Historical perspective of hypertension from the Framingham Study

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EPIDEMIOLOGICAL INSIGHTS FROM POPULATION RESEARCH

The Framingham Study established the utility of population-based research for finding correctable predisposing conditions for cardiovascular disease (CVD), placing prevention at the frontier of cardiology. It established the risk factor concept for evolving CVD, recognizing that there is no single cause that is essential or sufficient by itself for CVD occurrence. It demonstrated the importance of distinguishing between usual (average) and optimal risk factor levels. The Study corrected clinical misconceptions about hypertensive vascular disease including: the hazard of atrial fibrillation, relevance of diabetes as a macrovascular threat, significance of left ventricular hypertrophy, importance of small amounts of proteinuria, and the role of obesity, and weight gain. Framingham investigation dispelled the concept of "benign essential hypertension", and the greater importance of diastolic blood pressure.

It determined the full clinical spectrum of hypertension-induced CVD including sudden death, stroke, silent coronary and peripheral artery diseases. The study determined CVD incidence attributable to hypertension in the population at a time when only mortality statistics were available, and most recently the lifetime risk. The study provided insights on mechanisms of hypertension-induced CVD.

The Framingham Study devised CVD risk profiles enabling physicians to pull together risk factor information to assess the global risk of heart attacks, heart failure, strokes and peripheral artery disease. Findings of the Study stimulated pharmaceutical industry development of agents for controlling blood pressure, lipids, glucose and smoking, and trials demonstrating efficacy of correcting risk factors such as hypertension. National campaigns against smoking, hypertension, hypercholesterolemia, and obesity were motivated.

MISCONCEPTIONS ABOUT HYPERTENSION

Prior to the Framingham Study, there was a concept of *benign essential hypertension* and a lack of effective and tolerable means for lowering blood pressure, so that emphasis was placed on identifying and treating correctable causes of hypertension. Because of population research at Framingham and elsewhere, routine testing to identify causes of hypertension is no longer recommended unless there are history or physical findings of suggestive of secondary hypertension or blood pressure control can not be achieved. Identifiable underlying causes were found responsible for only a small percentage of the hypertension encountered in clinical practice. One common possible cause now being considered is obesity-induced *insulin resistance or the metabolic syndrome* which may be responsible for a substantial amount of hypertension[1].

Before investigation by the Framingham Study, it was believed that the common variety of hypertension was benign and that it was essential for the blood pressure to rise with age to ensure adequate perfusion of vital organs, hence the label "benign essential hypertension". Its cardiovascular sequelae were believed to derive chiefly from the diastolic pressure component and it was held that the disproportionate rise in systolic blood pressure with age was an innocuous accompaniment of arterial stiffening. Hence it was believed that treatment of isolated systolic hypertension would not only be fruitless but also intolerable and dangerous. The tenaciously held belief in the prime importance of the diastolic pressure was convincingly refuted by Framingham Study data and later confirmed by other prospectively obtained data, demonstrating that the impact of systolic pressure is actually greater than the diastolic component[2,3]. Examination of the increment in CVD risk per standard deviation increment in systolic vs. diastolic blood pressure, to take into account the different range of values for each, indicated

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a consistently greater impact for the systolic blood pressure (Table 1). Also, comparing isolated systolic with isolated diastolic hypertension, it is apparent that isolated systolic hypertension is dominant as a CVD hazard.

Women were thought to tolerate hypertension well, and it was believed that *normal* blood pressures in both sexes were substantially higher in the elderly than in middle-aged persons. Regarding hypertensive cardiovascular hazards, it was held that there were age-related critical thresholds for blood pressure. As indicated in table 2, Framingham Study data indicate that while the hypertensive risk ratios for all the major atherosclerotic CVD events are larger for those under than over age 65 years of age, the incidence of disease is clearly greater in the elderly. Systolic blood pressures formerly regarded as *normal* for the elderly (100 plus age mmHg) were shown to impose a substantial CVD risk. Also while the incidence of all events except stroke in the elderly are lower in women than men, the risk ratios in women are similar to those in men. Thus, neither the elderly nor women were found to tolerate hypertension well.

In the past, initiation of antihypertensive treatment was often delayed until there was evidence of target organ involvement. Framingham Study data indicated that this practice was imprudent because 40-50% of hypertensive persons developed overt CVD prior to evidence of organ damage such as proteinuria, cardiomegaly, or ECG abnormalities.

