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Hypertension: Reflections on Risks and Prognostication

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Framingham study cardiovascular prospective population epidemiological research has played an important role in the evolution of modern cohort study design and the advancement of preventive cardiology. Epidemiological CHD research at the Framingham study evolved the risk factor concept in 1961 indicating that multiple interrelated factors are promoting increased risk of the development of CHD [1]. To date no single essential factor has been identified. Epidemiologists were subsequently induced to conceptualize vascular disease as an outcome of multiple forces, now a critical tenet of modern epidemiology. Such thinking has had clinical, public health, preventive and therapeutic applications. The “risk factor” has become a prime feature of the current epidemiological model and elevated blood pressure has emerged as a prominent member of the major cardiovascular risk factors.

Framingham study population research demonstrated the importance of distinguishing between usual (average) and optimal risk factor levels as *normal and acceptable*. It determined the influence of hypertension on the full clinical spectrum of cardiovascular disease including sudden death, silent and overt myocardial infarction, heart failure and clinical and silent strokes. The study determined population CVD incidence attributable to hypertension at a time when only mortality statistics were available, and most recently, the lifetime risk of developing it and its vascular consequences. The study also provided some valuable insights on mechanisms of hypertension-induced cardiovascular disease. Furthermore, the study’s documentation of a strong linkage of blood pressure to development of cardiovascular events stimulated the pharmaceutical industry to develop medications for controlling blood pressure and to conduct trials indicating their efficacy for reducing elevated blood pressure and its adverse cardiovascular consequences. National campaigns to combat hypertension and its adverse vascular outlook by the American Heart Association, American College of Cardiology, American Society of Hypertension and the National Heart Lung and Blood Institute were then in turn stimulated.

Misconceptions corrected

Control of hypertension and its cardiovascular consequences required the correction of many clinical misconceptions about hypertensive vascular disease such as the significance of left ventricular hypertrophy, importance of small amounts of proteinuria and the role of obesity, and weight gain [2]. Of major importance was the Framingham study investigation dispelling the concept of “benign essential hypertension” and belief in the greater importance of controlling the diastolic than systolic blood pressure. The cardiovascular hazard of hypertension was believed to derive chiefly from the diastolic pressure component

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and it was held that the disproportionate rise in systolic blood pressure with age was an innocuous accompaniment of arterial stiffening. 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 and that even isolated systolic hypertension is dangerous [3,4].

Women were thought to tolerate elevated blood pressure well, and it was held that there were age-related critical cardiovascular risk thresholds for blood pressure so that normal blood pressures in both sexes should be designated at substantially higher levels in the elderly than in the middle-aged. There was a recent attempt to resurrect this faulty concept [5]. However, Framingham Study data soundly refuted this assertion indicating 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 absolute incidence of disease in hypertensive persons was clearly greater in the elderly. Systolic blood pressures formerly regarded as *normal* for the elderly (100 plus age mm Hg) were shown to impose a substantial excess cardiovascular risk. Also, while the absolute 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 [6].

Because of the concept of *benign essential hypertension* and a lack of effective and tolerable means for lowering blood pressure, emphasis in the past was placed on diagnosing and treating causes of secondary hypertension. As result of population research at Framingham and elsewhere, routine testing to identify specific underlying causes of hypertension is no longer recommended unless there are history or physical findings that suggest secondary hypertension or the blood pressure can not be controlled. Identifiable underlying causes were found responsible for only a small percentage of the hypertension encountered in clinical practice.

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 cardiovascular events prior to evidence of target organ damage such as proteinuria, cardiomegaly, or ECG abnormalities.

The perception 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 [7, 8]. An increased pulse pressure in advanced age was previously considered an innocuous feature of progressive arterial rigidity. However, assessment of the implications of blood pressure components by the Framingham Study indicated that increments of pulse pressure at any systolic pressure are associated with increased coronary heart disease incidence. With increasing age there is a shift in importance for risk of CHD from diastolic to systolic and finally to pulse pressure [7].

