Hypertension: Reflections on Risks and Prognostication

William B. Kannel, MD, MPH, FACC

Framingham Heart Study cardiovascular disease (CVD) prospective population epide-
molologic research has played an important role in the evolution of modern cohort study
design and the advancement of preventive cardiology. Epidemiologic research on
coronary heart disease (CHD) from the Framingham Study evolved the risk factor
concept in 1961, indicating that multiple interrelated factors are promoting increased
risk for development of CHD.¹ To date no single essential factor has been identified.
Epidemiologists subsequently were 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 epidemiologic model
and elevated blood pressure has emerged as a prominent member of the major
cardiovascular risk factors.

Framingham Study population research has demonstrated the importance of disting-
ishing between usual (average) and optimal risk factor levels as normal and accept-
able. It determined the influence of hypertension on the full clinical spectrum of CVD,
including sudden death, silent and overt myocardial infarction, heart failure, and clini-
cal 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 for developing it and its vascular consequences. The study also
provided some valuable insights on mechanisms of hypertension-induced CVD.
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

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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 in turn were 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 (LVH), importance of small amounts of proteinuria, and the role of obesity and weight gain. 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 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 be not only 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 greater than the diastolic component and that even isolated systolic hypertension is dangerous.

Women were believed 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 genders 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. Framingham Study data soundly refuted this assertion, however, indicating that although the hypertensive risk ratios for all the major atherosclerotic CVD events are larger for those under than over age 65, the absolute incidence of disease in hypertensive persons was 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, although 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 tolerated hypertension well.

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 in the Framingham Study and elsewhere, routine testing to identify specific underlying causes of hypertension no longer is recommended unless there is history or physical findings that suggest secondary hypertension or that blood pressure cannot be controlled. Identifiable underlying causes were responsible for only a small percentage of the hypertension encountered in clinical practice.

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

The perception of the hazard of hypertension was preoccupied with the diastolic blood pressure component since the beginning of the twentieth century and even today, there seems 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 previously was considered an innocuous feature of progressive arterial rigidity. Assessment of the implications of blood pressure components by the Framingham Study, however, indicated that increments of pulse pressure at any systolic pressure are associated with increased CHD incidence. With increasing age there is a shift in importance of risk for CHD from diastolic to systolic and finally to pulse pressure.7

Framingham Study data have altered the concept of an acceptable blood pressure from what is usual in the population to what is optimal for avoiding hypertension-related CVD. Epidemiologic data showed that at all ages and in both genders, CVD 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 CHD and all-cause mortality also have been reported in other cohorts.8,9 There is no threshold for blood pressure cardiovascular risk, as some claim, and in the Framingham Study cohort 45% of the CVD events in men occurred at a systolic blood pressure less than 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. The Multiple Risk Factor Intervention Trial (MRFIT) data on more than 350,000 men screened and followed for CVD mortality and the Prospective Studies Collaboration involving almost 1 million participants and 56,000 vascular deaths found no indication of a threshold of blood pressure risk down to 115/75 mm Hg.10,11 Persons aged 40 to 69 years 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 “nonhypertensive” 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 for a CVD event (Table 1). Based on these findings, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines have defined a “prehypertensive” blood pressure category.8

### COMMENTARY ON PREHYPERTENSION

Recently, Liszka and colleagues12 examined the CVD outlook for the JNC 7 promulgated prehypertension risk category, confirming that it carries an excess risk in a larger

<table>
<thead>
<tr>
<th>Blood Pressure (mm Hg)</th>
<th>Ten-Year Cumulative Incidence</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Women</td>
</tr>
<tr>
<td></td>
<td>Age-Adjusted Rate (%)</td>
</tr>
<tr>
<td>&lt;120/80</td>
<td>1.9</td>
</tr>
<tr>
<td>120–129/80–84</td>
<td>2.8</td>
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<tr>
<td>130–139/85–89</td>
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<tr>
<td><strong>P&lt;.001</strong></td>
<td><strong>P&lt;.001</strong></td>
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</table>

Framingham Study subjects, ages 35–90 years.

