Exploring a New Definition of Hypertension

A Report from the American Society of Hypertension Annual Meeting, May 14–18, 2005, San Francisco, CA

[*Rev Cardiovasc Med*. 2005;6(3):164-172]

Key words: Hypertension • Blood pressure • Aging • Renin-angiotensin system • Obesity

The best-attended session at the 2005 scientific meetings of the American Society of Hypertension (ASH) dealt with the question of whether creating a new definition of hypertension would allow this condition to be better understood and treated. Although, as a matter of policy, the Society does not officially produce or endorse clinical guidelines or scientific positions, an ad hoc working group has received support from the Society to write and publish a considered opinion on the issue of a new hypertension definition. Before considering the elements that were publicly discussed, however, it would be of value to look at some of the issues that first stimulated this initiative.

Reported by Michael A. Weber, MD, State University of New York Downstate Medical Center, Brooklyn, NY

An Ongoing Debate

Most simply, hypertension means high blood pressure, and some experts would argue that there is no need to go beyond that description. After all, there is ample clinical evidence linking blood pressure levels directly to cardiovascular outcomes across the full range of low to high blood pressure values.[1,2] The life insurance industry has long been keenly aware that high blood pressure indicates a poor prognosis. Moreover, there is also strong evidence that reducing blood pressure in hypertensive patients significantly decreases the incidence of major clinical outcomes like myocardial infarctions, heart failure, strokes, and mortality.[3] Indeed, it is now well established that among treated hypertensive patients, those whose blood pressure is better controlled have a clear prognostic advantage over those who respond less well.[4-6]

At the same time, though, it is known that high blood pressure rarely exists as a solitary abnormality but more typically is associated with such findings as dyslipidemias,

glucose intolerance, and obesity, as well as with early or subclinical evidence of changes in renal and cardiac structure and function.[7,8] Clearly, people who are affected by multiple risk factors are more likely to experience adverse outcomes than are those who only have an elevation in blood pressure. Even so, as demonstrated by the very clear contrast between the hypertension guidelines written in the United States and Europe,[9,10] it is possible to interpret this situation in different ways.

High blood pressure rarely exists as a solitary abnormality but more typically is found in association with such findings as dyslipidemias, glucose intolerance, and obesity.

The Disparity in Guidelines

In the United States, the most recent recommendations of the Joint National Committee on the Prevention, Detection, and Treatment of High Blood Pressure (JNC)[9] have taken a blood pressure–focused view of hypertension. Unlike previous reports,[11] which discussed the diagnosis and management of high blood pressure in the context of multiple risk factors, the newest iteration of these guidelines has based the diagnosis of hypertension and the recommended treatment goals predominantly on blood pressure criteria. For most people, the diagnosis of hypertension is made if blood pressure is 140/90 mm Hg or higher, and the goal of treatment is to reduce blood pressures to below this level; for individuals with diabetes or renal impairment, the blood pressure criterion is 130/80 mm Hg.[9]

Although obviously aware that high blood pressure is often part of a more complex series of findings, the JNC was seemingly influenced by 2 factors: first, that the importance of blood pressure is so well established, both in terms of prognosis and the value of treatment, that very few patients would be mismanaged when decisions are based on this measurement alone; and second, that because achievement of desirable treatment goals in the United States has been so disappointing,[12] the medical community would be best served by emphasizing the importance of identifying and treating high blood pressure rather than risking the distractions caused by more broadly based evaluations of total cardiovascular risk.

The recommendations of the European Society of Hypertension, in contrast, put hypertension very firmly in the setting of multiple cardiovascular risk factors.[10] Essentially, they argue that moderately elevated blood pressure, in the absence of other findings, might justify a delay in the institution of active therapy and provide an opportunity for a reasonably prolonged test of lifestyle modifications. In addition, at the other end of the spectrum, the guidelines indicate that the presence of concomitant risk factors, even with relatively modest increases in blood pressure, would demand a more aggressive approach to initiating pharmacologic therapy.

