Hypertension Curriculum Review

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Hypertensive Risk Assessment: Cardiovascular Risk Factors and Hypertension

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Hypertension is a prevalent and independent promoter of vascular damage to the heart, brain, kidneys, and limbs. This condition afflicts about 50 million persons in the United States and as the population ages its prevalence is expected to increase. Long-term investigation of its occurrence in the Framingham Study indicates that 90% of persons who are normotensive at age 55 years can expect to develop hypertension in their lifetime. The cardiovascular risk it imposes varies in relation to the height of the blood pressure, which component is elevated, the target organ affected, and the burden of coexisting risk factors. Recent guidelines of the Seventh Joint National Committee on Hypertension (JNC 7) recommend consideration of more modest blood pressure elevations (i.e., prehypertension 120/80 mm Hg to 140/90 mm Hg) for some treatment. Efficient treatment of this lowered range of blood pressure elevation requires multivariable risk stratification of the so-defined hypertension to be cost-effective and avoid needlessly alarming patients.

In 2003, a substantial amount of epidemiologic and clinical information was published concerning risk assessment of hypertension and its treatment. The JNC 7 guidelines for detection, evaluation, and treatment of elevated blood pressure specify, but do not quantify some of the criteria for risk assessment. The report emphasizes that systolic blood pressure is more important than diastolic blood pressure, citing an incremental cardiovascular disease (CVD) risk extending down to what was previously regarded as the normal range, defining a "prehypertensive" blood pressure category. Certain high-risk conditions like diabetes are designated "compelling indications" calling for more stringent blood pressure goals. A notable omission among these is dyslipidemia, a condition that should modify the blood pressure treatment goal because of its influence on hypertensive CVD risk.

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STRATIFICATION BY BLOOD PRESSURE LEVEL

Most physicians consider the height of blood pressure to be the most important consideration for undertaking treatment of hypertension. The British Hypertension Society guidelines concur, asserting that "the main determinant of benefit from blood pressure lowering is the achieved blood pressure, rather than the choice of therapy." There is a continuous, graded influence of blood pressure on the incidence and mortality of CVD (Table I). Nevertheless, there is an unfortunate tendency for some clinicians to accept higher blood pressures as relatively innocuous in the elderly. The current concept of a desirable blood pressure is no longer based on what is usual but rather on what is optimal for avoiding development of CVD. It is evident from prospective epidemiologic data that at all ages the hazard of a CVD event increases incrementally with the systolic

Table I. Incidence of Cardiovascular Disease by Systolic Blood Pressure (BP): Framingham Study 30-Year Follow-Up

	Average Annual Incidence					
	Men (Age in Years)			Women (Age in Years)		
Systolic BP (mm Hg)	45–54	55–64	65–74	45–54	55–64	65–74
74–119	8	16	16	3	6	12
120–139	11	18	23	5	9	17
140–149	19	31	37	9	16	22
160–179	29	43	52	9	24	20
180–300	35	62	78	16	36	45

Incidence rate per 1000; trends all significant in specified age and sex groups.

Table II. Systolic Blood Pressure (BP) and Coronary Mortality of 347,978 Men Screened for the Multiple Risk Factor Intervention Trial

Systolic BP (mm Hg)	No. CHD Deaths	Age-Adjusted Rate	Risk Ratio* (95% CI)
<120	1412	11.6	1.00 (ref)
120–129	2119	15.5	1.28 (1.19–1.36)
130–139	2511	20.8	1.66 (1.56–1.77)
140–159	3387	32.1	2.45 (2.30–2.61)
160–179	1120	48.4	3.42 (3.16–3.71)
180–209	376	79.6	5.26 (4.68–5.90)
>210	44	82.6	6.40 (4.74–8.65)

CHD=coronary heart disease; CI=confidence interval; ref=reference; *relative risk adjusted for age, race, income, cholesterol, cigarettes, and diabetes.
Source: Neaton et al. *Hypertension: Pathophysiology Diagnosis and Management.* 2nd ed. Philadelphia, PA: Raven Press; 1995.

blood pressure, and that at any blood pressure the risk is substantially greater in elderly persons (Table I). Elderly persons do not endure their higher average blood pressure well. Although their relative risk is somewhat lower, this is offset by a higher absolute risk. Examination of the systolic blood pressures at which CVD events occurred in Framingham Study male participants indicated that 45% occurred at systolic pressures <140 mm Hg, often designated as the threshold of hypertensive CVD risk.

