

# 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  $\geq$ 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).

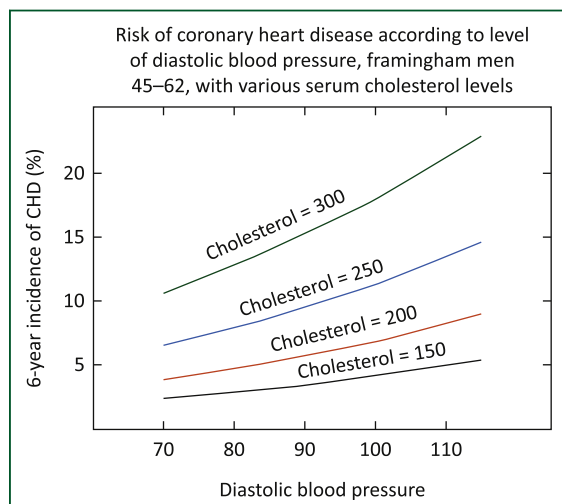
### SYSTOLIC VERSUS DIASTOLIC BP AND RISK OF CHD

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].



**FIGURE 1. Relation of diastolic blood pressure stratified by total cholesterol level to 6-year incidence of coronary heart disease events in the Framingham Heart Study.** Reprinted, with permission, from Kagan et al. [3].

DBP to predicting risk. By 1971, Kannel et al. [4] felt that it “is generally conceded that elevated levels of BP play an important role in the pathogenesis of atherothrombotic disease, the most prominent cause of mortality in the United States”; however, they noted that “the relative importance of various indices of BP such as PP, MAP, lability and SBP versus DBP in the pathogenesis of cardiovascular sequelae of hypertension have yet to be adequately explored.” These investigators felt that with 14 years of follow-up in Framingham and with the 492 accumulated cases of CHD that it was now possible to examine some of these issues.

Of particular interest, because SBP and DBP were highly correlated, it was necessary to do a “multivariate analysis of each as a discriminator of potential coronary heart disease.” Framingham is among the first studies to recognize the role of examining “independent contributions” of multiple, often correlated variables and, hence, has championed the development of the concept of multivariable analyses used nearly universally in epidemiologic research today. In this 1971 study [4], the investigators determined for each age-sex group the standardized mean differences in BP (the mean BP of subjects with CHD minus the mean BP of those without disease over the standard deviation of the population) between those where CHD did and did not develop, providing a direct method of comparing the power of these 2 measures. They then constructed a discriminatory function to be able to compare the contributions of each variable separately and then together.

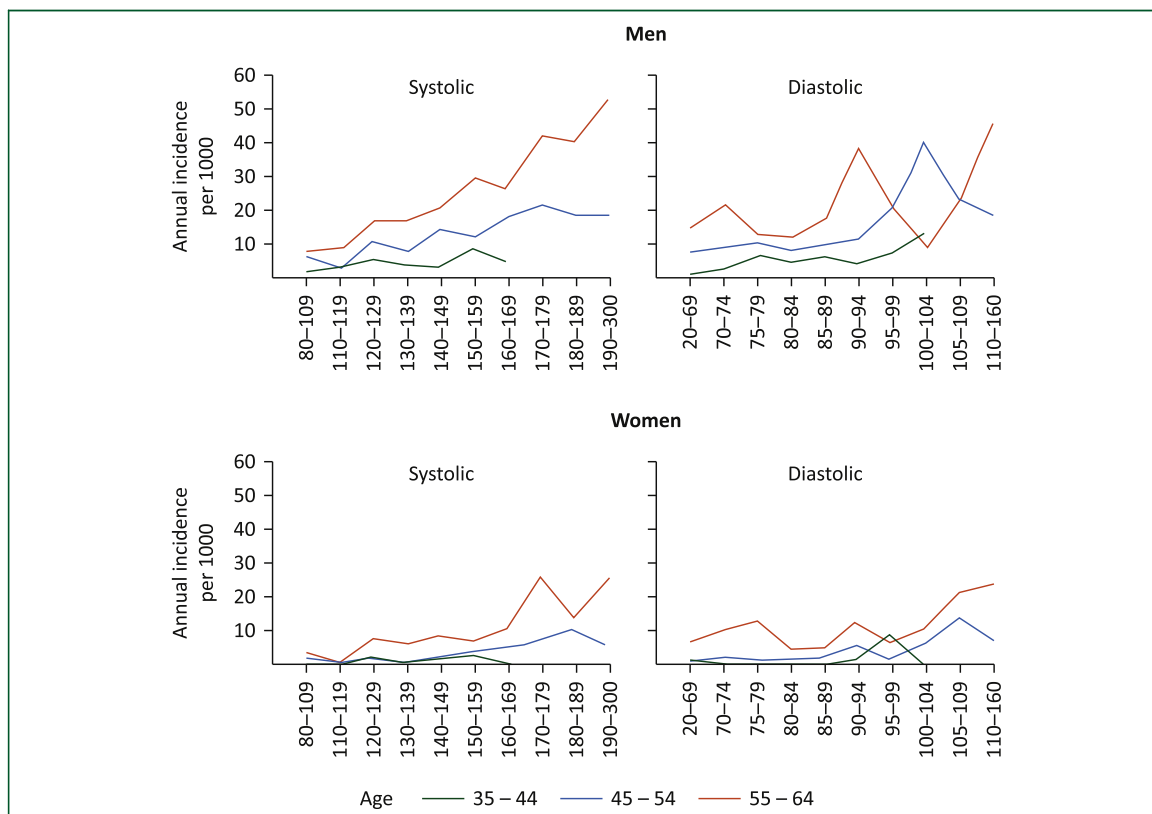
Figure 2 shows descriptively the average annual incidence of CHD over 14 years according to the level of SBP and DBP. Particularly in older men, there is a clearly stronger gradient of risk associated with increasing SBP as opposed to DBP. But because the investigators pointed out