An Even Broader View

Although the JNC[9] and the European Society of Hypertension[10] recommendations are pragmatic and relevant to a large number of people, it is also possible to see hypertension in a broader context. In particular, it seems likely that this condition reflects an underlying vascular disease that in all likelihood begins at a young age and typically predates the clinical appearance of high blood pressure. This, to a large extent, has been the motivation for the working group at ASH who believe that the most scientific approach to understanding hypertension is to see it as a life-long condition that progressively affects the structure and function of the entire circulation. Quite apart from the scientific validity of such a concept, this approach also could create the opportunity to diagnose hypertension at a far earlier stage in susceptible people and potentially provide strategies for preventing or delaying its clinical manifestations.

Presentations at the American Society of Hypertension Meeting

Because the proposed recommendations of the Society's working group are now awaiting publication elsewhere, it would be inappropriate to provide comprehensive details here. Suffice it to say that these recommendations will stress that a diagnosis of hypertension can depend on the discovery of vascular changes, even in the absence of an elevated blood pressure; and that a new staging system for hypertension should be developed that is based on evidence for vascular disease as well as on the more traditional findings of increased blood pressure and the presence of other cardiovascular risk factors.

It was emphasized, however, during the ASH meeting, that this project remains very much a work in progress. One of the major presentations on this subject focused on the broad array of evidence for the vascular properties of hypertension, and in particular outlined the many mechanisms that can mediate the

changes in the circulation that lead to structural changes and to hemodynamic abnormalities. At the same time, other data were presented to emphasize that, despite the strong interest in broadening our understanding of the hypertension paradigm, it would be foolhardy to ignore the overarching importance of blood pressure as a determinant of prognosis. Certainly, for clinical practitioners, a broader view of hypertension should not be allowed to obscure the immediate and compelling benefits of achieving blood pressure control with currently available clinical strategies.

Hypertension is a heterogeneous condition that manifests itself in a wide variety of ways. If anything, the multiplicity of hypertension phenotypes is one of the strongest incentives to rethink the current approach that clusters them together simply because they each include an increase in blood pressure as part of their clinical picture.

The Heterogeneity of Hypertension

Hypertension can be classified according to a wide variety of clinical, demographic, anthropometric, and inherited factors. Some of these criteria are listed in Table 1. It is not the purpose of this brief report to fully survey the range of findings that establish heterogeneity in hypertension but rather simply to point out some compelling examples of why regarding hypertension simply as a blood pressure problem—even if other risk factors are taken into account—clearly fails to address its diversity of mechanistic and prognostic features.

Blood Pressure and Age

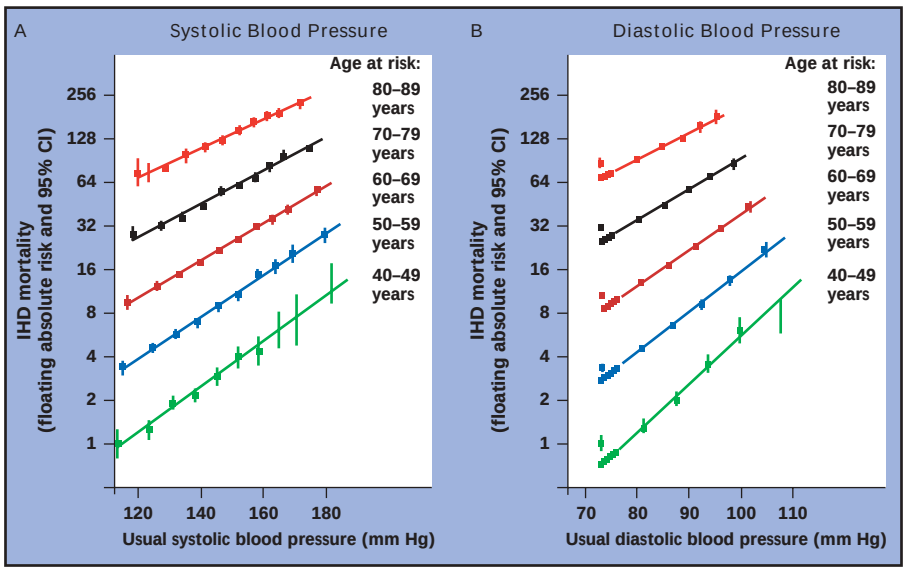
Blood pressure is an obvious starting point, and the data shown in Figure 1 are a strong documentation of the powerful impact on major events of even modest differences in blood pressure.[2] Overall, as far as coronary mortality is concerned, the event rate doubles for each increase in systolic blood pressure of 20 mm Hg. Indeed, even a difference of 2 mm Hg in systolic blood pressure translates approximately into a 10% effect on fatal stroke event rates and a 7% effect on fatal coronary events. It is also evident, when considering the deciles of age shown in Figure 1, that this powerful relationship exists at all ages, certainly among adults.