*Abbreviation:* HR, hazard ratio adjusted for age, BMI, cholesterol, diabetes, and smoking.

and more generalizable population sample than the Framingham Study. 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.” In the Framingham Study, 80% to 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. CVD risk in the prehypertensive blood pressure range, although significantly increased compared with lower blood pressures, still is 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 of changes of diet, weight control, and amount of exercise. For some who have 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 and at high diastolic blood pressure (a so-called J-curve) generating fear of lowering the diastolic blood pressure too much. The Framingham Study tested prospectively the hypothesis that the upturn in CVD incidence at low diastolic blood pressure largely is confined to persons who have increased systolic pressure, hence reflecting risk from an increased pulse pressure. The 10-year risk associated with 951 nonfatal CVD events and 205 CVD deaths was estimated at diastolic pressures of less than 80, 80 to 90, and greater than or equal to 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 genders, a statistically significant excess of CVD events was observed at diastolic blood pressures less than 80 mm Hg only when accompanied by a systolic pressure greater than 140 mm Hg, and this persisted after adjustment for age and associated CVD risk factors. This finding is corroborated in the large MRFIT data set. Persons who have this condition of isolated systolic hypertension have been shown in the large Systolic Hypertension in the Elderly Program

![Fig. 1. CVD incidence by diastolic blood pressure according to systolic blood pressure Framingham Study cohorts. (From Kannel WB, Wilson PW, Nam BH, et al. A likely explanation for the J-curve blood pressure cardiovascular risk. Am J Cardiol 2004;94:380–4; with permission.)](attachment://fig1.png)
(SHEP) and Systolic Hypertension in Europe (Syst-Eur) trials to safely benefit from anti-hypertensive treatment.\textsuperscript{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 now often is looked on as an anachronism (compared with the echocardiogram) when it comes to assessing ominous LVH. The original Framingham Study multivariable CVD risk profiles included ECG-LVH until the guideline committees decided it was too insensitive, too low in prevalence, and too poorly defined for clinicians to use. The ECG, however, is more available, less labor intensive, and less costly than the more elegant echocardiogram. When present, ECG abnormalities, such as LVH, nonspecific abnormality, intraventricular block, and unrecognized myocardial infarction, are important contributors to cardiovascular risk assessment. LVH originally was considered compensatory, helping the heart deal with a blood pressure overload. LVH 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 LVH is an ominous feature of hypertension that independently escalates the risk for future CVD, equivalent to that of persons who already have overt atherosclerotic CVD.\textsuperscript{19,20} Increases in voltage and repolarization were associated with further escalation of cardiovascular risk and decreases with reduction in the adverse consequences.\textsuperscript{21}

**ELECTROCARDIOGRAPHIC ABNORMALITIES**

Hypertension, particularly when associated with LVH, promotes ventricular premature beats. The Framingham Study evaluated the prevalence and prognostic significance of asymptomatic complex or frequent ventricular premature beats detected during ambulatory ECG monitoring of surviving participants of the Framingham Study cohort and offspring of the original cohort.\textsuperscript{22} Those men who do not have CHD with such premature beats on 1-hour ambulatory ECG, after adjusting for age and traditional risk factors for CHD, were at significantly increased risk for all-cause mortality (relative risk 2.30) and the occurrence of myocardial infarction or death from CHD (relative risk 2.12). Curiously, in men who had CHD and in women who had and who did not have CHD, 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 who did not have clinically evident CHD and 33% in the 302 men who had CHD. The corresponding values in women (3064 who did not have disease and 242 who had disease) were 12% and 26%.

Thus, in men who did not have clinically overt CHD, the incidental detection of ventricular ectopy was associated with a twofold increase in the risk for all-cause mortality and myocardial infarction or death resulting from CHD. The preventive and therapeutic implications of these findings await further investigation.\textsuperscript{22}

The risk for developing overt CHD also was examined in relation to occurrence of nonspecific ECG ST and T-wave abnormalities in the Framingham Study.\textsuperscript{23} In the course of follow-up, 14% of the 5127 men and women participating in the Framingham Study had or developed nonspecific ECG abnormalities without clinically apparent intervening CHD. During 30 years of surveillance, 760 men and 578 women developed a first overt clinical manifestation of CHD. Nonspecific ECG abnormality seemed to be
a hallmark of a compromised coronary circulation predicting the occurrence of every clinical manifestation of CHD independently of known risk factors, including hypertension, its chief determinant. Coronary morbidity and mortality was increased twofold in each gender. The more common T-wave abnormality alone carried a significant increased risk, although the combination of ST and T waves seemed most hazardous.\