Framingham Study data has altered the concept of an *acceptable* blood pressure from what is *usual* in the population to what is *optimal* for avoiding hypertension-related cardiovascular disease. Epidemiological data showed that at all ages and in both sexes, cardiovascular disease risk increases incrementally with the blood pressure even within what was perceived as the “normal” range. Similar continuous graded relationships of blood pressure level to

coronary heart disease and all-cause mortality have also been reported in other cohorts [8, 9]. There is no threshold for blood pressure cardiovascular risk as some claim, and in the Framingham cohort 45% of the CVD events in men occurred at a systolic blood pressure <140 mm Hg, the value recently claimed to be the threshold of risk [5]. Huge data sets are available that enable precise estimation of CVD incidence trends in the low 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 blood pressure risk down to 115/75 mm Hg [10, 11]. Persons aged 40–69 yrs. had a doubling of stroke or CHD mortality with every 20/10 mm Hg increment of blood pressure throughout its entire range. A recent analysis of the relation of “non-hypertensive” blood pressure to the rate of development of CVD in the Framingham Study confirmed a significant graded influence of blood pressure from optimal (<120/80 mm Hg) to normal (120–129/80–84 mm Hg) to high-normal (130–139/85–89 mm Hg) among untreated men and women (9). 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 1). Based on these findings the JNC-7 guidelines have defined a “pre-hypertensive” blood pressure category [8].

Commentary on pre-hypertension

Recently, HA Lizko and colleagues examined the CVD outlook for the JNC-7 promulgated prehypertension risk category, confirming that it carries an excess risk in a larger and more generalizable population sample than the Framingham study [12]. The incremental blood pressure risk noted within the prehypertensive range reflects the continuous graded influence of blood pressure without critical values delineating normal from “hypertension”. The Framingham study noted that 80–90% of the prehypertensive population sample had at least one additional cardiovascular risk factor. A weight gain driven tendency for other risk factors to cluster with elevated blood pressure has been well documented by the Framingham Study [13]. CVD risk in the prehypertensive blood pressure range while significantly increased compared to lower blood pressures, is still quite modest. The CVD risk in this prehypertensive blood pressure range increases with the number of associated risk factors present. Hence persons in this category require global risk assessment to select those in need changes of diet, weight control, and amount of exercise. For some with multiple risk factors predicting a high multivariable risk, antihypertensive monotherapy along with control of the other risk factors can be justified. Only by using multivariable risk assessment is it possible to avoid needlessly alarming or falsely reassuring these prehypertensive patients and subjecting them to therapy they do not require.

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) generating fear of lowering the diastolic blood pressure too much [14, 15]. 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]. The 10-yr. risk associated with 951 non-fatal CVD events and 205 CVD deaths was estimated at diastolic pressures of <80, 80–90, and ≥90 mm Hg, 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 (Fig. 1). 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 mm Hg, and this persisted after adjustment for age and associated CVD risk

factors [14]. This finding is corroborated in the large MRFIT data set [11, 16]. Persons with this condition of isolated systolic hypertension have been shown in the large SHEP and Syst-Eur trials to safely benefit from antihypertensive treatment [17, 18].

Left ventricular hypertrophy

The Framingham study has for a long time advocated use of ECG data for CVD risk assessment. Unfortunately the ECG is now often looked upon as an anachronism (compared to the echocardiogram) when it comes to assessing ominous left ventricular hypertrophy. The original Framingham multivariable CVD risk profiles included ECG-LVH until the guideline committees decided it was too insensitive, too low in prevalence and poorly defined for clinicians to use. However, the ECG is more available, less labor intensive and less costly than the more elegant echocardiogram. When present, ECG abnormalities such as LVH, NSA, IV Block and unrecognized MI, are important contributors for cardiovascular risk assessment. 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 [19, 20]. It was also shown that increases in voltage and repolarization were associated with further escalation of cardiovascular risk and decreases with reduction in the adverse consequences. [21].

Electrocardiographic Abnormalities

Hypertension, particularly when associated with left ventricular hypertrophy, promotes ventricular premature beats. The Framingham study evaluated the prevalence and prognostic significance of asymptomatic complex or frequent ventricular premature beats detected during ambulatory electrocardiographic monitoring of surviving participants of the Framingham Study cohort and offspring of the original cohort [22]. Those men without coronary heart disease with such premature beats on one-hour ambulatory electrocardiography, after adjusting for age and traditional risk factors for coronary heart disease, were at significantly increased risk for both all-cause mortality (relative risk, 2.30) and the occurrence of myocardial infarction or death from coronary heart disease (relative risk, 2.12). Curiously, in men *with* coronary heart disease and in women with and without coronary heart disease, complex or frequent arrhythmias were not associated with an increased risk for either outcome.

