlying causes of hypertension is no longer recommended. Initiation of antihypertensive treatment was often delayed unless the diastolic BP was very high or there was evidence of target organ involvement. Framingham Study data indicated that this practice was imprudent because even modest BP elevations were dangerous.

Framingham Study data altered the concept of an acceptable BP from what is usual to what is optimal for avoiding hypertension-related CVD. Epidemiological data showed that at all ages and in both sexes, CVD risk increases incrementally with BP, even within the normal range. Similar continuous graded relationships of BP to stroke, coronary heart disease, and all-cause mortality have also been reported in other cohorts.\textsuperscript{8,9} There is no threshold for the association between BP and cardiovascular risk—that is, in the Framingham cohort, 45% of CVD events in men occurred at a systolic BP of lower than 140 mm Hg—the value denoted as the threshold of risk.\textsuperscript{6}

Precise estimation of CVD incidence trends at the lower end of the BP range has since been elucidated. Both the Multiple Risk Factor Intervention Trial data on more than 350,000 men screened and observed for CVD mortality and the Prospective Studies Collaboration involving almost 1 million participants and 56,000 vascular deaths, found no indication of a threshold of BP risk as low as 115/75 mm Hg.\textsuperscript{8,9} Individuals aged 40 to 69 years had a doubling of stroke or coronary heart disease mortality with every 20/10-mm Hg increment of BP throughout the entire range. Recent analysis of the relation of “nonhypertensive” BP to CVD incidence in the Framingham Study confirmed a significant graded influence of BP from optimal (<120/80 mm Hg) to normal (120-129/80-84 mm Hg) to high-normal (130-139/85-89 mm Hg) in untreated participants.\textsuperscript{10} Compared with optimal BP, normal and high-normal BP conferred almost a 2-fold increased age and risk factor–adjusted CVD risk. Based on these findings, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines have defined a prehypertensive BP category.\textsuperscript{11}

Stroke is frequently considered to be the chief hazard of hypertension. The Framingham Study established that although its risk ratio is smaller than for stroke or heart failure, coronary disease is the most common hypertensive hazard at all ages.\textsuperscript{4} For stroke, the hypertensive hazard for intracerebral hemorrhage was thought to be greater than for atherothrombotic brain infarction. This proved to be incorrect; hypertension was found to be as strong a risk for atherothrombotic brain infarction as for intracerebral hemorrhage.\textsuperscript{3,9} It was also widely believed that mild hypertension promotes brain infarctions, whereas severe hypertension induces intracerebral hemorrhage. Framingham Study investigation indicated that most hypertension-related strokes were due to atherothrombotic brain infarction whether the hypertension was severe (70%) or mild (56%).\textsuperscript{12}

There is a need for greater use of risk stratification of hypertension to determine the most appropriate type and intensity of treatment. Evaluation of the hypertensive hazard for atherosclerotic CVD requires consideration of other metabolically linked risk factors such as blood lipids, elevated blood glucose, and visceral adiposity that often accompany it. The combination of these risk factors (the metabolic syndrome) greatly augments the cardiovascular hazard of elevated BP. These other risk factors should be routinely sought in all patients with elevated BP because of the tendency for clustering and the great influence of these coexistent risk factors on the CVD hazard of an elevated BP. Risk of CVD in hypertensive individuals was shown by the Framingham Study to vary widely depending on the size of the associated burden of other risk factors.\textsuperscript{12}

Because moderate BP elevations exceed severe elevations in prevalence, a large fraction of CVD attributable to hypertension derives from seemingly trivial elevations of BP. Despite the 1.5- to 2.0-fold increased risk associated with moderate degrees of hypertension, the absolute hazard is

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modest and many individuals in this category need to be treated to prevent 1 CVD case. Efficient selection of mildly hypertensive individuals for aggressive treatment with medication requires multivariable global risk assessment. Substantial risk in hypertensive individuals with mild to moderate hypertension is concentrated in those with coexistent dyslipidemia, diabetes, and left ventricular hypertrophy. The goal of therapy should be to improve the global risk profile as well as the BP. Targeted therapy, based on the composite risk, improves the cost-benefit ratio of antihypertensive therapy.

For stroke, the most feared hazard of hypertension in the elderly population, risk varies over a wide range and becomes substantial when accompanied by diabetes, left ventricular hypertrophy, atrial fibrillation, and coronary disease or heart failure. Tools for assessment of multivariable risk of coronary heart disease, stroke, peripheral artery disease, and heart failure are available using Framingham Study data. Recently, the Framingham Study reported on a risk assessment instrument for predicting total CVD, which enables convenient estimation of the global risk of hypertensive patients using ordinary office procedures and standard laboratory tests. Serial assessment of global CVD risk can be used to monitor progress of patients receiving treatment for hypertension. Demonstrating improvement in their multivariable risk score can help motivate patients to better adhere with the recommended preventive management of their hypertension.

Hypertension-induced CVD cannot be conquered solely by cardiologists caring for referred patients. Multiple elements of the health care system have to be mobilized. Unfortunately, our health care system rewards performance of procedures more than provision of preventive services. Despite means available to identify high-risk hypertensive CVD candidates and proof of the efficacy of controlling their BP and associated risk factors, goals for prevention of CVD are not often met. Established guideline goals need to be implemented more aggressively for management of hypertension, dyslipidemia, and diabetes in patients at risk of atherosclerotic CVD.

Financial Disclosures: None reported.
Funding/Support: This work was supported by the National Heart, Lung, and Blood Institute’s Framingham Heart Study (contract N01-HC-25195).
Role of Sponsor: Boston University School of Medicine had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

REFERENCES