Many studies have shown positive associations between heart rate and both all-cause and cardiovascular mortality. These relationships, however, were not investigated in persons who had 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 greater than or equal to 140 mm Hg systolic or greater than or equal to 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 twofold for women. Cardiovascular mortality increased 1.7-fold in men and women. Exclusion of outcomes in the first 2 or 4 years after measurement of heart rate did not change the results materially, suggesting that rapid heart is not merely an indicator of pre-existing illness. Consequently, heart rate on ECG examination is a useful independent risk factor for cardiovascular mortality in persons who have hypertension.

The clinical implications of newly acquired left bundle branch block (LBBB) were investigated prospectively in the Framingham Study population. During 18 years of observation, 55 subjects developed LBBB. The mean age at the onset was 62, the LBBB occurring largely in participants who had antecedent hypertension, cardiac enlargement, CHD, 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% who had this intraventricular conduction abnormality remained free of clinically overt cardiovascular events. Within 10 years of the onset of LBBB, 50% died from CVDs. In men, the ECG evidence of LBBB contributed independently to an increased risk for CVD mortality. Comparison with age- and gender-matched control subjects free from LBBB confirmed that in the general adult population, newly acquired LBBB most often is 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 usefulness of the ECG for CV risk assessment. Abnormalities in the ECGs of 14,749 healthy women predicted increased risk for cardiovascular events and mortality. Women who had minor abnormalities had a 55% increased risk for an event, and those who had major abnormalities had a threefold 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 counterintuitively 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. The high proportion of unrecognized infarctions among hypertensive persons persisted on adjustment for antihypertensive treatment, diabetes, and ECG-LVH (Table 2). This important finding seems to have escaped the notice of guideline crafters and prevention-minded physicians. Risk for all clinical manifestations of
coronary disease is increased in hypertensive persons, in particular 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 threefold. The chief hazard of hypertension often is believed a stroke. The 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. Hypertension predisposes to all clinical manifestations of CHD, including myocardial infarction, angina pectoris, and sudden death; imposing a two- to threefold increased risk. For hypertension-induced strokes, the risk ratio for intracerebral hemorrhage was believed greater than for an atherothrombotic brain infarction. This proved incorrect; hypertension was as strong a risk for atherothrombotic brain infarction as intracerebral hemorrhage. It also was 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 or not the hypertension was severe (70%) or mild (56%). The proportion of strokes resulting from hemorrhage in mild hypertension (5%) was virtually identical to that for severe hypertension.

RISK STRATIFICATION OF HYPERTENSION

There is a need for greater use of risk stratification of hypertension to determine the type and intensity of treatment that are 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 low-density lipoprotein cholesterol, reduced high-density lipoprotein (HDL) cholesterol, elevated blood glucose, and visceral adiposity, the combination of which has been

<table>
<thead>
<tr>
<th>High Blood Pressure Status</th>
<th>Percent Unrecognized</th>
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<tr>
<td></td>
<td>Excluding Diabetics</td>
</tr>
<tr>
<td></td>
<td>Men</td>
</tr>
<tr>
<td>Normal</td>
<td>18</td>
</tr>
<tr>
<td>Mild</td>
<td>28</td>
</tr>
<tr>
<td>Definite</td>
<td>33</td>
</tr>
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</table>
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 who have 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 approximately 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, LVH, visceral adiposity, proteinuria, cardiomegaly, sinus tachycardia, or insulin resistance. The urgency for and choice of treatment should take into account these associated risk factors and 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- to 20-fold increased risk associated with moderate degrees of hypertension, the absolute hazard is modest, and many persons in this category need to be treated 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 and the blood pressure. Targeted therapy, based on a composite risk profile, improves the cost-benefit ratio of antihypertensive therapy.