The age-adjusted prevalence of complex or frequent arrhythmia (more than 30 ventricular premature complexes per hour or multiform premature complexes, ventricular couplets, ventricular tachycardia, or R-on-T ventricular premature complexes) was as high as 12% in the 2425 men without clinically evident coronary heart disease and 33% in the 302 men with coronary heart disease. The corresponding values in women (3064 without disease and 242 with disease) were 12% and 26%.

Thus in men without clinically overt coronary heart disease, the incidental detection of ventricular ectopy is associated with a twofold increase in the risk for all-cause mortality and myocardial infarction or death due to coronary heart disease. The preventive and therapeutic implications of these findings await further investigation. [22].

The risk of developing overt coronary heart disease was also examined in relation to occurrence of non-specific electrocardiographic S-T and T-wave abnormalities in the Framingham Study [23]. In the course of follow-up, 14% of the 5127 men and women

participating in the Framingham study had or developed non-specific ECG abnormalities without clinically apparent intervening coronary heart disease. During 30 years of surveillance, 760 men and 578 women developed a first overt clinical manifestation of coronary heart disease. Non-specific ECG abnormality appeared to be a hallmark of a compromised coronary circulation predicting the occurrence of every clinical manifestation of coronary heart disease independently of known risk factors including hypertension, its chief determinant. Coronary morbidity and mortality was increased twofold in each sex. The more common T-wave abnormality alone carried a significant increased risk, although the combination of S-T and T-wave appeared most hazardous [23].

Many studies have shown positive associations between *heart rate* and both all-cause and cardiovascular mortality. These relationships, however, were not investigated in persons with hypertension until the Framingham Study did so using 36-year follow-up data evaluated from 4530 subjects, aged 35 to 74, whose blood pressures were ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic and who were not on antihypertensive medication. On pooled logistic regression analysis it was found that for each of 40 beats/min heart rate increment (adjusted for age and systolic blood pressure), all-cause mortality increased 2.2 fold for men and 2. fold for women. Cardiovascular mortality increased 1.7 fold in both men and women. Exclusion of outcomes in the first 2 or 4 years after measurement of heart rate did not materially change the results, suggesting that rapid heart is not merely an indicator of preexisting illness. Consequently, heart rate on ECG examination is a useful independent risk factor for cardiovascular mortality in persons with hypertension [24].

The clinical implications of newly acquired *left bundle-branch block* were investigated prospectively in the Framingham Study population [25]. During 18 years of observation 55 subjects developed LBBB. The mean age at the onset was 62; the LBBB occurring largely in participants with antecedent *hypertension*, cardiac enlargement, coronary heart disease, or a combination of these. Coincident with or subsequent to the onset of LBBB, 48% developed clinical coronary disease or congestive failure for the first time. Throughout the entire period of observation only 11% with this intraventricular conduction abnormality remained free of clinically overt cardiovascular events. Within 10 years of the onset of LBBB, 50% died from cardiovascular diseases. In men, the ECG evidence of LBBB contributed independently to an increased risk of cardiovascular disease mortality [25]. Comparison with age- and sex-matched control subjects free from LBBB confirmed that in the general adult population, newly acquired LBBB is most often a hallmark of advanced hypertensive or ischemic heart disease, or both.

Consequently it is no surprise to learn that recent Women's Health Initiative data support the utility of the ECG for CV risk assessment [26]. Abnormalities in the electrocardiograms of 14,749 healthy women were found to predict increased risk of cardiovascular events and mortality. Women with minor abnormalities had a 55% increased risk of an event, and those with major abnormalities had a 3-fold increase in risk.

Unrecognized Myocardial Infarction

Hypertension is a powerful risk factor for the occurrence of a myocardial infarction. An investigation of the occurrence of unrecognized infarctions by blood pressure status was undertaken by the Framingham Study. This counter-intuitively found that the proportion of infarctions that were unrecognized was substantially *greater* in hypertensive than normotensive persons. As many as 35% of infarctions in hypertensive men and 50% of such infarctions in women of the Framingham study went unrecognized [27]. The high proportion of unrecognized infarctions amongst hypertensive persons persisted on adjustment for antihypertensive treatment, diabetes and ECG-left ventricular hypertrophy (Table 2). This

important finding appears to have escaped the notice of guideline crafters and prevention-minded physicians. Risk of all clinical manifestations of coronary disease is increased in hypertensive persons, particularly unrecognized myocardial infarctions, necessitating periodic ECG surveillance to detect them.

