Hypertension and Cardiovascular Disease: Contributions of the Framingham Heart Study

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SUMMARY

This is a historical review of the contribution of the Framingham Heart Study to our understanding of the epidemiology of blood pressure (BP) and cardiovascular disease (CVD). Framingham investigators initially explored the epidemiological relationship of various BP components to coronary heart disease in men and women and how this risk is further modified by age, that is, how diastolic blood pressure (DBP) is the stronger predictor of coronary heart disease risk in young people versus systolic blood pressure (SBP) in middle-aged and elderly people. Framingham investigators then examined the natural history of various BP components over a 30-year follow-up in normotensive and untreated hypertensive individuals and showed how this provides hemodynamic insights into the importance of pulse pressure as a marker of large artery stiffness in middle-aged and elderly people. Importantly, pulse pressure was also found to be superior to SBP or DBP as a predictor of coronary heart disease in a middle-aged and elderly Framingham population. Lastly, dual models of SBP with DBP and pulse pressure with mean arterial pressure were superior to single BP component models for predicting CVD events; thus, increases in both peripheral vascular resistance and central large artery stiffness contribute to CVD in varying proportions depending on age. Furthermore, the Framingham Heart Study provided evidence that DBP <70 mm Hg with SBP ≥ 120 mm Hg was associated with a CVD risk equivalent to approximately 20 mm Hg of additional elevation in SBP, thus further supporting the importance of large artery stiffness as a CVD risk factor in elderly people. These original Framingham studies have contributed greatly to BP risk classification tables for the "Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" and for the European Society for Hypertension. Moreover, Framingham originally brought attention to hypertension, which is now the leading cause of mortality globally.

In 1949, Charles Friedberg [1] noted that there was "a lack of correlation between the severity and duration and hypertension and the development of cardiac complications." In 1970, Karl Engleman and Eugene Braunwald [2] stated, "systolic hypertension in the presence of normal or reduced diastolic blood pressure is rarely considered to be responsible for organ damage, but usually reflects other pathologic processes." Thus, the medical conventional wisdom in the second half of the 20th century was frequently in error in overlooking hypertension in general and systolic hypertension in particular as important risk factors for cardiovascular disease (CVD).

In 1959, an original article by Kagan et al. [3] from the Framingham Heart Study noted that "the relation of hypertension and atherosclerosis was still poorly understood." Importantly, the contribution of more than a half century of work from Framingham Heart Study investigators has provided significant insight into the epidemiology and CVD outcomes associated with hypertension and on the relation of systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), and mean arterial pressure (MAP) with CVD outcomes. This review describes the methodology and findings related to 5 key publications about the epidemiology of BP and its clinical significance: 1) BP and its relation to CHD [3]; 2) SBP versus DBP and risk of CHD [4]; 3) hemodynamic patterns of age-related changes in BP [5]; 4) PP and risk of CHD [6]; and 5) the role of single versus combined BP components in relation to CVD risk [7].

BLOOD PRESSURE AND ITS RELATION TO CORONARY HEART DISEASE

Kagan et al. [3], in 1959, first described the relation of the distribution of BP in Framingham and the relation of BP to the development of coronary heart disease (CHD) over an initial 6-year follow-up period. Between 1949 and 1952, 4,469 participants of 6,510 selected agreed to participate and be examined. A detailed medical history and physical examination was included, and BP were taken on both arms in the seated position. Height, weight, vital capacity, and a 12-lead electrocardiogram and postero-anterior chest film in addition to a urinalysis and blood analysis for hemoglobin, glucose, uric acid, and cholesterol were done. A second physician examined each subject performing a second left arm BP as well, but analyses in this first report were based on the first examiner's left arm BP.