that there was no critical level for SBP or DBP identified, they felt it was necessary to look at the net contribution to risk from the actual level of each of the pressures in further analyses, and in particular for comparing SBP versus DBP, to determine the standardized slopes of the incidence of CHD. In doing this analysis, they found that the standardized slopes for women and or men ages 45 years and over were greater for SBP than for DBP. For example, in those ages 55 to 64 years, the standardized slope of annual incidence of CHD in men was 0.54 for SBP and 0.41 for DBP and for women was 0.69 and 0.41 (all  $p < 0.05$ ). Furthermore, the standardized mean difference of SBP and DBP is another way of demonstrating discriminatory power of these 2 components of BP, and these values were indeed also greater for most age groups in both men and women for SBP as compared to DBP (overall weighted average in men 0.41 for SBP and 0.28 for DBP and for women 0.68 and 0.39). This indicated that the association with CHD was stronger for SBP than for DBP.

This Framingham Heart Study [4] was the first to dispel the notion of DBP being the key BP component associated with hypertensive risk for the majority of middle-aged and elderly subjects that had predominantly systolic hypertension. In contrast, in the pre-antihypertensive treatment era, very high DBP was commonly associated with “malignant” or “accelerated” hypertension—frequently resulting in a rapid, fatal course; however, it was noted that invariably these persons had an accompanying very high level of SBP. Importantly, this Framingham study showed a declining relative importance of DBP and increasing importance of SBP with age; in contrast, only in those under age 45 years was DBP more important than SBP—with the exception of the ominous, malignant/accelerated forms of hypertension, which were very rare in the Framingham cohort. The investigators concluded, “Neither the systolic and diastolic pressure measurements in combination nor the pulse pressure and the mean arterial pressure measurements alone discriminated better than the systolic measurement alone.” Thus, the current practice of assessing the importance of BP at all ages largely based on DBP had to be re-examined. It should be noted historically, however, that it took an additional 20 years (1991) with the publication of the SHEP (Systolic Hypertension in the Elderly Program)—the first randomized controlled trial in an elderly population with isolated systolic hypertension—to prove the value of antihypertensive therapy in reducing cardiovascular morbidity and mortality in persons with isolated systolic hypertension.