Cardiovascular hazards

Hypertension ((140/90 mm Hg) increases atherosclerotic CVD incidence on average, two-to three-fold. The chief hazard of hypertension is often believed to be a stroke. Framingham Study established that although its risk ratio is smaller than for stroke or heart failure, coronary disease is the most common hazard for hypertensive patients of all ages [2]. Hypertension predisposes to all clinical manifestations of CHD including myocardial infarction, angina pectoris and sudden death; imposing a 2–3 fold increased risk. For hypertension induced strokes, the risk ratio for intracerebral hemorrhage was thought to be greater than for an atherothrombotic brain infarction. This proved to be incorrect; hypertension was found to be as strong a risk for atherothrombotic brain infarction as intracerebral hemorrhage [28]. It was also widely believed that mild hypertension promotes brain infarctions whereas severe hypertension induces intracerebral hemorrhage. Framingham study investigation indicated that the preponderance of hypertension related strokes were atherothrombotic brain infarctions whether the hypertension was severe (70%) or mild (56%). The proportion of strokes due to hemorrhage in mild hypertension (5%) was virtually identical to that for severe hypertension [28].

Risk stratification of hypertension

There is a need for greater use of risk stratification of hypertension in order to determine the type and intensity of treatment that is most appropriate. Hypertension per se can 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 blood pressure and its accompanying established cardiovascular risk factors. Evaluation of the hypertensive hazard for development of atherosclerotic CVD requires consideration of other metabolically linked risk factors. Hypertensive persons often have increased triglycerides, small-dense LDL-cholesterol, reduced HDL-cholesterol, elevated blood glucose and visceral adiposity, the combination of which has been characterized as a *metabolic syndrome*. This cluster of risk factors derived from insulin resistance induced by weight gain and visceral adiposity, greatly augments the cardiovascular hazard of elevated blood pressure. These other risk factors should be routinely sought in all patients with elevated blood pressure because of the tendency for clustering, and the great influence that these coexistent risk factors have on the CVD hazard imposed by an elevated blood pressure.

Hypertension occurs in isolation of the aforementioned metabolically linked risk factors in only about 20% of patients. The size of the cluster of accompanying risk factors mirrors weight gain and loss [29]. High-risk hypertension is that accompanied by one or more of the following: dyslipidemia, glucose intolerance, left ventricular hypertrophy, visceral adiposity, proteinuria, cardiomegaly, sinus tachycardia or insulin resistance. The urgency for and choice of treatment should take into account these associated risk factors as well as the character and severity of the blood pressure elevation.

Because moderate blood pressure elevations are much more prevalent than severe elevations, a large fraction of the CVD attributable to hypertension derives from seemingly trivial elevations of blood pressure. Despite the 1.5–2.0 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, based on a composite risk profile improves the cost-benefit ratio of antihypertensive therapy.

Hypertension was found to occur in isolation of other standard risk factors in only 20% of patients. Clusters of three or more additional risk factors occur at four times the rate expected by chance [30]. Hypertension is often a consequence of decreased arterial compliance and an insulin resistance metabolic syndrome characterized by abdominal obesity, hypertension, glucose intolerance and dyslipidemia. Abdominal obesity also imposes a natriuretic penalty that may increase sensitivity to salt intake promoting a rise in blood pressure [31] (Table 3). Risk of CVD in persons with hypertension was shown by the Framingham Study to vary widely depending on the size of the associated burden of other risk factors [30].

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 crafted using Framingham Study data [32–37]. Recently a global risk assessment instrument for predicting total CVD has been produced [38]. This makes it convenient to estimate the global risk of hypertensive patients using ordinary office procedures and standard laboratory tests..

Guidelines Vs global risk assessment for antihypertensive therapy

Various guidelines and numerous updates of guidelines have been promulgated to refine the definition of hypertension and improve its treatment for prevention of the adverse cardiovascular consequences it promotes [8, 39–41]. In response to clinical trials showing efficacy of treating milder degrees of hypertension lower and lower blood pressure goals have been set. Recent guidelines have also factored in the coexistence of associated conditions and *compelling indications* into therapeutic decisions for more aggressive BP lowering and individualized antihypertensive therapy for *diabetes, chronic renal disease, post-MI, recurrent stroke prevention* [8].