Initial findings regarding the description of BP measures noted by the investigators were: 1) the choice of left versus right arm for taking BP did not differ, and differences were random to a similar degree to what

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measurements on the same arm would exhibit; and 2) there was a digit preference for recording even numbers for BP, with 0 being the most commonly measured digit. Importantly, Framingham noted that both mean SBP and DBP rose steadily with age in both men and women; although, among men, there was no further increase after the age of 50 years in DBP. Interestingly, there was a crossover between men and women in SBP in the 45 to 49 years age group, after which levels were higher in women and a similar crossover in DBP at the next highest (50 to 54 years) age group. Finally, the investigators observed a "white coat" BP effect in subjects attending early biennial visits, noting that there was a downward trend both in SBP that averaged 136.5 mm Hg at the first exam, but decreased to 131.4 by the third exam, and DBP decreasing from 85.4 mm Hg to 81.6 mm Hg, respectively. They attributed this as "due to the familiarity with the examination procedure and a decreasing psychogenic reaction to the examination."

Realizing that the increasing BP with age might be related to the greater prevalence of CVD, the Framingham investigators also examined the age-BP relationship among so-called normal persons, which excluded any with known evidence of CVD, cardiac enlargement by x-ray, or significant electrocardiographic abnormalities. They found the upward trend of BP persisted as well in this "normal" group. Further analysis also characterized BP levels according to different diagnostic categories of CHD and found significantly elevated BP to be present in particular among those with angina pectoris.

Of particular interest, Framingham was among the first to describe the prevalence of normal, borderline, and elevated (hypertension) BP according to what were newly recommended criteria by the Subcommittee on Blood Pressure of the Conference on Longitudinal Cardiovascular Studies held in June 1957. At that time, a normal BP was defined as readings of $<$140 mm Hg systolic and $<$90 mm Hg diastolic by 2 examiners and definite hypertension as readings of a systolic of 160 mm Hg or diastolic of $\geq$95 mm Hg, with readings in between defined as possible high BP. In addition, this group defined a subgroup of systolic hypertension based on elevated SBP but normal DBP at these cut points. Among the 4,469 persons evaluated, 801 (17.9%) had definite hypertension, 1,577 (35.3%) borderline hypertension, and 2,091 (46.8%) were normotensive.

In the same paper [3], the investigators also went on to describe the close relation between cardiac enlargement and BP. Whereas cardiac enlargement was found at all BP levels, there were also persons with normal-sized hearts no matter how high their BP was, indicating individual variability in the susceptibility to cardiac enlargement at any BP levels. They found that electrocardiographic evidence of left ventricular hypertrophy was a more definite indicator of hypertension than was cardiac enlargement by x-ray.

With regard to follow-up for CHD events, this paper describes the total cohort of 5,209 subjects with 6-year follow-up, of which only 4 were lost to follow-up. Over these initial 6 years, there were 186 new CHD events, including 125 in men and 61 in women, of which 71 were definite myocardial infarction. Incident CHD was approximately twice as great in men as in women. The investigators noted a rate of new CHD (per 1,000) that was highest in those with definite and probably hypertensive heart disease, intermediate in those with hypertension, and lowest in those with borderline and normal BP among both men and women (Table 1). CHD rates were also highest in those with left ventricular hypertrophy by electrocardiogram as opposed to left ventricular hypertrophy or generalized cardiac enlargement by x-ray. The investigators also described the relation of DBP to CHD events, stratified by cholesterol levels, noting a more dramatic rise in CHD event risk with DBP among those with higher versus lower cholesterol levels (Fig. 1).

SYSTOLIC VERSUS DIASTOLIC BP AND RISK OF CHD

Critical to the further development of BP as a risk factor for CHD was deciphering the relative contributions of SBP and

TABLE 1. Six-year rate of coronary heart disease events (per 1,000) according to blood pressure category and presence of left ventricular hypertrophy and/or cardiac enlargement (n = 1,246)

	Men Ages 29–44 Years	Men Ages 45–62 Years	Women Ages 45–62 Years
All	24.9	90.6	44.6
Definite hypertensive heart disease	62.5	182.9	101.4
Definite hypertension	28.8	125.8	64.7
Possible hypertensive heart disease	50.8	141.2	51.9
Borderline hypertension	24.2	93.8	38.6
Normotension	22.0	40.9	10.2
LVH (definite or possible) or cardiac enlargement by x-ray	32.3	118.4	60.0
LVH (Definite or Possible) by ECG	64.5	285.7	106.4

ECG, electrocardiograph; LVH, left ventricular hypertrophy.
Adapted, with permission, from Kagan et al. [3].