Heterogeneity among Hypertensive Subjects: a Tool for Clinical Decision-Making

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Current antihypertensive treatment strategy tends to approach all patients similarly, with decision to treat, the goal of treatment, and medication use based largely on blood pressure measurement. Clearly, it would make far more sense if a management strategy could be developed that was not solely dependent on measurement of blood pressure, but rather reflected a clearer understanding of individual likelihood of adverse outcome, the nature of blood pressure control, and the importance of associated clinical and biological characteristics. New tools make it possible to accurately assess the status of the heart, kidney, and blood vessels, both as a guide to the need for therapy and as a measure of treatment progress when the treatment is used. New understanding of the vasoconstrictror and volume contributions to blood pressure control coupled with a rich armamentarium of therapeutic agents make it possible to tailor therapy more appropriately. Finally, growing awareness of the contribution of concomitant risk factors has made it clear that overall success depends on attention to the whole patient.

For more than half a century, it has been clear that high blood pressure was associated with increased cardiovascular disease (CVD). Then, with the development of orally effective antihypertensive pharmacological agents in the 1950s, it became feasible to test and, by the late 1960s, to confirm the hypothesis that reducing blood pressure could save lives by preventing cardiovascular events. Thus, measurement of blood pressure, long recognized to be useful in estimating risk for heart attack and stroke, had become a tool to guide clinical therapeutics as well.

Subsequent clinical research has been based on the convenient fiction that some arbitrary blood pressure value can distinguish hypertensives—those who are to be treated—from normotensive subjects—those who are not to be considered for drug intervention. In subjects classified as hypertensive, it has been consistently demonstrated that much of the excess stroke mortality attributable to above-normal blood pressure can be averted by antihypertensive drug therapy (Figure 1) (1–3). By contrast, the reduction of coronary artery disease events achieved in these same trials is far less than one might expect from the risk attributed to hypertension in observational studies. Indeed, it is not at all certain that current treatment strategies actually produce any reduction in coronary artery disease events in hypertensive patients. Moreover, because most mild hypertensive subjects are unlikely to experience a premature cardiovascular event, universal treatment of these patients commits very large numbers of individuals to drug therapy from which only a small minority can or will benefit (4). Moreover, as the clinical trials show, even that small CVD risk is only partially reduced (by about 20% overall) by this treatment process. From these experiences, one can reasonably conclude that our current clinical strategies, based on the premise that all patients whose blood pressure is above a certain cutoff value should be treated, are both woefully inefficient and not sufficiently effective.

Nevertheless, this strategy has produced some demonstrable benefit in the aggregate. It has certainly contributed to the dramatic decline in stroke disease seen in the U.S. over the past 30 years. However, because antihypertensive drugs can cause metabolic derangements that, in themselves, might contribute to cardiovascular morbidity, and because excessive reduction of blood pressure, as illustrated by the J-shaped curve in Figure 2 (5), has been shown to actually increase cardiac mortality, standard drug therapy clearly is not an invariably benign procedure (6). Given the hazards of therapy, perhaps the modest decline in heart attacks observed in these clinical trials is actually the net result of events prevented by treatment, less the events actually produced by excessive manipulation of blood pressure. Although such a process might produce a slightly positive "bottom line," it masks the unpleasant possibility that standard treatment results in both harm and benefit, these opposing consequences of treatment being experienced by different individuals. If true, this situation clearly represents less than optimal intervention.

This disturbing situation is, I believe, due to the

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therapeutic decision-making strategy, which depends almost exclusively on the measured blood pressure. This pattern was the basis for the major clinical trials, and has been subsequently cast in stone by National Consensus conferences (7). By fiat, it has been recommended that all persons whose diastolic blood pressure (DBP) exceeds some specific number—usually 90 or 95 mmHg—should be treated. Presumably, such a strategy is based on two tacit assumptions. First, because only a very few mild hypertensive subjects are likely to experience a premature cardiovascular event without treatment and therefore stand to benefit from treatment, presumptively treatment itself carries only trivial potential for harm. As noted above, this assumption is no longer tenable. Exposure of vast numbers of hypertensive subjects to drug treatment carries the potential of provoking a great deal of damage.

The second unspoken assumption must be that the risk of cardiovascular events among patients grouped by pressure is stochastically distributed. This assumption also fails to withstand careful scrutiny. If persons homogeneous with regard to blood pressure are heterogeneous in other important regards, it is possible that the risk of a CVD event is not randomly distributed. Clinical and prognostic heterogeneity does, in fact, characterize patients classified on the basis of blood pressure. As Dr. Kannel and his colleagues in Framingham have so elegantly demonstrated over the past 40 years, blood pressure alone offers only a modest ability to segregate risk (8). Indeed, other well-recognized and easily identified patient risk factors (glucose intolerance, hypercholesterolemia, and smoking) are at least as powerful predictors of CVD disease as above-normal blood pressure is (Figure 3) (9). Thus, although there is a gradient of risk related to blood pressure, the absolute risk is best defined by the overall characteristics of the person. Because these and other prognostically relevant risk factors are not randomly distributed, and because these factors can be quantified, individually and collectively, they may provide a basis for further precision in therapeutic decision making.

In addition to these risk factors, careful patient eval-

Fig. 2. Relationship of myocardial infarction (MI) and non-CVD mortality to magnitude of decrease in blood pressure among treated hypertensive subjects.
A large fall in diastolic blood pressure (DVP) was >17 mmHg, a moderate fall 7-17 mmHg, and a small fall <7 mmHg. Adapted from Alderman et al. (5).