Age itself, however, is also an interesting story. Figure 2 uses the same data as are shown in Figure 1 but now focuses on the effects of age on coronary events. For a given level of systolic blood pressure, for instance 140 mm Hg, there is a 20- to 30-fold increase in event rates when going from ages in the 40s up to the 80s. This approximates to a doubling of event rates for every 8 to 10 years of increased age. What is remarkable is that this relative multiplication in coronary event rates occurs even at blood pressures that would be considered normal or only minimally elevated, emphasizing a powerful effect of age that might be independent of conventional cardiovascular risk factors. This phenomenon is probably not mediated by the same

Table 1
Selected Clinical Factors Establishing Heterogeneity in Hypertension

- Blood pressure
- Age
- Concomitant risk factors
- Renin status
  - Prognosis
  - Volume/vasoconstriction
- Vascular disease markers
- Left ventricular hypertrophy
- Renal involvement (microalbuminuria)
- Body habitus
- Family history (heredity?)

Figure 1. *Relationship between systolic and diastolic blood pressures and coronary heart disease mortality according to deciles of age. IHD, ischemic heart disease; CI, confidence interval. Reproduced with permission from Lewington et al.*[2]



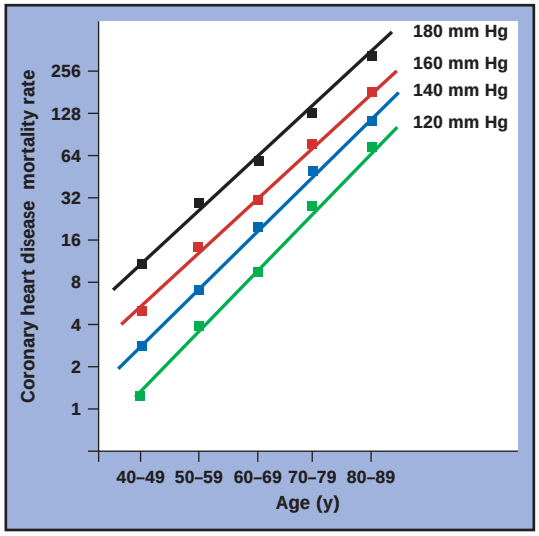


Figure 2. *Effects of age on coronary heart disease mortality rates according to differing levels of systolic blood pressure. Data from Lewington et al.*[2]

process that causes isolated systolic hypertension in the elderly—generally attributed to a progressive loss of the hemodynamic buffering effects of large artery elasticity—because the impact of aging on prognosis can be observed even at normal levels of blood pressure.

Further research is required to determine how to deal with the aging factor, for almost certainly different vascular processes are at work in elderly as compared with younger patients, even at the same level of blood pressure. There are several possible explanations for this phenomenon, including inflammatory processes, degenerative or apoptotic changes in the vasculature, and the chronic effects of heightened activity of the renin–angiotensin system. Presumably, effective therapies designed for elderly patients, even those with a clear diagnosis of hypertension, might have to use treatments that go beyond blood pressure reduction and that directly address mechanisms that mediate age-related vascular changes.