Hypertension occurred in isolation of other standard risk factors in only 20% of patients. Clusters of three or more additional risk factors occur at 4 times the rate expected by chance.30 Hypertension often is 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 pressure31 (Table 3). Risk for CVD in persons who have hypertension was shown by the Framingham Study to vary widely depending on the size of the associated burden of other risk factors.30

| Table 3 |
| Influence of obesity on odds of low plasma natriuretic peptides |

<table>
<thead>
<tr>
<th>Risk Factor–Adjusted Odds Ratios</th>
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<tbody>
<tr>
<td>Low BNP</td>
</tr>
<tr>
<td>Low N-ANP</td>
</tr>
<tr>
<td>BMI</td>
</tr>
<tr>
<td>Normal (≤25)</td>
</tr>
<tr>
<td>Men 1.00</td>
</tr>
<tr>
<td>Women 1.00</td>
</tr>
<tr>
<td>Overweight (25–29)</td>
</tr>
<tr>
<td>Men 1.64*</td>
</tr>
<tr>
<td>Women 1.43**</td>
</tr>
<tr>
<td>Obese (≥30)</td>
</tr>
<tr>
<td>Men 2.51***</td>
</tr>
<tr>
<td>Women 1.84***</td>
</tr>
<tr>
<td>Odds ratios adjusted for age, prior myocardial infarction, atrial fibrillation, diabetes, smoking, blood pressure, serum creatinine, left atrial size, left ventricular systolic function, left ventricular mass.</td>
</tr>
<tr>
<td>Low BNP = 4 pg/mL; low N-ANP = &lt;195 pmol/L.</td>
</tr>
<tr>
<td>* P&lt;.01.</td>
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<tr>
<td>** P&lt;.05.</td>
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<td>*** P&lt;.001.</td>
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</table>

Substantial risk in hypertensive persons who have mild to moderate hypertension was concentrated in those who had coexistent dyslipidemia, diabetes, and LVH. For stroke, the most feared hazard of hypertension in the elderly, risk varied over a wide range, reaching substantial proportions when accompanied by diabetes, LVH, atrial fibrillation, and coronary disease or heart failure. Hypertensive elderly commonly already had 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 who had hypertension in the Framingham Study had one or more of these conditions.

Instruments for the global assessment of multivariable risk for 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 for hypertensive patients using ordinary office procedures and standard laboratory tests.

GUIDELINES VERSUS GLOBAL RISK ASSESSMENT FOR ANTIHYPERTENSIVE THERAPY

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

Despite advocacy of these revised guidelines by prestigious organizations, it seems that the recommendations are not being implemented acceptably 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 controlled better than systolic pressures. A survey of self-reported hypertension rates from National Health and Nutrition Examination Survey (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 who had diabetes found that more aggressive therapy for blood pressure is needed because 73% had blood pressures above 140/90 mm Hg. Persons who had diabetes received less intensive therapy than those who did not have diabetes and this was not attributed to distraction by the need to treat the diabetes itself.44 Compliance with guidelines for treatment of dyslipidemia with hypertension also is suboptimal.45

It is uncertain why there is such a high failure rate in achieving adequate blood pressure control. One possibility is physician inertia, disenchanted by multiple complex sets of guidelines, each targeting a specific risk factor. It seems that multiple iterations of guidelines may be too difficult for an 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 who have 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, renaming current stage 1 and stage 2 hypertension categories to stages 2 and 3,
respectively, and introducing further complexity into the guidelines by using ill-defined “early disease markers,” “target organ disease,” and “vascular damage” to develop a risk algorithm for therapy. Practicing clinicians may have difficulty in applying and adhering to such guidelines.

It now is evident that it is the degree of blood pressure elevation that promotes CVD 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 CVD risk varies widely in relation to the number accompanying risk factors. It is advantageous, therefore, to link the aggressiveness of blood pressure–lowering therapy to the level of multivariable CVD risk. This policy has become critical because near-average levels of blood pressure now are recommended for treatment of high-risk persons. Because the number needed to treat to prevent one cardiovascular event is inversely proportional to the level of absolute CVD 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 with therapy disregarding absolute cardiovascular risk) are lacking; nevertheless, it seems eminently likely that such an approach would prove more cost effective and efficacious. Many clinical trials have tested the hypothesis that treatment of hypertension is most effective in patients who have multiple risk factors and higher risk for CVD events. For example, using the American Heart Association multiple risk factor equation on data from SHEP, a global CVD risk score was calculated for 4189 participants free of cardiovascular events and in 264 participants who had CVD 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.