#### HEMODYNAMIC PATTERNS OF AGE-RELATED CHANGES IN BP

In 1997, Franklin et al. [5] had the unique opportunity to study age-related changes in SBP, DBP, PP, and MAP with biannual examinations over a 30-year follow-up period in both normotensive and untreated hypertensive subjects from the original Framingham Heart Study, which



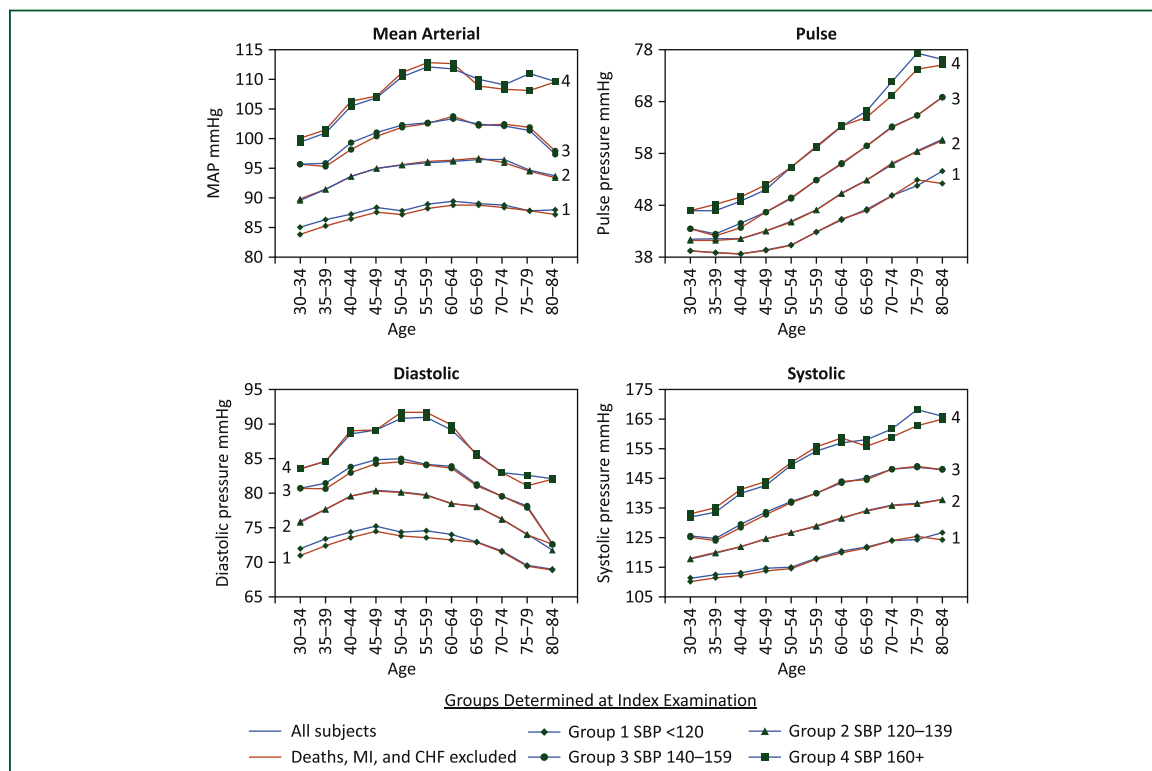
**FIGURE 2.** Average annual incidence of coronary heart disease, 14-year follow-up, according to systolic and diastolic blood pressure, Framingham Heart Study, men and women ages 35 to 64 years. Reprinted, with permission, from Kannel et al. [4].

provided new insight into the importance of PP as a surrogate marker of large artery stiffness with aging. They divided 2,036 participants without CVD or who were not on antihypertensive therapy into 4 SBP groups (Fig. 3). Regression of BP versus age produced slope and curvature estimates for the various BP components: SBP (linear rise), DBP (quadratic pattern), MAP (late asymptote), and PP (late linear rise). After 50 years of age, SBP increased disproportionately to DBP, and after 60 years of age, DBP fell, resulting in a further widening of PP. Age-related linear increases in SBP, PP, and MAP, as well as the curvilinear rise and fall in DBP, were greatest for subjects with the highest baseline SBP.

The Framingham findings also supported the concept of an interaction between aging and hypertension in the progressive fall in DBP and rise in SBP; the changing pattern with aging suggested 3 hemodynamic phases. Under age 50 years, the progressive rise in DBP and SBP suggested the predominance of increased vascular resistance. The constancy of DBP for those in their 50s, together with the asymptotic leveling of MAP and increased slope of PP, suggested increased vascular resistance and large artery stiffness were both increasing in a parallel manner. The fall in DBP during later ages signaled preponderance of large

artery stiffness as the cause of further rise in SBP and, hence, dramatic widening of PP in the elderly. We hypothesized that the age-related stiffening of the aorta was associated with a decreased capacity of the elastic reservoir and, hence, a greater peripheral runoff of stroke volume during systole. Thus, with less blood remaining in the aorta at the beginning of diastole, and with diminished elastic recoil, DBP decreased with increased steepness of diastolic decay.