Heterogeneity Due to Renin

Two important discoveries in the 1970s established renin as a major determinant of prognosis in hypertension and as a key regulator of blood pressure. The first report compared clinical outcomes in hypertensive patients divided into high, normal, and low renin subgroups; those patients whose plasma renin values were high (as determined by a renin-sodium nomogram) were significantly more likely than other patients to experience a myocardial infarction.[13] This discovery, confirmed subsequently by a large prospective study,[14] was critical in establishing key clinical differences among hypertensive patients. Of broad interest, the hypothesis that increased activity of the renin-angiotensin system was predictive of a poor prognosis was to lay the foundation for the development of drugs designed to block this system, chiefly angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. These classes of agents have been shown in numerous clinical trials to provide strong survival and clinical outcomes benefits in patients at risk across a broad spectrum of cardiovascular and renal diseases.

The second construct with renin was used to devise what became known as the volume–vasoconstriction model of hypertension.[15] It was demonstrated that drugs that interrupt the renin pathway were more effective in reducing blood pressure in high-renin than in normal- or low-renin hypertensive patients, indicating that the renin–angiotensin system was playing a key role in sustaining blood pressures in such individuals.[16] On the other hand, as shown in Figure 3, diuretics were shown to be most effective in low-renin and least effective in high-renin hypertensive patients, indicating that low renin measurements were indicative of volume-dependent hypertension.[17]

Apart from the practical implications of this model—suggesting that measurements of renin could be of considerable clinical value in selecting the most appropriate classes of antihypertensive agents for individual patients—it clearly established that there are very definite subtypes of hypertensive patients. Indeed, even the reactivity of the renin–angiotensin–aldosterone system during treatment was shown to be a major determinant of antihypertensive efficacy, providing yet further evidence of heterogeneity.[17] So, from the important viewpoints of prognosis, hemodynamic mechanisms, and therapeutic responsiveness, measurements of the renin system provide clinical information that defines and categorizes hypertensive patients well beyond their blood pressure measurements.

Body Weight as a Differentiator

There is a well-described relationship between blood pressure and body weight; many people with hypertension are overweight or obese, and it is widely accepted that losing weight is a successful strategy for reducing blood pressure.[9] But this relationship is even more complex: excess body weight is associated not only with increased blood pressure but also with

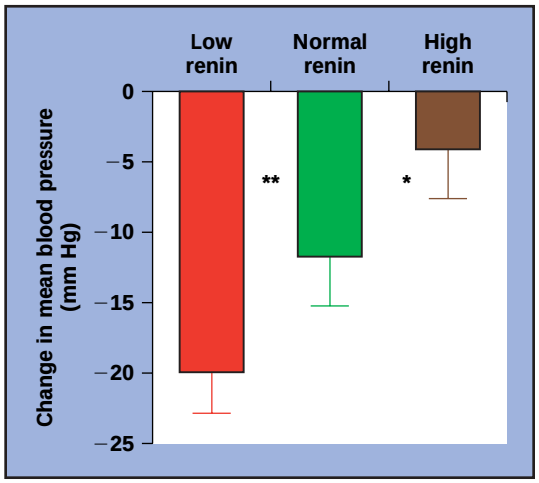


Figure 3. *Effects of treatment with chlorthalidone on mean blood pressure in hypertensive patients classified into high, normal, and low renin subgroups. *P < .05; **P < .025. Reproduced with permission from Weber et al.*[17]

key metabolic and clinical findings like dyslipidemias, insulin resistance, and left ventricular hypertrophy.

Even so, there is an interesting paradox: obese hypertensive patients, despite the presence of other concomitant cardiovascular risk factors, as shown in Figure 4, actually have a better prognosis than lean hypertensive patients.[18] In addition, although clinical outcomes in obese hypertensive patients are poorer than in either obese or lean people with normal blood pressures,[18] it is quite evident that body weight—independent of the so-called metabolic syndrome—is another factor that determines heterogeneity in hypertension.