The concept of the hazard of hypertension was preoccupied with the diastolic blood pressure component since the beginning of the 20th century and even today, there appears to be lingering uncertainty about the CVD impact of the various components of the blood pressure. Influenced by Framingham Study findings, the focus has shifted to the systolic blood pressure and most recently, to the pulse pressure[4]. An increased pulse pressure in advanced age was previously considered an innocuous accompaniment of progressive arterial rigidity. However, assessment of pressure components in the Framingham Study indicated that increments of pulse pressure at any systolic pressure are associated with increased coronary heart disease incidence. Framingham Study investigation found that with increasing age there is a shift in importance from diastolic to systolic and finally to pulse pressure for prediction of coronary heart disease (CHD)[5].

Based on Framingham Study data, the current concept of an *acceptable* blood pressure is now based on what is *optimal* for avoiding hypertension-related CVD rather than on what is *usual* in the population. Epidemiological data from the Framingham Study clearly indicated that at all ages and in both sexes, CVD risk increases incrementally with the blood pressure even within what was perceived as the "normal" range. Similar continuous graded relationships of blood pressure to CHD and all-cause mortality have been reported in several other cohorts[6-8]. There is

Table 1. Risk of Cardiovascular Disease by Systolic vs. Diastolic Blood Pressure. Framingham Study 38-Year Follow-up

Risk Factor Adjusted Increment per Standard Deviation Increase				
Blood Pressure				
	Systolic		**Diastolic**	
Age	**Men**	**Women**	**Men**	**Women**
35-64	40%	38%	37%	29%
65-94	41%	25%	25%	15%
Type of Hypertension				
Age-Adjusted Risk Ratio				
Age	**Isolated Systolic**		**Isolated Diastolic**	
35-64	2.4***	1.9**	1.8*	1.2
65-94	1.9**	1.4**	1.2*	1.6***

Covariates: cholesterol, glucose, cigarettes, ECG-left ventricular hypertrophy.
All Differences in incremental risk significant at $p < 0.001$.
For risk Ratios: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.
Fonte: Kannel WB. Am J Cardiol 2000;85:251-5.

Table 2. Risk of Cardiovascular Events in Hypertension According to Age and Sex; 36-Year Follow-up Framingham Study

	Age 35-64 Years				**Age 65-94 Years**			
	Rate*		**Risk Ratio***		**Rate***		**Risk Ratio***	
Events	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
CHD	45	21	2	2.2	72	44	1.6	1.9
Stroke	12	6	3.8	2.6	36	38	1.9	2.3
PAD	10	7	2	3.7	17	10	1.6	2
CHF	14	6	4	3	33	24	1.9	1.9

** All biennial rates per 1000 at risk and risk ratios are age-adjusted and statistically significant at $p < 0.0001$.*
CHD is coronary heart disease, PAD is peripheral artery disease, CHF is heart failure.

no threshold for blood pressure risk as claimed by some, and in the Framingham cohort 45% of the CVD events in men occurred at a systolic blood pressure < 140 mmHg, the value recently claimed by some to be the threshold of risk[6,9]. Huge data sets are available that can precisely estimate CVD incidence trends in the lower blood pressure range. Both the Multiple Risk Factor Intervention Trial data on over 350,000 men screened and followed for CVD mortality, and the Prospective Studies Collaboration involving almost one million participants and 56,000 vascular deaths found no indication of a threshold of risk down to 115/75 mmHg[7,8]. Persons aged 40-69 years had a doubling of stroke or CHD mortality with every 20/10 mmHg increment of blood pressure throughout its entire range. Recent examination of the relation of non-hypertensive blood pressure to the rate of development of CVD in the Framingham Study found a significant graded influence of blood pressure from optimal (< 120/80 mmHg) to normal (120-129/80-84 mmHg) to high-normal (130-139/85-89 mmHg) among untreated men and women[10]. Compared with optimal pressure, high-normal blood pressure conferred a 1.6 to 2.5 fold age and risk factor adjusted risk of a CVD event (Table 3).

The chief hazard of hypertension was believed to be a stroke. Framingham Study established that although its risk ratio is smaller than for stroke or heart failure, the most common hazard for hypertensive patients of all ages is coronary disease, and in persons under age 65 years, equaling in incidence all the other hypertensive atherosclerotic consequences combined (Table 2). Hypertension was shown to predispose to all clinical manifestations of CHD including myocardial infarction, angina pectoris and sudden death; imposing a 2-3 fold increased risk.

Despite the demonstrated efficacy of treating *systolic* hypertension, poor blood pressure control is overwhelmingly due to failure to control the systolic pressure component[11] (Table 4).