Despite advocacy of these revised guidelines by prestigious organizations, it appears that the recommendations are not being acceptably implemented in clinical practice. A Framingham Study assessment of control of systolic and diastolic blood pressure by the physicians of participants in that cohort found that 50% of hypertensive persons referred for treatment do not have blood pressure levels at the recommended systolic blood pressure goals [42]. Also, diastolic pressures were being better controlled than systolic pressures. A survey of self-reported hypertension rates from NHANES data over the past decade suggests an *increase* in hypertension prevalence with only 31% achieving target goals of adequate control [43]. A survey of hypertension management of veterans with diabetes found that more aggressive therapy of blood pressure is needed because 73% had blood pressures above 140/90 mm Hg. Persons with diabetes received *less* intensive therapy than those without diabetes and this

was not attributed distraction by the need to treat the diabetes itself [44]. Compliance with guidelines for treatment of dyslipidemia with hypertension is also suboptimal [45].

It is uncertain why there is such a high failure rate in achieving adequate blood pressure control. One possibility is that physician inertia may be disenchanted by multiple complex sets of guidelines, each targeting a specific risk factor. It appears that multiple iterations of guidelines may be too difficult for the average primary care physician to keep up with, let alone remember and implement. Understandingly, guidelines may be unable to take into consideration all the diverse problems clinicians encounter in practice such as patients under treatment with medications for a variety of coexisting medical conditions. The JNC-7 hypertension guideline modifications recommends reclassification of blood pressure categorizing prehypertension as stage 1 hypertension and renaming current stage 1 and stage 2 hypertension categories to stage 2 and 3, respectively and introducing further complexity into the guidelines by utilizing ill-defined “early disease markers” and “target organ disease” and “vascular damage” to develop a risk algorithm for therapy [8]. Practicing clinicians may have difficulty in applying and adhering to such guidelines.

It is now evident that it is the degree of blood pressure elevation that promotes cardiovascular disease, and not arbitrarily defined “hypertension stages”. Cardiovascular risk increases incrementally with the blood pressure with no critical blood pressure values defining risk stages. Furthermore, blood pressure is best regarded as one component of a multivariable cardiovascular risk profile because at any level of blood pressure the cardiovascular disease risk varies widely in relation to the number accompanying risk factors [30]. It is therefore advantageous to link the aggressiveness of blood pressure lowering therapy to the level of multivariable cardiovascular disease risk. This policy has become critical because near average levels of blood pressure are now recommended for treatment of high-risk persons [8]. Because the number needed to treat to prevent one cardiovascular event is inversely proportional to the level of absolute cardiovascular disease risk, only in this way is it possible to efficiently target the population segment with moderate blood pressure elevation for treatment. Trials specifically testing the efficacy of multivariable risk-linked therapy (compared to therapy disregarding absolute cardiovascular risk) are lacking, nevertheless it seems eminently likely that such an approach would prove more cost-effective and efficacious. Actually, many clinical trials have tested the hypothesis that treatment of hypertension is most effective in patients with multiple risk factors and higher risk of CVD events. For example, using the AHA multiple risk factor equation on data from Systolic Hypertension in the Elderly Program, a global CVD risk score was calculated for 4,189 participants free of cardiovascular events and in 264 participants with cardiovascular disease at baseline. Cardiovascular event rates in the placebo group were progressively higher in relation to higher quartiles of predicted cardiovascular risk. The protection afforded by treatment was similar across quartiles of risk, but the number needed to treat to prevent one cardiovascular event decreased progressively at higher predicted CVD risk quartiles [46].

The absolute long-term benefit associated with a 12 mm Hg reduction in blood pressure over 10 years was estimated by Ogden et al according to the JNC VI risk stratification system using data from the NHANES follow-up study. As expected, the number needed to treat to prevent a CVD event/death was reduced in relation to increasing levels of blood pressure in each of the risk strata and furthermore, the number needed to treat was much smaller in persons with one or more additional major cardiovascular risk factors compared to those without additional risk factors. This analysis demonstrates that the absolute benefit of antihypertensive therapy depends, not only the level of blood pressure, but also on the presence or absence of additional risk factors [47]. It is also virtually certain that a subgroup analysis of existing trials of antihypertensive therapy using competing drugs would show

that the therapy was more effective in those with dyslipidemia or impaired glucose tolerance (which most hypertensive patients have) compared to those without these conditions.

The ATP III lipid guidelines have linked the treatment of dyslipidemia to the Framingham coronary heart disease multivariable risk algorithm thereby simplifying the process of risk assessment [48]. It is likely that such a multivariable assessment applied to hypertension will result in better risk assessment and control of hypertension and more appropriate targeting of antihypertensive therapy.