The differences between obese and lean hypertensive patients go beyond the obvious metabolic findings. For instance, whereas obese patients are more likely to have dyslipidemias and evidence of insulin resistance, lean patients have greater evidence of early cardiovascular changes, such as decreased arterial compliance.[19] Interestingly, when looking at factors that might mediate changes in arterial stiffness, we find further evidence of heterogeneity: in obese individuals, arterial compliance is linked far more strongly to plasma insulin levels than to neuroendocrine measurements, whereas in lean patients arterial compliance is most strongly related to plasma norepinephrine.[19]

In fact, it is possible that the unexpectedly poorer outcomes in lean hypertensive patients could be explained by greater activity of neuroendocrine factors. During treadmill exercise, as shown in Figure 5, there are significantly greater increases in plasma renin and plasma epinephrine levels in lean people (either hypertensive or normotensive) than in obese individuals (either hypertensive or normotensive).[19] Furthermore, the Systolic Hypertension in the Elderly Program demonstrated yet another point of differentiation.[20] Treatment with a diuretic, chlorthalidone, was most effective (particularly in women) in reducing fatal events in overweight and obese patients but seemed to have potentially adverse effects on prognosis in lean individuals.

Again, this observation indicates that different mechanisms are at work in the 2 types of patients: potentially a volume-dependent form of hypertension in obese individuals; and a neuroendocrine (possibly renin)-dependent form of hypertension—which is not appropriate for treatment with a diuretic—in lean patients. Finally, unlike lean hypertensive patients, overweight or obese people with hypertension might have another basic advantage: good adherence to lifestyle strategies, particularly weight loss, has the potential for substantially improving the poor outcomes associated with high blood pressure and other risk factors.

The Hypertension Syndrome

Hypertension rarely exists as a solitary finding of high blood pressure

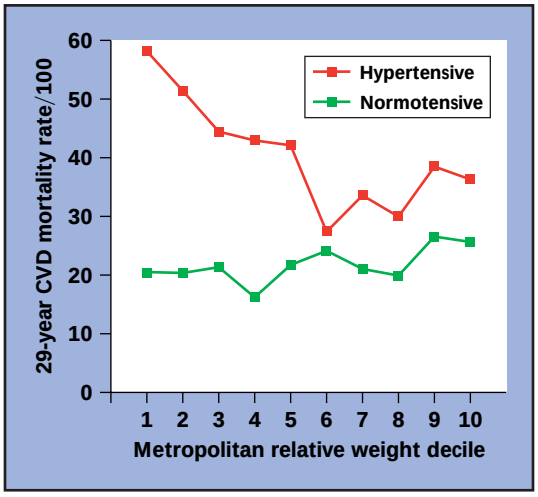


Figure 4. *Relationship between body mass (expressed as Metropolitan relative weight deciles) and mortality in people classified as hypertensive or normotensive. CVD, cardiovascular disease. Reproduced with permission from Carman et al.*[18]

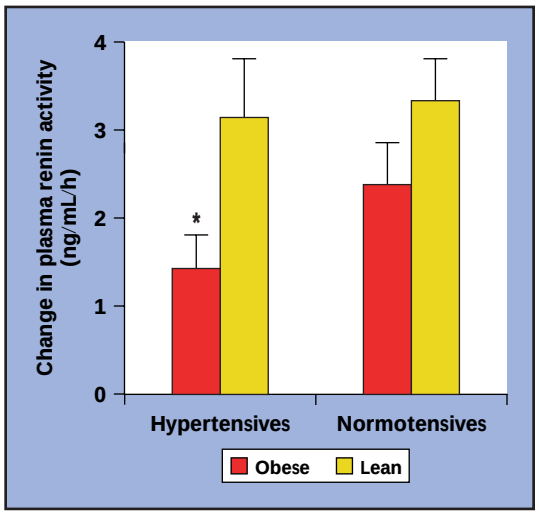


Figure 5. *Changes in plasma renin activity measured during standardized treadmill testing in hypertensive and normotensive subjects classified into obese and lean subgroups. *P < .01 vs lean hypertensives and lean normotensives. Reproduced with permission from Weber et al.*[19]