The “healthy” subjects with a mean baseline BP of 111/70 mm Hg (Fig. 3, group 1) had no rise in PP and only a minimal increase in MAP from age 30 to mid-50 years. Nevertheless, these normotensive subjects showed a significant rise in PP and fall in DBP after age 55 years, presumably caused by an increase in large artery stiffness secondary to aging. In contrast, hypertensive subjects with baseline mean BP of 130/84 mm Hg (Fig. 3, group 4) showed a shallow rise in PP from age 30 years onward, followed by a steeper widening of PP and a steeper fall in DBP after age 55 years than was observed in group 1 subjects. These findings suggest a linkage between hypertension left untreated and the subsequent acceleration of large artery stiffness. Although increased peripheral vascular resistance may initiate essential hypertension,



**FIGURE 3. Arterial pressure components by age: group averaged data for all subjects and with deaths, myocardial infarction (MI), and coronary heart failure (CHF) excluded. Averaged blood pressure levels from all available data from each subject within 5-year age intervals (30 to 34 years through 80 to 84 years) by systolic blood pressure (SBP) groupings 1 through 4. Thick lines represent entire study cohort (2,036 subjects); thin line represents study cohort with deaths and nonfatal MI or CHF excluded (1,353 subjects). Reprinted, with permission, from Franklin et al. [5].**

acceleration of large artery stiffness is the driving force leading to steeper rise in SBP after age 55 years in the hypertensive groups 3 and 4 as compared to the normotensive groups 1 and 2 (Fig. 3).

The clinical implications that can be derived from this study are that, after the sixth decade of life: 1) increasing PP and decreasing DBP are surrogate measurements for large artery stiffness; 2) large artery stiffness rather than vascular resistance becomes the dominant hemodynamic factor in both normotensive and hypertensive subjects; 3) hypertension, left untreated, may accelerate the rate of development of large artery stiffness, which can perpetuate a vicious cycle of worsening hypertension and further increases in large artery stiffness; and 4) these factors may play a role in risk stratification of elderly people and decision making in the selection of treatment modalities.

### IS PP USEFUL IN PREDICTING RISK FOR CHD?

When Kannel et al. [4], in 1971, showed that SBP was superior to DBP as a predictor of CHD in middle-aged and older persons, they concluded that PP added nothing to the discriminating power of SBP; in part, this conclusion

rested on the close correlation between SBP and PP as predictors of CHD. In 1999, when Franklin et al. [6] reexamined this question, using an updated Framingham population, Cox regression analysis was available to allow adjustment for various covariates that might confound results. They studied 1,924 men and women, ages 50 to 79 years at baseline, with no clinical evidence of CHD, not on antihypertensive drug treatment, and with a 20-year follow-up for incident fatal and nonfatal CHD. Cox regression was adjusted for age, sex, body mass index, cigarettes smoked per day, glucose intolerance, and total cholesterol/high-density lipoprotein ratio. Comparison of dual BP component models (Table 2) showed that the combination of DBP and SBP (model 1) showed a modest incremental contribution to risk as compared to SBP alone, whereas a model of the combination of DBP and PP (model 2) or a third model of SBP and PP (model not shown) showed no additional increased risk as compared to PP alone. Thus, when considered jointly in this older age group, SBP was positively associated with risk and DBP was inversely related to risk. Furthermore, when the joint influence of SBP and PP on CHD risk was plotted at 4 different SBP groupings (110, 130, 150, and 170 mm Hg)