Framingham multivariable risk evaluation tools exist for evaluating hypertensive hazards for developing coronary disease, stroke, heart failure, peripheral artery disease and most recently, total cardiovascular disease [32–38]. The Framingham study has recently crafted a global total CVD risk assessment instrument [38] that enables risk assessment in hypertensive persons based on the standard major risk factors which tend to cluster with hypertension (Table 4). This profile was also shown to be a robust predictor of each of its components. Furthermore, a simplified version substituting BMI for the laboratory components, was also produced which can be used to target high risk CVD candidates for the more complete profile (Table 5).

Framingham Study investigation of the major risk factors, including hypertension, has long contended that each risk factor needs to be dealt with as ingredients of a multivariable cardiovascular risk profile because each is often accompanied by a cluster of other metabolically linked risk factors that markedly influence their cardiovascular. Guidelines for all these individual risk factors need to be coalesced to reflect the goal of reducing global cardiovascular risk rather than correction of an individual risk factor. Since all the risk factors for which guidelines are being formulated are contained in the Multivariable CVD risk formulations (eg. blood pressure, dyslipidemia, diabetes) the time has come to consider abandoning multiple complex guidelines, each targeting individual risk factors, shifting instead to multivariable cardiovascular formulations for risk assessment and goals for therapy. This provides a less complex means for hypertensive risk assessment than the current guidelines.

Risk factors predisposing to hypertension

An assessment of the frequency of progression to hypertension in participants in the Framingham study cohort without hypertension was undertaken to establish the best frequency of blood pressure screening by assessing the rates and determinants of progression to hypertension [13]. It was found that patients with optimum (<120/80 mm Hg), normal (120–129/80–84 mm Hg), and high normal (130–139/85–89 mm Hg) blood pressure commonly progress to “hypertension” (>140/90 mm Hg). In subjects below age 65 years a stepwise increase in hypertension incidence occurred across three non-hypertensive blood pressure categories; 5.3% of participants with optimum blood pressure, 17.6% with normal, and 37.3% with high normal blood pressure progressed to hypertension over 4 years. Corresponding 4-year rates of progression to hypertension for subjects 65 years and older were 16.0%, 25.5%, and 49.5% respectively (Table 6). Obesity and weight gain greatly contributed to progression; a 5% weight gain on follow-up was associated with 20–30% increased odds of developing hypertension. The finding that high normal and normal blood pressure frequently progress to hypertension over a short period (4 years), especially in older adults, support recommendations for yearly monitoring of persons with high normal blood pressure and monitoring those with normal blood pressure every 2 years. The data also indicate the importance of blood pressure monitoring in the obese and emphasize the importance of weight control for primary prevention of hypertension.

In fact, a number of population determinants of hypertension have been documented. A high-normal systolic blood pressure is 2–3 times more likely to progress to “hypertension”. A 5% increase in *Obesity and weight gain* is associated with 20–30% increase in odds of developing hypertension. *Arterial stiffness* disproportionately increases systolic pressure causing increased pulse pressure and isolated systolic hypertension. High intake of salt promotes hypertension in salt-sensitive persons. *Low circulating natriuretic peptides* associated with increased activation of the sympathetic renin-angiotensin system results in hypertension. Elevated *aldosterone* causes excessive renal sodium retention, K-wasting and blood volume expansion resulting in hypertension.

The Framingham study has crafted a risk assessment instrument for predicting likelihood of developing hypertension from the following ingredients: sex, parental history of hypertension, BMI, smoking, systolic and diastolic blood pressure in the normotensive range (Table 7). In multivariable analysis each of these variables were significant predictors of hypertension. According to the risk score derived from these predisposing factors, the 4-year incidence of hypertension was deemed low (< 5%) in 34% of participants, medium (5–10%) in 19% and high (>10%) in 47%. The risk score needs to be validated in other cohorts and is based on single measurements of risk factor and blood pressure. However, such a risk factor scoring instrument can be used to refine management of prehypertensive persons [49].

Addition of natriuretic peptides and aldosterone to this hypertension risk algorithm could further enhance its predictive value. The prevalence of hypertension is strongly related to the degree of obesity. Risk of developing hypertension in overweight or obese subjects of the Framingham Study Offspring Cohort was 3-fold increased. As much as 59% of the hypertension developing in men and 42% in women ages 20–49 years was found to be attributable to overweight and obesity. As people gain weight their blood pressure rises, and as they lose weight it falls. Obesity appears to impose a natriuretic handicap because both BNP and N-ANP decline with increase in weight leaving overweight and grossly obese persons with low natriuretic peptide levels. This imposed natriuretic handicap could well contribute to the susceptibility of obese persons to hypertension and its cardiovascular sequelae [31].