but most commonly includes a variety of metabolic abnormalities as well as changes in the structure and function of the left ventricle and evidence for changes in arterial compliance. Similarly, early changes in renal function, including microalbuminuria, are often found. This last feature is of particular interest because it is highly predictive of major cardiovascular events,[21] perhaps indicating that microalbuminuria is a marker of endothelial dysfunction or some other systemic abnormality throughout the circulation. Clearly the presence or absence of such a finding, as discussed previously with other findings, would assign hypertensive patients into differing risk categories.

The presence of hypertension or the metabolic syndrome—dyslipidemias and insulin resistance—is a further way of dividing hypertensive patients. If diabetes is present, this obviously will have a powerful impact on the probability of subsequent cardiovascular events. But even apparently lesser metabolic abnormalities could be important. This was demonstrated in an important recent study, the lipid arm of the Anglo-Scandinavian Cardiac Outcomes Trial. Treatment with a low-dose statin in hypertensive patients whose low-density lipoprotein cholesterol levels were essentially normal and clearly too low to meet the conventional guideline criteria for statin therapy significantly reduced major clinical events.[22]

This finding seems to emphasize that even relatively subtle changes in hypertensive patients might carry important consequences and again supports the relevance of evaluations of hypertensive patients that could differentiate the treatments they receive. It would be helpful, however, if tests or classification methods were available, as part of the definition of hypertension, that could provide guidance in assigning these patients to appropriate categories. For example, noninvasive methods for measuring early or more advanced arterial stiffening, which might not be evident from more conventional clinical evaluations, could be of value in optimizing management in individual patients.

Noninvasive methods for measuring early or more advanced arterial stiffening, which might not be evident from more conventional clinical evaluations, could be of value in optimizing management in individual patients.

Family History

Perhaps at some point in the future a detailed understanding of the genetics of hypertension will allow underlying disease mechanisms to be accurately defined in each patient so that a specific course of personalized medication (or other types of therapy) could be offered. At present, with the exception of some relatively rare single-gene abnormalities that have been described, this type of targeted approach is not yet possible.

Still, there is evidence to suggest that there are important familial trends in hypertension. If nothing else, these characteristics can be used for early detection of hypertensive disease, making it possible to alter its natural history before major cardiovascular changes occur. The offspring of hypertensive patients, either children or young adults, often manifest clinical differences when compared with age-matched individuals who do not have a family history of hypertension. For instance, young people with normal blood pressure but with a positive family history of hypertension can have higher plasma concentrations of insulin, renin, norepinephrine, and triglycerides than are found in cohorts without a family history.[7] Similarly, left ventricular muscle mass and measures of left ventricular diastolic function, arterial compliance, and renal function can also be influenced by a family history of hypertension.[7,8]

Admittedly, family history must be interpreted with caution: although

it might be a useful indicator of genetically mediated early clinical changes, it is also possible that family members—particularly if they live in the same or similar environments—may share common lifestyle attributes that, rather than genetics, could be responsible for the clinical changes. Even so, early clinical changes seem to offer the opportunity of identifying hypertension-prone candidates sooner than would be possible simply by screening people with conventional blood pressure measurements. Which tests should be performed, and the practicality and cost-effectiveness of such strategies, are questions that remain to be resolved. But this type of approach clearly could play an important part in broadening our definition of hypertension, ultimately leading to earlier diagnosis and more focused management.

Other Points of Differentiation

One of the most obvious ways of defining hypertension is by the ethnicity of patients. It is well established, for instance, that African Americans are more likely than whites or other ethnic groups to develop hypertension and that they are more likely to experience adverse consequences, particularly renal failure.[23] Moreover, it has been argued that certain antihypertensive drug classes are more efficacious in African Americans, whereas others seem to work better in whites. Despite these trends, however, there is a large overlap in clinical features across most large ethnic and racial groups, and it is difficult to define hypertension characteristics that are unique to one group or another.