Table 4. Control of Systolic vs. Diastolic Blood Pressure

Framingham Study Participants 1990-1995		
	All Hypertensives	**On Treatment**
Control of:	**(n = 1995)**	**(n = 1189)**
Systolic Blood Pressure (< 140 mmHg)	33%	49%
Diastolic Blood Pressure (< 90 mmHg)	83%	90%
Both (<140/90 mmHg)	30%	48%

Covariates associated with poor systolic BP control: older age, obesity, left ventricular hypertrophy.

Fonte: Lloyd-Jones et al. Hypertension 2000;36:594-9.

Guidelines now place greater emphasis on achieving specified *systolic* blood pressure goals[4].

THE J-CURVE CONTROVERSY

It has been alleged that there is an increased CVD risk at low as well as at high diastolic blood pressure (a so-called J-curve) causing fear of lowering the diastolic blood pressure too much[12,13]. The Framingham Study tested prospectively the hypothesis that the upturn in CVD incidence at low diastolic blood pressure is largely confined to persons with increased systolic pressure and hence reflecting risk from an increased pulse pressure[14]. The10-year risk associated with 951 non-fatal CVD events and 205 CVD deaths was estimated at diastolic pressures of < 80, 80-89, and ≥ 90 mmHg, according to concomitant systolic blood pressure. An increasing tendency for a J-curve relation of CVD incidence to diastolic blood pressure was observed with successive increments in accompanying systolic blood pressure

Table 3. Relation of Non-Hypertensive Blood Pressure Categories

To Development of Cardiovascular Disease				
Framingham Study Subjects Ages 35-90 Years				
10-Year Cumulative Incidence				
BP Category	**Women**		**Men**	
(mmHg)	**Age-adj. Rate**	**HR (CI)**	**Age-adj. Rate**	**HR (CI)**
Optimal (120/80)	1.9%	1	5.8%	1
Normal (120-129/80-84)	2.8%	1.5 (0.9-2.5)	7.6%	1.6 (1-1.9)
High-normal (130-139/85-89)	4.4%	2.5 (1.6-4.1)	10.1%	2 (1.1-2.2)
P for trend across Categories:	**< 0.001**		**< 0.001**	

Stratified by examination. Hazard Ratio (HR) adjusted for age, BMI, cholesterol, diabetes, cigarette smoking.

Fonte: Vasan R et al. N Engl J Med 345:1291.

Rev Bras Hipertens vol.13(4): 243-248, 2006.

(Table 5). In both sexes, a statistically significant excess of CVD events was observed at diastolic blood pressures < 80 mmHg only when accompanied by a systolic pressure > 140 mmHg, and this persisted after adjustment for age and associated CVD risk factors[14]. Persons with this condition of isolated systolic hypertension have been shown to benefit from antihypertensive treatment[15,16]. The hypothesis that this also applies to the subset of the population who have already sustained a myocardial infarction is under investigation in the Framingham Study.

LEFT VENTRICULAR HYPERTROPHY

Hypertrophy of the left ventricle was originally considered to be compensatory, helping the heart deal with a blood pressure overload. Left ventricular hypertrophy was shown by the Framingham Study to be an ominous harbinger of CVD rather than an incidental compensatory response to hypertension, CHD, and heart valve deformity. The Framingham Study showed that left ventricular hypertrophy is an ominous feature of hypertension that independently escalates the risk of future CVD, equivalent to that of persons who already have overt atherosclerotic CVD[17]. It was also shown that increases in voltage and repolarization were associated with further escalation of cardiovascular risk and improvement in these ECG features with reduction in the adverse CVD consequences (Table 6)[18]. ECG evidence of left ventricular hypertrophy characterized by both increase in R-wave voltage and repolarization abnormality was more hazardous than voltage alone (Figure 1). On adjustment for blood pressure the impact of the voltage abnormality, but not the combination including S-T and T-wave changes, disappeared. This suggests that the combination variety of ECG-left ventricular hypertrophy also reflects ischemic myocardial damage.