**TABLE 2.** BP and CHD risk dual BP component models

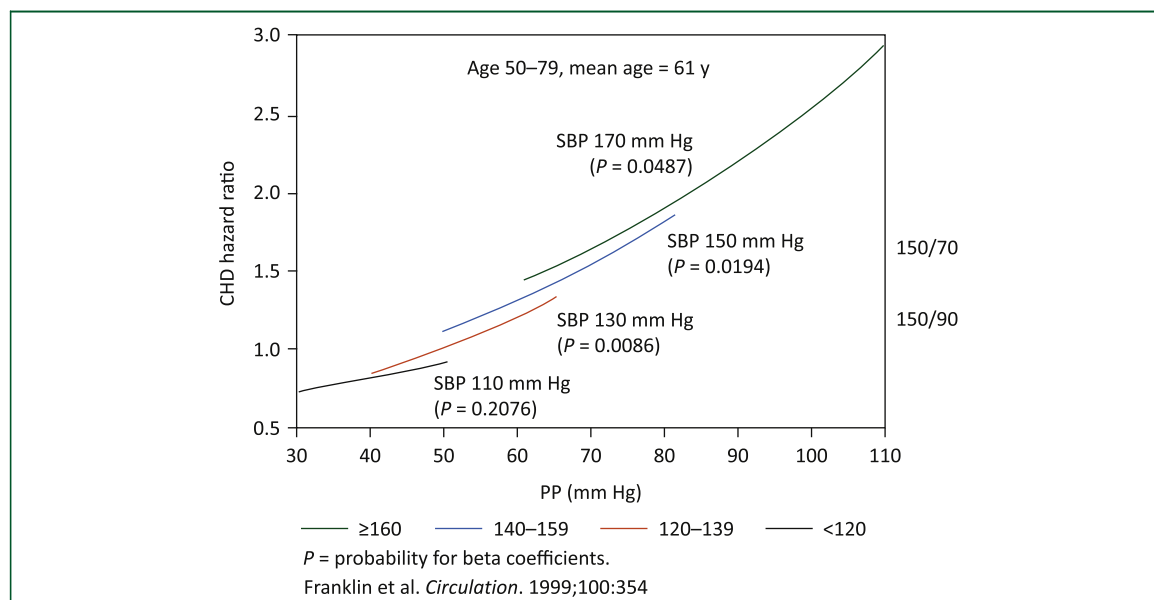
	Chi-Square	Hazard Ratio	p Value
<b>Model 1</b>			
SBP	35.6	1.22 (1.15–1.30)	<0.001
DBP	5.2	0.86 (0.75–0.98)	<0.05
<b>Model 2</b>			
DBP	0.7	1.04 (0.94–1.16)	NS
PP	35.6	1.22 (1.15–1.30)	<0.001

Hazards associated with 10 mm Hg increment in the corresponding BP component. Likelihood ratio statistics are for each BP variable added to a model that contains 1 other BP variable. Associated with a 1-SD increment in the corresponding BP component. Adjusted for age, sex, cigarettes smoked per day, electrocardiograph-detected left ventricular hypertrophy, body mass index, glucose intolerance, and total and high-density lipoprotein cholesterol.  
BP, blood pressure; CHD, coronary heart disease; DBP, diastolic blood pressure; NS, not significant; PP, pulse pressure; SBP, systolic blood pressure.  
Reprinted, with permission, from Franklin et al. [6].

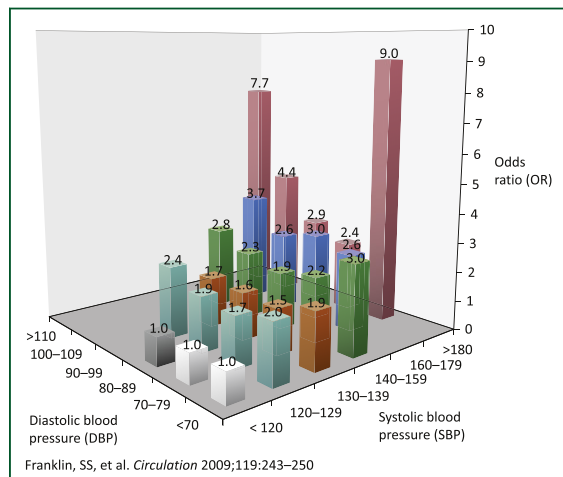
with SBP of 130 mm Hg set to a reference value of 1.0 (Fig. 4), one could examine the influence of risk over a wider range of PP and DBP values. For any given level of SBP  $\geq 130$  mm Hg, subjects with the higher PP (i.e., the lower the DBP) had a considerable increased CHD risk. Indeed, there was a far greater increase in CHD risk with increments in PP without a change in SBP than with increments in SBP without a change in PP.