Preventive implications

Because modifiable risk factors predisposing to hypertension have been identified and hypertension risk assessment algorithms have been developed we now have an opportunity to prevent much of hypertension itself as well as its cardiovascular consequences [49]. This opportunity should be acted upon.

Moderate blood pressure elevations are much more prevalent than severe elevations, so that a large fraction of the CVD in the population is attributable to seemingly trivial elevations of blood pressure. Because the absolute hazard associated with moderate degrees of hypertension is modest, and many persons in this category need to be treated in order to prevent one CVD event, efficient selection of mildly hypertensive persons for treatment with medication requires multivariable global risk assessment. The goal of therapy should be more to improve the global risk profile than the blood pressure level per se. Targeting therapy based on a composite risk profile should be used to improve the cost-benefit ratio of antihypertensive therapy for the prehypertensive patient.

Despite the fact that it is now firmly established that systolic blood pressure exerts a greater influence on CVD incidence than diastolic blood pressure (particularly in the elderly) control of systolic pressure still lags behind diastolic blood pressure control (ref Lloyd-Jones). We need to investigate why physicians still regard the diastolic blood pressure as the chief culprit in hypertension. There is also unjustified fear of aggressive treatment of

systolic hypertension because of an apparent excess CVD risk at low diastolic blood pressure (the J-curve). This apprehension is unfounded because the excess of CVD observed at low diastolic blood pressure is confined to those with a high pulse pressure incriminating the pulse pressure. The SHEP and Syst-Eur trials have shown that treatment of elderly patients with isolated systolic hypertension and therefore a disproportionately low diastolic pressure and increased pulse pressure are benefited by treatment without penalty of feared intolerable side effects [17, 18]. Isolated systolic hypertension and a widened pulse pressure auger ill and need to be treated at all ages. Such antihypertensive therapy is safe, well tolerated and efficacious for CVD without any penalty of overall mortality.

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 is important and can be guided by the total/HDL-cholesterol ratio, and the aggressiveness of therapy of both the hypertension and dyslipidemia linked to the global CVD risk.

Physicians treating hypertension can also 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, other ECG abnormalities, 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 CVD risk. Because CVD risk factors usually cluster with hypertension, and the risk imposed by it varies widely in relation to this, such multivariable CVD risk assessment is a necessity, especially now that near average blood pressure levels are recommended for treatment. Measures taken to prevent any particular 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 with calibration in culturally diverse populations around the world. [27]. The risk profiles have been shown to be accurate even in low-risk areas such as the Chinese and Spanish populations [50, 51].

Health care providers might be encouraged to undertake multivariable risk assessment whenever a patient is evaluated or treated for hypertension if laboratories being sent blood samples for testing of blood sugar, or blood lipids, could 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 CVD 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 better 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 and associated risk factors, goals for prevention of CVD are not often met. There is an unmet 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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Figure 1. CVD Incidence by Diastolic Blood Pressure According to Systolic Blood Pressure Framingham Study Cohorts

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Table 1

Relation of *Non-HBP* Blood Pressure to CVD
Framingham Study Subjects, Ages 35–90 Yrs.

10-yr. Cumulative Incidence				
Blood Pressure	Women		Men	
	Age-adj. Rate	H.R.	Age-adj. Rate	H.R.
<120/80 mm Hg	1.9%	1.0	5.8%	1.0
120–129/80–84 mm Hg	2.8%	1.5	7.6%	1.3
130–139/85–89 mm Hg	4.4%	2.5	10.1%	1.6
	P<.001		P<.001	

H.R.=Hazard Ratio adjusted for age, BMI, Chol., Diabetes and Smoking.

Vasan R et al. N Engl J Med 2001; 345:1291–1297

Table 2

Myocardial Infarctions *Unrecognized* by Hypertensive Status
Framingham Study Cohort. Age-adjusted.

HBP Status	Percent Unrecognized			
	Excluding Diabetics		Excluding Anti-HBP RX	
	Men	Women	Men	Women
Normal	18	30	18	27
Mild	28	36	30	36
Definite	33	48	35	49

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Table 3

Influence of Obesity on Odds of Low Plasma Natriuretic Peptides

<i>Risk Factor Adjusted Odds Ratios</i>				
BMI	Low BNP		Low N-ANP	
	Men	Women	Men	Women
Normal(<25)	1.00	1.00	1.00	1.00
Overweight (25–29)	1.64 **	1.43 *	3.47 ***	1.89 ***
Obese (≥30)	2.51 ***	1.84 ***	4.81 ***	2.85 ***

Odds Ratios adjusted for: age, prior MI, AF, diabetes, smoking, blood pressure, serum creatinine, left atrial size, left ventricular systolic function, left ventricular mass.