RISK STRATIFICATION OF HYPERTENSION

Hypertension per se may directly induce encephalopathy, renal insufficiency, and acute heart failure whereas its promotion of accelerated atherogenesis is more complex involving lipid atherogenesis, thrombogenesis, insulin resistance and endothelial dysfunction, all of which are influenced by the established cardiovascular (CVD) risk factors. Evaluation of the hypertensive hazard for development of atherosclerotic CVD requires consideration of other metabolically linked risk factors. Despite the 1.5-2 fold increased risk associated with moderate degrees of hypertension, the absolute hazard is modest, and many persons in this category need to be treated in order to prevent one case of CVD. Efficient selection of mildly hypertensive persons for aggressive treatment with medication requires multivariable global risk assessment of their level of risk. Also, the goal of therapy should be to improve the global risk profile as well as the blood pressure. Targeted therapy,

Table 5. Incidence of Non-fatal Cardiovascular Events by Diastolic Pressure at Specified Levels of Systolic Blood Pressure. Framingham Study Cohorts. Men and Women Ages 35-80 Years

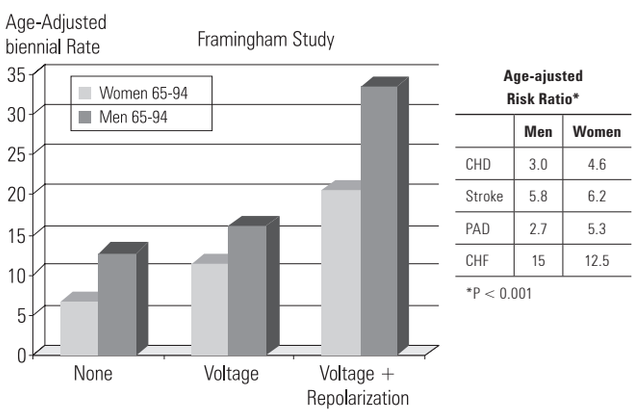
10-year Incidence Rate (%)			
	Systolic Blood Pressure		
Diastolic B.P:	**< 140 mmHg**	**140-159 mmHg**	**≥ 160 mmHg**
< 80 mmHg	7.2	29.8	36
80-89 mmHg	9.2	16.7	29
≥ 90 mmHg	16.2	17.2	27.9

Fonte: Kannel WB et al. Am J Cardiol 2004;94:380-4.

Table 6. Risk of Cardiovascular Events as a Function of Serial Electrocardiographic Changes in Left Ventricular Hypertrophy

	Odds Ratio (95% confidence interval)	
	Men	**Women**
Voltage change*		
Serial voltage decrease	0.46 (0.26-0.84)	0.56 (0.30-1.04)
No change	1	1
Serial voltage increase	1.86 (1.14-3.03)	1.61 (0.91-2.84)
Repolarization changes**		
Improved	0.45 (0.20-1.01)	1.19 (0.56-2.49)
No change	1	1
Worsened	1.89 (1.05-3.40)	2.02 (1.07-3.81)

** Odds ratios for serial voltage changes between examinations are adjusted for age and baseline voltage quartile. ** Odds ratios for serial repolarization changes reflect adjustment for age and baseline repolarization at examination. From Levy et al. Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy. Circulation 1994;90:1786, with permission.*



Fonte: WB Kannel. Hollenberg Hypertension Atlas 2004.

Figure 1. Risk of CVD in Hypertension by Features of ECG-Left Ventricular Hypertrophy

based on a composite risk profile improves the cost-benefit ratio of antihypertensive therapy.

Hypertension was found to occur in isolation of other risk factors in only 20% of patients. Clusters of three or more additional risk factors occur at four times the rate expected by chance[19]. Insulin resistance, induced by visceral adiposity and weight gain, promotes this clustering of associated risk factors. Hypertension is often a consequence of decreased arterial compliance and an insulin resistance syndrome characterized by abdominal obesity, hypertension, glucose intolerance and dyslipidemia[1]. Risk of CVD in persons with hypertension (Figure 2) was shown by the Framingham Study to vary widely according to the associated burden of other risk factors[20].

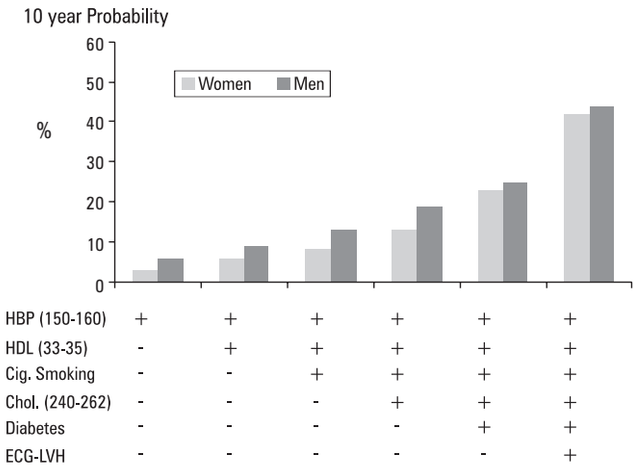
Substantial risk in hypertensive persons with mild to moderate hypertension was shown to be concentrated in those with coexistent dyslipidemia, diabetes, and left ventricular hypertrophy. For stroke, the most feared hazard of hypertension in the elderly, risk was shown to vary over a wide range, reaching substantial proportions when accompanied by diabetes, left ventricular hypertrophy, atrial fibrillation and coronary disease or heart failure. Hypertensive elderly were commonly found to already have target organ damage such as impaired renal function, silent myocardial infarction, strokes, transient ischemic attacks, retinopathy, or peripheral artery disease. At least 60% of older men and 50% of elderly women with hypertension in the Framingham Study had one or more of these conditions.