From these findings, we can hypothesize that CHD risk is more related to the pulsatile stress caused by large artery stiffness during systole than to the steady-state stress due to small-vessel resistance during diastole. Moreover, this concept also explains the paradox of CHD risk being directly related to DBP when considered alone and inversely related to DBP when SBP and DBP were jointly entered in the model. Considered alone, DBP is a measure of vascular resistance. In individuals  $< 50$  years of age, elevation of SBP and DBP are nearly concordant, strongly supporting the major influence of vascular resistance in young adults. In contrast, in middle-aged and elderly people, PP, which is an indicator of large-artery stiffness, becomes the predominant factor predicting CHD risk. These findings suggest that those older subjects with elevated SBP and discordantly low DBP values have by far the greatest CHD risk.

The clinical implications from this study are that in individuals with identical levels of elevated SBP, those with isolated systolic hypertension are at greater risk for CHD than are those with combined systolic-diastolic hypertension (in the absence of malignant/accelerated hypertension). This may have public health implications, because isolated systolic hypertension is the most common type of hypertension among untreated adults  $> 50$  years of age [8]. For middle-aged and older persons, these new findings call into question the prevailing belief that elevations of SBP and DBP contribute equally to CHD risk. Indeed, the age-related changes in PP suggest an interaction between vascular aging and hypertension.



**FIGURE 4.** Joint influences of systolic blood pressure (SBP), and pulse pressure (PP) on coronary heart disease (CHD) risk. CHD heart rates (HR) were determined from level of PP within SBP groups. HR were set to a reference value of 1.0 for SBP of 130 mm Hg and PP of 50 mm Hg and are plotted for SBP values of 110, 130, 150, and 170 mm Hg, respectively. All estimates were adjusted for age, sex, body mass index, cigarettes smoked per day, glucose intolerance, and total cholesterol. Reprinted, with permission, from Franklin et al. [6].

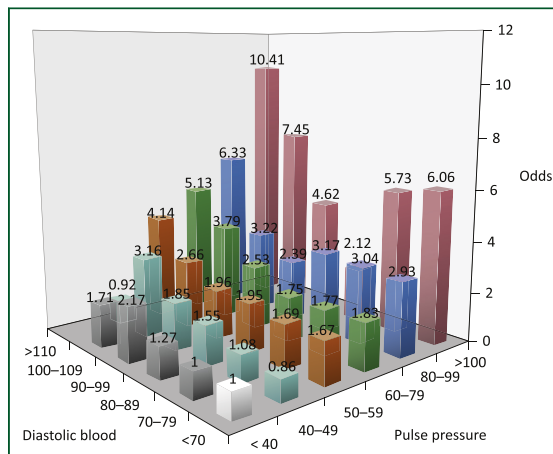


**FIGURE 5.** Odds for the likelihood of a cardiovascular event with combined systolic blood pressure (SBP) and diastolic blood pressure (DBP) categories in a  $6 \times 6$  cross-classification bar graph, adjusted for age, sex, total cholesterol, smoking, body mass index, diabetes, and secular trend. An interaction term of SBP  $\times$  DBP improved the model fit. CI, confidence intervals; CVD, cardiovascular disease. Reprinted, with permissions, from Franklin et al. [8].

Consequently, increased large artery pulsatility has become an important biomarker of CVD.

### SINGLE VERSUS COMBINED BP COMPONENTS AND RISK FOR CVD

When Kannel et al. [4], in 1971, showed that SBP was superior to DBP as a predictor of CHD risk in middle-aged and older persons, they concluded that the discriminating power of DBP when added to SBP or of PP when added to MAP was not superior to SBP alone in predicting CHD risk; however, there remained controversy regarding which BP component was the best predictor of CVD risk overall and whether combined BP components were superior to single ones. We further examined with greater statistical power the CVD predictive value of combined BP components versus single ones in a follow-up report [7] using a Framingham population that consisted of the original ( $n = 4,700$ ) and offspring ( $n = 4,897$ ) cohorts, free of CVD events and without antihypertensive therapy over a 50- versus previous 20-year period. We included 1,439 CVD events that consisted of myocardial infarction, thrombotic and hemorrhagic stroke, heart failure, and CHD and CVD deaths. Furthermore, we used pooled logistic regression to examine 12 serial 4-year intervals from 1952 to 2000, using a new index examination for determining baseline BP for each 4-year cycle; this maximized person-observations (41,525 multiple person-observations).