The absolute long-term benefit associated with a 12–mm Hg reduction in blood pressure over 10 years was estimated by Ogden and colleagues 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; furthermore, the number needed to treat was much smaller in persons who had one or more additional major cardiovascular risk factors compared with those who did not have additional risk factors. This analysis demonstrates that the absolute benefit of antihypertensive therapy depends not only on the level of blood pressure but also on the presence or absence of additional risk factors. It also is 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 who have dyslipidemia or impaired glucose tolerance (which most hypertensive patients have) compared with those who do not have these conditions.

The Adult Treatment Panel III lipid guidelines have linked the treatment of dyslipidemia to the Framingham Study CHD multivariable risk algorithm, thereby simplifying the process of risk assessment. 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 Study multivariable risk evaluation tools exist for evaluating hypertensive hazards for developing coronary disease, stroke, heart failure, peripheral artery disease, and, most recently, total CVD. The Framingham Study recently crafted
a global total CVD risk assessment instrument 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 a robust predictor of each of its components. Furthermore, a simplified version substituting body mass index (BMI) for the laboratory components also was 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 an ingredient of a multivariable cardiovascular risk profile because each often is accompanied by a cluster of other metabolically linked risk factors that markedly influence their cardiovascular risk. 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. Because all the risk factors for which guidelines are being formulated are contained in the multivariable CVD risk formulations (eg, blood pressure, dyslipidemia, and 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.

<table>
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<tr>
<td>6</td>
<td>50–54</td>
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RISK FACTORS PREDISPOSING TO HYPERTENSION

An assessment of the frequency of progression to hypertension in participants in the Framingham Study cohort who did not have hypertension was undertaken to establish the best frequency of blood pressure screening by assessing the rates and determinants of progression to hypertension.13 Patients who had 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, a stepwise increase in hypertension incidence occurred across three nonhypertensive blood pressure categories: 5.3% of participants who had optimum blood pressure, 17.6% who had normal blood pressure, and 37.3% who had 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% to 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, supports recommendations for yearly monitoring of persons who have high normal blood pressure and monitoring those who have normal blood pressure every 2 years. The data also indicate the importance of blood pressure

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
<th>Points vasc.</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>30–34</td>
<td>35–39</td>
<td>40–44</td>
</tr>
<tr>
<td>Systolic blood pressure (untreated)</td>
<td>130–139</td>
<td>140–159</td>
<td>160+</td>
</tr>
<tr>
<td>Systolic blood pressure (treated)</td>
<td>—</td>
<td>—</td>
<td>120–129</td>
</tr>
<tr>
<td>BMI</td>
<td>—</td>
<td>—</td>
<td>25–30</td>
</tr>
<tr>
<td>Smoker</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
</tr>
<tr>
<td>Diabetes</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
</tr>
<tr>
<td>Points</td>
<td>Risk (%)</td>
<td>Points</td>
<td>Risk (%)</td>
</tr>
<tr>
<td>1</td>
<td>2.8</td>
<td>9</td>
<td>11.2</td>
</tr>
<tr>
<td>2</td>
<td>3.3</td>
<td>10</td>
<td>13.3</td>
</tr>
<tr>
<td>3</td>
<td>4.0</td>
<td>11</td>
<td>15.7</td>
</tr>
<tr>
<td>4</td>
<td>4.7</td>
<td>12</td>
<td>18.5</td>
</tr>
<tr>
<td>5</td>
<td>5.6</td>
<td>13</td>
<td>21.7</td>
</tr>
<tr>
<td>6</td>
<td>6.7</td>
<td>14</td>
<td>25.4</td>
</tr>
<tr>
<td>7</td>
<td>8.0</td>
<td>15</td>
<td>29.6</td>
</tr>
<tr>
<td>8</td>
<td>9.5</td>
<td>16+</td>
<td>&gt;30</td>
</tr>
</tbody>
</table>

monitoring in the obese and emphasize the importance of weight control for primary prevention of hypertension.