One clinical finding that has attracted a lot of interest by investigators is left ventricular hypertrophy. This finding is not only relatively common in hypertension but—by mechanisms that have not yet been well elaborated—is also highly predictive of stroke. The preliminary recommendations for the new definition of hypertension take findings like left ventricular hypertrophy very much into account, making the assumption that even though such findings are at least partly blood pressure–dependent, they provide sufficient heterogeneity across hypertensive patient populations to provide a functional basis for differentiation and definition. The fact that certain therapeutic interventions are more efficacious than others in causing regression of left ventricular hypertrophy further indicates that this finding might also be a marker for underlying neurohormonal abnormalities.

The preliminary recommendations for the new definition of hypertension take findings like left ventricular hypertrophy or reduced arterial compliance very much into account.

Other types of clinical findings will further add to a better understanding of individual patients. As discussed earlier, microalbuminuria is a particularly valuable tool. Similarly, some of the measures of arterial compliance (or its reciprocal, stiffness) will provide valuable methods for identifying early disease and providing an opportunity for appropriate management. Confusingly, at present there are several competing methods, all reasonably valid and useful, that have been made available for this purpose. Ultimately, expert guidance may be required to determine how to select and interpret these differing noninvasive tests and apply them to identifying the presence of hypertensive disease in the vasculature.

Other methods for studying the circulation include such indicators as endothelial function, as well as assays of inflammatory markers like high-sensitivity C-reactive protein (which, of course, is now available as a routine laboratory test). A variety of cytokines, growth factors, and other molecules that can affect oxidative, proliferative, and connective tissue processes could also eventually be part of assessing hypertensive patients.

A New Definition of Hypertension

The proceedings at the ASH meetings that focused on the new definition of hypertension reached an inevitable conclusion: that this task is still very much a work in progress. The preliminary report of the Working Group, expected to be published during 2005, will emphasize that hypertension cannot be diagnosed or defined on the basis of blood pressure alone but rather must take into account an evaluation of blood vessels and target organ involvement.

In turn, evidence for vascular, renal, cardiac, and central nervous system changes must integrate the factors that govern these findings. All the issues discussed in this brief report, including age, gender, renin, concomitant risk factors, body habitus, heredity, and a variety of humoral factors, must also be incorporated into a broad view of hypertension. The key to this process will be a pragmatic approach to identifying the cluster of pivotal findings that can at least provide a broad and clinically useful classification of hypertensive disease. Unless this process is relatively simple and accessible to most physicians and their patients, it cannot be effective.

Finally, as the ASH working group and experts in other settings consider and debate this issue, it will be important to remember that high blood pressure—even if it does not tell the whole story—can explain a great deal about hypertension. Clearly, clinicians should continue to focus on the well-proven benefits of controlling blood pressure in their hypertensive patients, at least until a new definition of hypertension is more fully translated into practical clinical strategies. ■