**FIGURE 6.** Odds for the likelihood of a cardiovascular event with combined pulse pressure (PP) and mean arterial pressure (MAP) categories in a  $6 \times 6$  cross-classification bar graph, adjusted for age, sex, total cholesterol, smoking, body mass index, diabetes, and secular trend. An interaction term PP  $\times$  MAP improved the model fit. Reprinted, with permission, from Franklin et al. [8].

Using the combination of BP components of SBP with DBP and PP with MAP in Figures 5 and 6, respectively, rather than single BP components separately, improved the fit for predicting CVD risk. Introducing the interaction

**TABLE 3.** Prediction of CVD events by JNC-6 staging

JNC-6 Group	BP Limits, mm Hg	SBP/DBP, mm Hg	OR (95% CI)
Optimal	SBP <120 DBP <80	109/69	Ref. = 1.0
Pre-hypertension	SBP 120–139 DBP <70	127/65	2.0 (1.5–2.6)*
Stage 1 ISH	SBP 140–159 DBP 70–89	147/81	2.0 (1.6–2.5)*
	SBP 140–159 DBP <70	147/64	3.0 (2.1–4.3)*
Stage 2 ISH	SBP $\geq$ 160 DBP <90	171/81	3.1 (2.4–4.1)*
Stage 2 SDH	SBP $\geq$ 160 DBP 90–99	172/94	2.7 (2.0–3.6)*
	SBP 160–179 DBP $\geq$ 100	168/106	3.6 (2.5–5.1)*

CI, confidence intervals; CVD, cardiovascular disease; ISH, isolated systolic hypertension; JNC-6, Sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; OR, odds ratio; SDH, systolic-systolic hypertension; other abbreviations as in Table 2.

\* $p < 0.0001$ .

Adapted, with permission, from Franklin et al. [7].

terms in Figures 5 and 6, respectively, further improved the fit over the main effects of the 2-component models, indicating that the effect of 1 BP component on risk varied accordingly to the level of the other. The same results were obtained when BP was treated as a continuous variable. These results confirmed the superiority of combining SBP and DBP as noted in the MRFIT (Multiple Risk Factor Intervention Trial) [9] and extended the findings to older adults and to women.

In the SBP and DBP model, CVD risk increased at both the low and high extremes of DBP when combined with increased SBP in the 2-component model. Therefore, there was a DBP J-curve for CVD risk that was independent of antihypertensive therapy and antecedent CVD events. The J-curve relation to CVD risk that is associated with DBP presumably reflects increased arterial stiffness as manifested by a low DBP and by definition, a wide PP. It was concluded that both 2-component models were superior to any single BP component in predicting CVD risk because they assessed both stiffness and resistance (afterload). When PP, a measure of stiffness, was combined with MAP, a measurement of resistance, one could relate the 2 major physiologic components of hydraulic load to clinical outcome.

In the models based on the “Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure” (JNC-6) categories for SBP and DBP groupings (Table 3), SBP is usually superior to DBP as a predictor of CVD risk; however, very low or very high DBP add to the SBP risk. Indeed, a DBP <70 mm Hg can add approximately 20 mm Hg of SBP risk, in other words, a potential shift from pre-hypertension to stage 1 hypertension or from stage 1 to stage 2 hypertension. In contrast, a DBP  $\geq$ 100 mm Hg versus 90 to 99 mm Hg added considerable increased CVD risk, despite somewhat lower SBP values (Table 3).

The importance of PP as a risk predictor was not emphasized in the 2003 “Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure” (JNC-7) recommendations [10]. The Framingham 2009 findings support the 2007 European Guidelines [11] for the Management of Arterial Hypertension as a high-risk designation when elevated SBP is associated with DBP of <60 to 70 mm Hg and further suggest that the high-risk designation may also apply to those individuals with pre-hypertension and DBP <70 mm Hg. These findings may represent an important insight to guide preventative and therapeutic care. Moreover, recent Framingham analyses by Vasani et al. [12,13] showed that up to one-third of those classified currently by the JNC-7 [10] as pre-hypertensive (previously normal and high normal categories by the JNC-6) would develop clinical hypertension in the next 4 years [12]. They also found that pre-hypertension is associated with increased risk of CVD events [13] and was a major impetus toward the JNC-7 designation of the categorization of pre-hypertension and the plea to healthcare providers to

provide lifestyle advice and modifications to prevent such persons from developing clinical hypertension.