Several population determinants of hypertension have been documented. A high-normal systolic blood pressure is 2 to 3 times more likely to progress to “hypertension.” A 5% increase in obesity and weight gain is associated with 20% to 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, potassium 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: gender, parental history of hypertension, BMI, smoking, and systolic and diastolic blood pressure in the normotensive range (Table 7). In multivariable analysis, each of these variables was a significant predictor 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. Such a risk factor scoring instrument can be used, however, to refine management of prehypertensive persons.

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 for developing hypertension in overweight or obese subjects of the Framingham Study offspring cohort was increased threefold. As much as 59% of the hypertension developing in men and 42% in women ages 20 to 49 years was attributable to overweight and obesity. As people gain weight their blood pressure rises, and as they lose weight it falls. Obesity seems to impose a natriuretic handicap because brain natriuretic peptide and N-terminal pro-atrial natriuretic peptide decline with increase in weight leaving overweight and grossly obese persons with low natriuretic peptide levels. This imposed natriuretic handicap could contribute to the susceptibility of obese persons to hypertension and its cardiovascular sequelae.

**PREVENTIVE IMPLICATIONS**

Because modifiable risk factors predisposing to hypertension have been identified and hypertension risk assessment algorithms developed, there now is an opportunity

<table>
<thead>
<tr>
<th>Baseline Blood Pressure (mm Hg)</th>
<th>High Blood Pressure Rate (%)</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimum (&lt;120/80)</td>
<td>16</td>
<td>Referent</td>
</tr>
<tr>
<td>Normal (120–129/80–84)</td>
<td>25.5</td>
<td>2.0 (1.4–2.7)</td>
</tr>
<tr>
<td>High-normal (130–139/85–89)</td>
<td>49.5</td>
<td>5.5 (4.0–7.4)</td>
</tr>
</tbody>
</table>

Four-year high blood pressure rate adjusted for age, gender, BMI, and systolic and diastolic blood pressure. Framingham Study subjects were ages 65–94 years.

to prevent much of hypertension itself and its cardiovascular consequences.\textsuperscript{49} This opportunity should be acted on.

Moderate blood pressure elevations are 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 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 prehypertensive patients.

Despite 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.\textsuperscript{42} Why physicians still regard diastolic blood pressure as the chief culprit in hypertension needs to be investigated. There also is 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 who have a high pulse pressure, incriminating the pulse pressure. The SHEP and Syst-Eur trials have shown that treatment of elderly patients who have 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.\textsuperscript{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 on 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 lipid ratio and the aggressiveness of therapy for hypertension and dyslipidemia linked to the global CVD risk.

Physicians treating hypertension also can seek out more aggressive therapy for those who have preclinical atherosclerotic disease signified by an abnormal ankle brachial index, arterial vascular bruits, coronary artery calcification, LVH, other ECG abnormalities, a low ejection fraction, silent myocardial infarction, or proteinuria, among other risk factors.

High-risk hypertensive candidates for CVD who have an ominous multivariable risk profile indicating a 10-year risk for a CVD event exceeding, for example, 20% require more aggressive risk factor modification. The goal of therapy for 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 also can be expected to benefit the other adverse CVD events. Novel risk factors deserve attention, but the standard CVD risk factors seem to account for as much as 85% of CVD arising within the population.

Just as the cardiovascular risk factors identified by the Framingham Study have been found to apply universally, the Framingham Study multivariable risk functions have been validated and found to have transportability with calibration in culturally diverse populations around the world. The risk profiles have been shown accurate even in low-risk areas, such as in Chinese and Spanish populations.

Health care providers might be encouraged to undertake multivariable risk assessment whenever patients are 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 of hypertension. Demonstrating improvement in their multivariable risk score can be used to motivate patients to comply better with the recommended preventive management of their hypertension.

The hypertension-induced CVD epidemic cannot be conquered solely by cardiologists caring for referred patients. Multiple elements of the health care system have to be mobilized. Unfortunately, the 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 for atherosclerotic CVD.
REFERENCES