The large dataset of more than 347,000 male screenees in the Multiple Risk Factor Intervention Trial (MRFIT) allows a precise estimate of the incremental CVD incidence at systolic blood pressures below 140 mm Hg. These data confirm the influence of systolic blood pressure on coronary heart disease (CHD) mortality at pressures below 140 mm Hg, based on 6122 events with similar regression coefficients at all ages (Table II). The Prospective Studies Collaboration meta-analysis of data from almost 1 million participants and 56,000 deaths, found that blood pressure is related to vascular mortality with no indication of a threshold down to 115/75 mm Hg. Risk of stroke or coronary mortality doubled with every 20-mm Hg increment in systolic blood pressure (or 10 mm Hg diastolic) throughout the entire range. In the Framingham Study this incremental risk for nonhypertensive blood pressures was seen in age and risk factor-adjusted analyses. Compared with optimal, high-normal blood pressure (130–139/85–89 mm Hg) conferred a 1.6–2.5-fold risk of a hard CVD event. Antecedent blood pressure within the normal range has also been shown to be a determinant of future hypertension in the Framingham Study, indicating another reason for concern about even minimal blood pressure elevation.

Thus, there is overwhelming evidence that a continuous graded influence of blood pressure to CVD morbidity and mortality exists at all ages in both sexes. A prudent blood pressure for avoiding CVD is <140/90 mm Hg with no clearly defined critical blood pressure that distinguishes normal from abnormal. However, for cost-effective treatment of prehypertension and stage 1 hypertension (140–160/90–100 mm Hg), multivariable risk stratification is needed, and the goal of therapy should be to improve the global CVD risk rather than to simply lower the blood pressure.

STRATIFICATION BY COMPONENTS OF BLOOD PRESSURE—THE PULSE PRESSURE

There appears to be lingering uncertainty about the CVD impact of the various components of blood pressure. Medical concepts about the hazards of hypertension have been preoccupied with the diastolic blood pressure component since the beginning of the 20th century. Only lately has the focus shifted to systolic blood pressure and most recently, to pulse

Table III. Risk of Atherosclerotic Cardiovascular Events by Pulse Pressure: 30-Year Framingham Follow-Up

	Age-Adjusted Rate Per 1000			
	Age 35–64 Years		Age 65–94 Years	
Pulse Pressure (mm Hg)	Men	Women	Men	Women
<40	9	4	2	17
40–49	13	6	6	19
50–59	16	7	32	22
60–69	22	10	39	25
≥70	33	16	58	32
Increase per 10 mm Hg (%)	19.7	20.9	23.4	10.5

Source: Kannel WB. Elevated systolic blood pressure as a cardiovascular risk factor. *Am J Cardiol.* 2000;85:251–255.

Table IV. Risk Factor Clustering With Elevated Blood Pressure in Framingham Study Offspring Cohort Ages 18–74 Years

	Percent With Other Risk Factors*	
No. of Risk Factors	Men	Women
None	19	17
One	26	27
Two or more	55	56

*Other risk factors: upper quintile levels of total and low-density lipoprotein cholesterol, triglyceride, body mass index, glucose, and bottom quintile high-density lipoprotein cholesterol

Source: Kannel WB. Cardiovascular risk assessment in hypertension. In: Braunwald E, Hollenberg NK. *Atlas of Hypertension*. 4th edition. Philadelphia, PA: Current Medicine; 2003:115.

pressure. Framingham Study data, based on 30 years of follow-up of subjects in relation to their pulse pressure, indicate a continuous graded increase in cardiovascular event rates of about 20% for each 10-mm Hg increment in pulse pressure for subjects ages 35–64 years. The incremental risk is somewhat lower (10.5% per 10 mm Hg) in older women, but not in older men (Table III). Vascular hemodynamics suggest pulse pressure plays an important role in development of CVD. Diastolic blood pressure increases with peripheral artery resistance and declines as the central arterial circulation stiffens. The relative contributions of these opposing forces determine the diastolic and ultimately, the pulse pressure. Pulse pressure and systolic pressure are highly correlated because both components rise with increase in vascular resistance and large artery stiffness. Assessment of these pressure components individually in the Framingham Study indicated that increments of pulse pressure at particular systolic pressures are associated with greater CHD incidence than the converse.