Instruments for the global assessment of multivariable risk of coronary disease, stroke, peripheral artery disease and heart failure have been produced using Framingham Study data (21-26). This makes it convenient to estimate the global risk of hypertensive patients using ordinary office procedures and standard laboratory tests.

PREVENTIVE IMPLICATIONS

Risk factor alteration has been shown to significantly reduce risk of initial and recurrent atherosclerotic CVD. Hypertension, dyslipidemia and diabetes are best regarded as ingredients of a CVD multivariable risk profile comprised of metabolically linked risk factors because the hazard of each varies widely, contingent upon the associated burden of other risk factors. Maximum CVD risk reduction in hypertensive persons is best achieved by concomitant control of the accompanying burden of risk factors.

Evaluation and treatment of the dyslipidemia that often accompanies hypertension can be guided by the total/HDL-cholesterol ratio, and the aggressiveness of therapy of each linked to the global risk. In evaluation and treatment of hypertension there is no justification for reliance on the diastolic component of the blood pressure. Isolated systolic hypertension and a widened pulse pressure auger ill and need to be treated at



Fonte: Kannel WB. ***European Heart Journal*** 1992;13:34-42.

Figure 2. Risk of CHD in Hypertension by Cluster of Risk Factors: Framingham Study: Subjects 42-48 Years

all ages. Antihypertensive therapy is safe, well tolerated and efficacious for CVD without any penalty of overall mortality. Physicians treating high-risk hypertension can seek out for more aggressive therapy those with preclinical atherosclerotic disease signified by an abnormal ankle brachial index, arterial vascular bruits, coronary artery calcification, left ventricular hypertrophy, a low ejection fraction, silent myocardial infarction, or proteinuria, among others. High risk hypertensive candidates for CVD with an ominous multivariable risk profile indicating a 10-year risk of a CVD event exceeding, for example, 20% require more aggressive risk factor modification. The goal of therapy of hypertension should be linked to the global level of risk. Framingham Study multivariable risk formulations, requiring input of ordinary office procedures and readily available blood tests, are procurable to facilitate office estimation of the hypertensive risk of coronary disease, stroke, peripheral artery disease, and heart failure outcomes[21-26]. Because CVD risk factors usually cluster with hypertension, and the risk imposed by it varies widely in relation to this, multivariable CVD risk assessment is a necessity, especially now that near average blood pressure levels are recommended for treatment. Measures taken to prevent any one CVD hypertensive outcome can be expected to also benefit the others. Novel risk factors deserve attention, but the standard CVD risk factors appear to account for as much as 85% of the CVD arising within the population.

Just as the cardiovascular risk factors identified by the Framingham Study have been found to apply universally, the Framingham multivariable risk functions have been validated and found to have transportability in culturally diverse populations around the world. With calibration[27] they have been to be accu-

rate in low-risk areas such as the Chinese and Spanish populations[28,29]. Health care providers should undertake a multivariable risk assessment whenever a patient is evaluated or treated for hypertension. The laboratory being sent blood samples for testing of blood sugar, or blood lipids, should be encouraged to request the other ingredients of the CVD risk profile, including blood pressure and cigarette smoking and provide a multivariable estimate of risk along with the requested lipid or glucose determination. Serial assessment of global risk can be used to monitor progress of patients on treatment for hypertension. Demonstrating improvement in their multivariable risk score can be used to motivate patients to comply with the recommended preventive management of their hypertension.

The hypertension induced CVD epidemic can not 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 doing procedures more than preventive services. Despite means available to identify high-risk hypertensive candidates for CVD and proof of the efficacy of controlling their blood pressure, goals for prevention of CVD are not often met. Physicians need to more aggressively implement established guideline goals for management of hypertensive dyslipidemic, and diabetic patients at risk of atherosclerotic CVD.

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