References

1. Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking and death from coronary heart disease: overall findings and differences by age for 316,099 white men. *Arch Intern Med.* 1992;152:56-64.
2. Lewington S, Clarke R, Qizilbash N, et al. Prospective Studies Collaboration. Age-specific relevance of usual BP to vascular mortality: a meta-analysis of individual data for one million adults in 60 prospective studies. *Lancet.* 2002; 14:1903-1913.
3. Staessen JA, Gasowski, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcomes trials. *Lancet.* 2000;104:865-872.
4. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ.* 1998;317:703-713.
5. Hansson L, Zanchetti A, Carruthers S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. *Lancet.* 1998;351:1755-1762.
6. Julius S, Kjeldsen S, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomized trial. *Lancet.* 2003;363:2022-2031.
7. Neutel JM, Smith DHG, Graettinger WF, et al. Metabolic characteristics of hypertension: importance of positive family history. *Am Heart J.* 1993;126:924-929.
8. Weber MA. Role of hypertension in coronary artery disease. *Am J Nephrol.* 1996;16:210-216.
9. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA.* 2003;289:2560-2572.
10. 2003 European Society of Hypertension–-European Society of Cardiology guidelines for the Management of Arterial Hypertension. *J Hypertens.* 2003;21:1011-1054.
11. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med.* 1997,157:2413-2446.
12. Hajjar J, Kotchen TA. Trends in prevalence, awareness, treatment and control of hypertension in the United States, 1988-2000. *JAMA.* 2003;290:199-206.
13. Brunner HR, Laragh JH, Baer L, et al. Essential hypertension: renin and aldosterone, heart attack and stroke. *N Engl J Med.* 1972;286:441-449.
14. Alderman MH, Madhaven S, Ooi WL, et al. Association of the renin-sodium profile with the risk of myocardial infarction in patients with hypertension. *N Engl J Med.* 1991;324:1098-1104.
15. Laragh JH. Vasoconstriction volume analysis for understanding and treating hypertension: the use of renin and aldosterone profiles. *Am J Med.* 1973;55:261-274.
16. Buhler FR, Laragh JH, Baer L, et al. Propranolol inhibition of renin secretion. A specific approach to diagnosis and treatment of renin-dependent hypertensive diabetes. *N Engl J Med.* 1972;287:1209-1214.
17. Weber MA, Drayer JI, Rev A, et al. Disparate patterns of aldosterone response during diuretic treatment of hypertension. *Ann Intern Med.* 1977;87:558-563.

Main Points

- An ad hoc working group of the American Society of Hypertension has received support from the Society to write and publish a considered opinion on the issue of a new hypertension definition.
- This working group's recommendations will stress that a diagnosis of hypertension can depend on the discovery of vascular changes, even in the absence of an elevated blood pressure, and that a new staging system for hypertension should be developed, based on evidence for vascular disease as well as more traditional findings of increased blood pressure and the presence of other cardiovascular risk factors.
- In terms of age, it is almost certain that different vascular processes are at work in elderly as compared with younger patients, even at the same level of blood pressure; possible explanations for this phenomenon include inflammatory processes, degenerative or apoptotic changes in the vasculature, and the chronic effects of heightened activity of the renin-angiotensin system.
- Measurements of the renin system provide clinical information that defines and categorizes hypertensive patients (in terms of prognosis, hemodynamic mechanisms, and therapeutic responsiveness) well beyond their blood pressure measurements.
- Regarding body weight, observations indicate that different mechanisms are at work in obese versus lean patients: potentially a volume-dependent form of hypertension in obese individuals and a neuroendocrine (possibly renin)-dependent form of hypertension in lean patients.
- Evidence suggests that there are important familial trends in hypertension; these characteristics can be used for early detection of hypertensive disease, making it possible to alter its natural history before major cardiovascular changes occur.
- Clinicians should continue to focus on the well-proven benefits of controlling blood pressure in their hypertensive patients, at least until a new definition of hypertension is more fully translated into practical clinical strategies.

18. Carman WJ, Barrett-Connor E, Sowers M, Khaw K. Hypertension/risk factors: higher risk of cardiovascular mortality among lean hypertensive individuals in Tecumesh, Michigan. *Circulation*. 1994;89:703-711.
19. Weber MA, Neutel JM, Smith DHG. Contrasting clinical properties and exercise responses in obese and lean hypertensive patients. *J Am Coll Cardiol*. 2001;37:169-174.
20. Wassertheil-Smoller S, Fann C, Allman RM, et al. Relation of low body mass to death and stroke in the systolic hypertension in the elderly program. *Arch Intern Med*. 2000;160:494-500.
21. Agrawal B, Berger A, Wolf K, et al. Microalbuminuria screening by reagent predicts cardiovascular risk in hypertension. *J Hypertens*. 1996;14:223-228.
22. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383-1389.
23. Consensus statement of the Hypertension in African Americans Working Group of the International Society on Hypertension in Blacks. Management of high blood pressure in African Americans. *Arch Intern Med*. 2003;163: 525-541.