A major impediment to evaluation of the net impact of the components of the blood pressure on the structure and function of the heart and other vital organs is their high correlation with each other. The correlation between systolic blood pressure and pulse pressure is 0.90, making it extremely difficult to statistically dissociate their effects. Also, there appears to be an interaction with age such that diastolic pressure declines in importance as a CHD predictor as age advances, whereas the influence of systolic pressure increases. Recent Framingham Study investigation found that with increasing age there is a shift in importance from diastolic to systolic and finally to pulse pressure for prediction of CHD. From age 60 years on, diastolic pressure is negatively correlated with CHD incidence so that pulse pressure becomes superior to systolic pressure. However, investigators disagree about the relative importance of systolic and pulse pressure, even in elderly persons.

In the past it was argued that it was the underlying damaged stiff artery that was directly responsible for the increased CVD found to be associated with isolated systolic hypertension and increased pulse pressure. However, investigation by the Framingham Study many years ago suggested an effect of the systolic and pulse pressure taking arterial compliance into account. Contrary to the fears of many, trials demonstrated that antihypertensive treatment of isolated systolic hypertension actually reduces the risk of CVD, and does so rather promptly.

There is mounting evidence supporting the contention that the cardiovascular hazards of hypertension involve large artery stiffness and early wave reflection as well as peripheral resistance. Until very recently the dominant concept of hypertension pathogenesis overemphasized vascular resistance and underestimated the influence of arterial stiffness. Despite the demonstrated efficacy of treating systolic hypertension, the reported poor blood pressure control is overwhelmingly

Table V. Framingham Multivariate Point Scores for Men According to Age and Cholesterol Level

Risk Factor	Points
Age (years)	
35–39	0
40–44	1
45–49	2
50–54	3
55–59	7
Total cholesterol (mg/dL)	
<160	–3
160–199	0
200–239	1
240–279	2
>280	3
High-density lipoprotein cholesterol (mg/dL)	
<35	2
35–44	1
45–49	0
50–59	0
>60	–2

Source: Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. *Circulation.* 1998;97:1837–1847.

due to failure to control the systolic component. Guidelines now place greater emphasis on achieving specified systolic blood pressure goals.

PRIMARY VS. SECONDARY HYPERTENSION

In the past, great emphasis was placed on identifying correctable causes of hypertension. Now, extensive testing to identify causes of hypertension is not recommended unless there are suggestive findings pointing to secondary hypertension, or blood pressure control cannot be achieved. The causes commonly considered are sleep apnea, drug-induced or drug-related elevated blood pressure, chronic kidney disease, primary aldosteronism, renovascular disease, steroid therapy, Cushing syndrome, pheochromocytoma, coarctation of the aorta, and thyroid or parathyroid disease. These conditions are generally pointed to by the history and physical examination. They account for only a small percentage of the hypertension encountered in clinical practice. A more common cause now being considered is obesity-induced insulin resistance or metabolic syndrome.

STRATIFICATION BY SPECIAL SITUATIONS

The JNC 7 report reflects upon a number of special considerations that require attention in the treatment of hypertension. Included among these are "compelling indications" and other "special situations." Among the latter there are minority populations; obesity and the metabolic syndrome; left ventricular hypertrophy; peripheral artery disease; older persons; postural hypotension; dementia; hypertension in women, children, and adolescents; and hypertensive urgencies and emergencies.

Although treatment recommended in minorities is similar for all demographic groups, there are socioeconomic and lifestyle barriers to blood pressure control in Mexican Americans and Native Americans. The prevalence, severity and impact of hypertension are greater in African Americans and they do not respond as well to monotherapy. 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 an atherosclerotic disease. Peripheral artery disease is another condition equivalent to having CHD. Older persons have the bulk of hypertension in the population and the lowest rate of blood pressure control. Postural hypotension is more frequent in older patients with systolic hypertension and diabetes, and in those using diuretics, psychotropic drugs, and venodilators such as α blockers and sildenafil.