### CLINICAL PERSPECTIVE

The first 60 years of the population-based Framingham Heart Study have contributed greatly to our knowledge of the relation between various BP components and CVD events in general and for CHD in particular. Ten years into the study, there was enough data to show: 1) both mean SBP and DBP rose steadily with age in both men and women; 2) 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; 3) a “white coat” BP effect of 5/4 mm Hg was noted during the first 3 biennial examinations; 4) there was a correlation between BP level and left ventricular hypertrophy by electrocardiogram; and 5) there was a correlation between BP level and CHD that was stronger in men than in women.

Twenty years into the study, Kannel et al. [4], in 1971, noted the following: 1) The relative importance of various indices of BP such as PP, MAP, SBP, and DBP in the prediction of CHD had not been adequately explored. 2) Because SBP and DBP were highly correlated, it was necessary to do a multivariate analysis of each BP component to determine the best predictor of CHD. 3) The standardized mean BP of subjects with and without CHD for each age-sex grouping was determined in order to compare the power of these 2 measures. 4) Kannel et al. then made the seminal observation that while DBP was a stronger predictor of CHD in young people <45 years of age, SBP became the dominant predictor of CHD risk in middle-aged and elderly people.

By about 50 years into the study, there was the unique opportunity to study the natural history of both normotensive and untreated hypertensive subjects over a 30-year follow-up interval with adjustment for covariates and to infer underlying hemodynamic mechanisms from age 30 to 84 years. It was concluded that: 1) after age 55 years of age, SBP increased disproportionately to DBP, and after 60 years of age DBP fell, resulting in a further widening of PP; 2) the increase in PP, in association with the late fall in DBP after age 60 years and the continual rise in SBP, was most consistent with large artery stiffness; 3) PP is a marker for large-artery stiffness; and 4) large-artery stiffness is the dominant factor in the rise of SBP from middle age onward. It was hypothesized that elevated SBP left untreated could accelerate arterial stiffness and thus perpetuate a vicious cycle.

Our further report in 1999 concluded the following: 1) When considered jointly in the older age group, SBP was positively associated with CHD risk and DBP was inversely related. 2) There was a far greater increase in CHD risk with increments in PP without a change in SBP than with increments in SBP without a change in PP. 3) Consequently, PP as a surrogate measure of arterial stiffness, emerged as the best single BP predictor of risk in this older



age group. 4) In middle-aged and elderly subjects, CHD risk increased with lower DBP at any level of SBP  $\geq 120$  mm Hg, suggesting that wide PP was an important component of risk. 5) CHD events are more related to the pulsatile stress of large artery stiffness during systole than steady-state stress of resistance during diastole.

Lastly, in 2009, examination of single versus combined BP components and risk for CVD showed the following: 1) Combined BP models [SBP +DBP or PP + MAP] were similar to each other in predicting risk, but they were clearly superior to any single BP component in risk prediction. 2) PP + MAP had a monotonic relation in predicting risk and, therefore, may give greater insight into the hemodynamics of altered stiffness versus altered peripheral resistance. 3) Only DBP had a quadratic relation to CVD risk so that there was a DBP J-curve in predicting CVD risk. 4) DBP <70 mm Hg in the presence of elevated SBP is a powerful risk factor that is approximately equivalent to a rise of 20 mm Hg in SBP. 5) Current JNC-7 guidelines consider the risk of elevated DBP, but they ignore the increased risk of low DBP.

The original Framingham papers have helped pave the way for the development of BP categories by both the United States' JNC and the European Society for Hypertension. The greater risk conferred by increasing BP levels in the presence of multiple risk factors, as shown originally by Framingham, set the stage for the risk-based classification scheme recommended by the European Society for Hypertension [11]. Both these classifications have been crucial in the development of targets for initiation and goals of BP treatment by these and other societies internationally. We believe our recent Framingham articles [5–7] have set the stage for newer guidelines to place a greater emphasis of PP, isolated systolic hypertension, and low DBP in identifying patients at increased risk of CVD. Perhaps most important, however, is that the Framingham Heart Study has raised awareness regarding hypertension, now the leading cause of mortality globally, for which renewed efforts to reduce sodium intake and improvement in hypertension control are an important focus of cardiovascular societies worldwide.

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