* P<.05,

** P<.01,

*** P<.001

Low BNP= 4 pg/mL, low N-ANP= < 195 pmol/l

Wang TR et al. Framingham Study Circulation 2000; 109:594–6000

Table 4

Framingham Study CVD Risk Profile for Men

Points	Age	HDL-C	T. Chol.	SBP	SBP Rx'd	Smoker	Diabetic
-2		60+		<120			
-1		50-59					
0	<35	40-49	<160	120-120	<120	No	No
1		35-44	160199	130139			
2	35-39	<35	200-239	140-159	120-129		
3			240-279	160+	130-139		Yes
4			280+		140-159	Yes	
5	40-44				160+		
6	45-49						
7							
8	50-54						
9							
10							

Points	Risk %	Points	Risk %	Points	Risk %	Points	Risk %
3	<1	2	2.4	7	5.9	12	13.9
-2	1.2	3	2.9	8	7.0	13	16.4
-1	1.4	4	3.5	9	8.3	14	19.2
0	1.7	5	4.1	10	9.9	15	22.6
1	2.0	6	4.9	11	11.7	16	26.4

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Table 5

Framingham Simplified CVD Risk Profile for Men

Risk Factor	Points:1	2	3	4	5	6	7	8	9	10
Age (yrs)	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75+
Systolic BP (untreated)	130–139	140–159	160+							
Systolic BP (treated)		120–129	130–139	140–149	160+					
BMI	25–30	>30								
Smoker				Yes						
Diabetes		Yes								

Points	Risk	Points	Vasc Age
1	2.8%	1	35
2	3.3%	2	37
3	4.0%	3	39
4	4.7%	4	41
5	5.6%	5	44
6	6.7%	6	46
7	8.0%	7	49
8	9.5%	8	52
9	11.2%	9	55
10	13.3%	10	58
11	15.7%	11	62
12	18.5%	12	65
13	21.7%	13	69
14	25.4%	14	73
15	29.6%	15	78
16+	>30%	16	>80

D'Agostino RB et al. Circulation 2008; 117:743–753

Table 6

Development of Hypertension by Non- Hypertensive Blood Pressure Status

<u>Baseline BP (mm Hg)</u>	<u>HBP Rate</u>	<u>Odds Ratio</u>
Optimum (<120/80)	16 %	referent
Normal (120–129/80–84)	25.5%	2.0 (1.4–2.7)
Hi-Normal (130–139/85–89)	49.5%	5.5 (4.0–7.4)

4-Yr. HBP Rate Adjusted for: age, sex, BMI, systolic and diastolic BP. Framingham Study subjects age 65–94 yrs.

Vasan RS et al. Lancet 2001; 358:1682–1686.

Table 7

Framingham Study Risk Score Predicting HBP

SBP (mm Hg)	Points
<110	-4
110-114	0
115-119	2
120-124	4
125-129	6
130-134	8
135-139	10

AGE	DBP (mm Hg)				Points		
	<70	70-74	75-79	80-84	85-89		
20-29	-7	-2	0	3	5		
30-39	-4	0	2	4	6		
40-49	-1	2	4	6	7		
50-59	2	5	6	7	8		
60-69	5	7	8	8	9		
70-79	9	9	9	10	10		

Sex	Points	Smoking	Points
Men	1	No	0
Women	0	Yes	1

Parental HBP	Points	BMI	Points
None	0	<25	0
One	1	25-29	1
Both	2	> 30	3

Points	4-Yr. Risk
<0	< 1.0%
0	1.2%

Points	4-Yr. Risk
1	1.4%
2	1.7%
3	2.1%
4	2.5%
5	3.0%
6	3.6%
7	4.4%
8	5.2%
9	6.3%
10	7.5%
11	9.0%
12	10.7%
13	12.6%
14	14.9%
15	17.5%
16	20.5%
17	23.8%
18	27.4%
19	31.4%
20	35.7%
21	40.3%
22	45.0%
23	49.7%
24	54.5%
25	59.3%

Parikh NI, Pencina MJ, Wang TJ et al. A risk score for predicting near term hypertension. Ann Intern Med 2008; 148: 102-110