Dementia and cognitive impairment occur more commonly in persons with hypertension and the rate of progression may be reduced by effective antihypertensive therapy. Although hormone replacement therapy does not raise blood pressure, oral contraceptives may. Pregnant women with hypertension need to be followed more closely, and for the safety of the fetus methyldopa, β blockers, and vasodilators are recommended therapy. Choices of antihypertensive drugs are similar for children and adults but effective doses are generally smaller.

Obesity and the metabolic syndrome are common features of the hypertensive population. Interest in diabetes as an important component of hypertensive CVD risk now focuses on lesser degrees of glucose intolerance functioning as a component of an insulin-resistant metabolic syndrome. The connection between abdominal adiposity, insulin resistance, and hypertension has received considerable attention in the past year. Uncertainty has been expressed as to whether elevated blood pressure is an intrinsic feature of the metabolic syndrome or an associated condition, but it is clear that when blood pressure elevation is accompanied by the other features of the syndrome, the hazard is escalated. Hypertension is often a component of a metabolic syndrome composed of dyslipidemia,

Table VI. Framingham Multivariate Point Scores for Men by Blood Pressure (BP) and Diabetes and Smoking Status

	Diastolic BP (Points)								
Systolic BP (mm Hg)	<80 mm Hg	80–84 mm Hg	85–89 mm Hg	90–99 mm Hg	>100 mm Hg	Diabetes?	Points	Smoker?	Points
120–129	0	0	0	2	3	No	0	No	0
130–139	0	0	1	2	3	Yes	2	Yes	2
140–149	2	2	2	2	3				
>160	3	3	3	3	3				

Source: Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97:1837–1847.

Table VII. Ten-Year Multivariate Risk Estimate as Determined by Number of Points (Tables V and VI) and Age

Coronary Disease Risk		Comparative Average Risk	
Points	10-Year Risk (%)	Age (Years)	10-Year Risk (%)
1	3	35–39	5
2	4	40–44	7
3	5	45–49	11
4	7	50–54	14
5	8	55–59	16
6	10	60–64	21
7	13	65–69	25
8	16		
9	20		
10	25		
11	31		
12	37		
13	45		
≥14	≥53		

Source: Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97:1837–1847.

elevated blood pressure, and abdominal obesity. A clinically useful definition of this entity has been proposed by the National Cholesterol Education Program Adult Treatment Panel III. The diagnosis requires presence of three or more of the following: blood pressure ≥130/85 mm Hg, fasting glucose ≥110 mg/dL, reduced high-density lipoprotein cholesterol level (<40 mg/dL for men and <50 mg/dL for women), triglycerides ≥150 mg/dL, waist circumference >40 inches for men and >35 inches for women. Some 40 million Americans ≥20 years of age have the syndrome; 22% of men and 24% of women. It imposes a three-fold increased risk of CHD and five-fold risk of CVD mortality. It carries a lesser risk than overt diabetes, but because it is much more prevalent it imposes a greater attributable risk for the general population.

STRATIFICATION BY COMPELLING INDICATIONS

The JNC 7 notes a number of "compelling indications" that merit special attention and follow-up. Included in this list are: heart failure, postmyocardial infarction status, high coronary heart disease risk (i.e., >20% hazard for 10 years), diabetes, chronic renal disease, and prior stroke. Different choices of antihypertensive therapy are advocated for each based on trial data. These conditions also require more stringent blood pressure targets. Diabetic hypertension usually requires two or more drugs to achieve the recommended blood pressure goal of <130/80 mm Hg. Renal disease requires aggressive blood pressure management, often needing use of three drugs to reach the recommended target of <130/80 mm Hg.

STRATIFICATION BY BURDEN OF CVD RISK FACTORS

Elevated blood pressure seldom occurs in isolation of other CVD risk factors. More than 80% have one or more coexistent risk factors and 55% of men and women have two or more, qualifying them for designation as having the metabolic syndrome (Table IV). Because the amount of risk

factor clustering profoundly influences the CVD risk of elevated blood pressure, all patients with hypertension should be tested for other risk factors, such as elevated total and low-density lipoprotein cholesterol, high triglycerides and glucose, increased body mass index or waist girth, and reduced high-density lipoprotein cholesterol.

MULTIVARIABLE RISK ASSESSMENT

Prevention of CHD by controlling CVD risk factors that accompany elevated blood pressure deserves a high priority because the risk of CVD in general, and of CHD (its most common hazard) is greatly influenced by the burden of associated risk factors. Multivariable risk formulations for quantifying the impact of a set of risk factors for development of CVD have been developed from Framingham Study data. The composite risk factor score derived from it corresponds to the probability of an event over 10 years. These estimated event rates when compared with average risk for same-aged persons provide absolute and relative risks (Tables V–VII). Persons at high risk for CHD have been shown to also be at increased risk of other atherosclerotic vascular disease. This point system of risk estimation was recently adopted by the National Cholesterol Education Program guidelines for assessment and treatment of dyslipidemia, linking the indication, intensity, and goal of therapy to the 10-year multivariable risk. A 10-year risk exceeding 20% is regarded as a CHD equivalent meriting the intensity of treatment afforded those trying to avoid recurrences of CVD. This approach would also appear to be appropriate for persons with hypertension. The British and European guidelines for assessment and treatment of hypertension (to a greater extent than the JNC 7 guidelines) provide the means and incentive for identifying treatment for high-risk hypertensive patients such as persons with diabetes and those with target organ damage or a 10-year cerebrovascular risk of 20% or more.

Hypertension, dyslipidemia, and diabetes promote accelerated atherogenesis and correcting them stabilizes lesions and slows progression. Treatment is of proven benefit for initial and recurrent events without a penalty in overall mortality. The prevalence of these conditions in the general population is unacceptably high and isolated occurrence of these major CVD risk factors relatively uncommon. Persons with hypertension usually have dyslipidemia, abdominal obesity, and/or impaired glucose tolerance. Dyslipidemic persons and diabetics have a distinct excess of elevated blood pressure. These risk factors are components of the metabolic or insulin resistance syndrome. However, because most of the ingredients of the syndrome are also components of the Framingham multivariable risk formulation, the value of detecting persons with the metabolic syndrome applies more to therapeutic choices than to risk stratification.

Because the average blood pressure, blood lipid, and glucose levels at which most coronary events occur is rather modest, multivariable risk assessment to target a high-risk subset is required. Elevated blood pressure is at all ages a major risk factor for all clinical manifestations of atherosclerosis including CHD, brain infarction, peripheral artery disease, and heart failure. Hypertension increases the rate of atherosclerotic vascular disease two- to threefold. The risk ratio is greatest for heart failure, but CHD is the most common hazard, equaling in incidence all the other hypertensive sequelae combined. Because CVD risk increases incrementally with the blood pressure (even within the high-normal range) and the fact that moderate blood pressure elevation is so much more prevalent than severe hypertension, a large fraction of the CVD attributable to hypertension derives from seemingly innocuous levels of blood pressure elevation. Its high prevalence, powerful impact and controllability give it a high priority for detection, risk stratification, and treatment.

Hypertension accelerates atherogenesis by a complex process involving coexisting risk factors all of which impair endothelial function. Optimal cardiovascular protection of persons with elevated blood pressure requires more than simply lowering blood pressure. Each major risk factor that clusters with the elevated blood pressure must be corrected if optimal protection is to be afforded. Because the burden of risk factors accompanying hypertension is promoted by weight gain leading to visceral adiposity and insulin resistance weight control is of paramount importance. Multivariate risk assessment enables health care providers to pull together all the major risk factor information and arrive at a composite risk estimate for patients with hypertension. Because the risk imposed varies over a wide range depending on the burden of associated risk factors, the absolute benefit to be derived from treatment depends on the pretreatment global risk. Patients with hypertension at high multivariable risk stand to benefit the most from treatment and the number needed to treat to prevent one event is lowest in this high-risk segment.

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