Fig. 3. Risk of cardiovascular disease according to systolic blood pressure (BP) at specified values of other risk factors in 40-year-old men; 18-year follow-up. Reprinted with permission from WB Kannel, Am J Cardiol (9). ECG-LVH, electrocardiographically determined left ventricular hypertrophy.

Fig. 4. Relation of total mortality (top) and cardiovascular events (bottom) to patterns of left ventricular (LV) geometry in 253 patients with essential hypertension.
Mortality and event rates are highest in patients with concentric hypertrophy (C), lowest in patients with normal ventricular geometry (B), and intermediate in patients with eccentric hypertrophy (E) and concentric remodeling (B). P <0.001 for total mortality and P = 0.03 for CV events (by analysis of variance). Reprinted with permission from MJ Koren et al. Ann Intern Med, March 1, 1991.
patients with increased blood pressure are not the same with regard to likelihood of adverse CVD outcomes or in expectation of benefit from treatment. For example, in the Medical Research Council trial (10), participants having the same values for blood pressure could be segregated into high-risk and low-risk subgroups (Figure 5) with very different expectations of outcome, both in terms of absolute numbers of events in both the treated and the control groups and in numbers of events prevented. Despite the wide difference in absolute risk, however, the relative benefit of reducing blood pressure was essentially the same. Therefore, the great difference between the two groups was in the number of subjects who had to be treated without benefit for each one who did avoid a stroke or heart attack.

These observational and experimental studies provide the underpinning for a management strategy that exploits the prognostic and physiological heterogeneity of patients with high blood pressure. Management must start with the comprehensive assessment of each patient, beginning with the measure of blood pressure itself. Whatever the blood pressure that defines hypertension, it must have a time dimension. It is well known that, as with other gaussianly distributed biological phenomena, blood pressure, over time, has a tendency to regress toward the mean. The magnitude and significance of that regression have not always been fully appreciated in regard to mild hypertension. In fact, for example, in the Australian National Trial (11), nearly 50% of mild hypertensive subjects in the control group (prestudy mean DBP of two visits, 102 mmHg) had, after three years without treatment, a final DBP <95 mmHg. In fact, only about 22% of the controls whose pretreatment DBP was 100–104 mmHg maintained pressures >100 mmHg throughout the study. And, most importantly, excess CVD morbidity was restricted to the latter group. In short, the first step in prognostic stratification should be the prolonged pretreatment observation of mild hypertensive subjects. A declining blood pressure value is associated with a risk that is, if anything, lower than that experienced by persons at similar starting pressures who were treated to reach that lower pressure (Figure 6) (11).

The next step in prognostic stratification is assessment of associated risk factors. As noted, the Framingham Study established the strong and step-wise independent relationship of total cholesterol, fasting blood sugar, and cigarette smoking to CVD events. Among hypertensive subjects, these additional risk factors tended to be multiplicative when they coexisted in the same patient. In an occupationally related group of New Yorkers, my colleagues and I determined that these same risk factors have a prognostic impact that persists among treated hypertensive subjects.

In addition to these traditional factors, we have prospectively examined the predictive power of the renin/angiotensin system in 1717 hypertensive subjects (12). Relating plasma renin activity to urinary sodium excretion, we stratified patients into high-, medium-, and low-renin categories. About 12% of the subjects had high renin; these subjects tended to be younger, white, and male. In univariate analysis, those subjects who had a high-renin profile determined before the initiation of therapy were about three times as likely as the low-renin subjects to have had a heart attack. This robust predictive value was best displayed in regard to myocardial infarction (Figure 7) and did not appear in regard to strokes, although the very small number of strokes (n = 12) provided little power to detect a relationship if one did exist (12). The predictive power of renin was in evidence in hypertensive subjects who had other risk factors, but was most discriminative among mild hypertensive subjects free of any of the other conventional risk factors. In fact, among such lower-risk subjects, high-renin patients were seven times as likely as the low- and medium-renin subjects to experience a CVD event. It is this lowest risk subgroup, whose members are at such little inherent risk of CVD, that has the greatest need for tools other than blood pressure to guide management decisions.

Ultimately, through multivariate analysis, four risk factors were identified, including renin and the three well-established risk factors—cholesterol ≥2400 mg/L,
(6.2 mmol/L), fasting blood sugar $\geq 1400$ mg/dL (7.8 mmol/L), current smoker—which we combined to create an overall prognostic index involving stratification into three subgroups. Figure 8 displays the relative CVD risk for low-risk subjects, who have none of these four characteristics; medium-risk subjects, who have one of the characteristics; and high-risk subjects, who have two or more. As shown, the high-risk, mildly hypertensive subjects were roughly 20-fold more likely to experience a CVD event, despite effective blood pressure control, than were the low-risk subjects. Of the patients with DBP of 90–104 mmHg, i.e., the vast bulk of all hypertensive subjects, only 18% were high risk; 35% were low risk (Figure 9) (13).

Prognostic stratification thus identifies a minority of all persons with sustained blood pressure increases who, even when successfully treated for high blood pressure, remain at very high CVD risk. For low-risk patients, the process of prognostication can be made even more precise by determining whether target organ disease is present. Available and accessible technology makes it possible to detect preclinical damage of the heart—either left ventricular hypertrophy by electrocardiography (or more sensitively, by echo) (14) or prior myocardial infarction—or damaged blood vessels (carotid atherosclerosis detected by Doppler/ECHO or peripheral vascular disease detected by the measurement of arm and ankle blood pressure), or damaged kidney, as evidenced by a plasma creatinine $\geq 17$ mg/dL (150 $\mu$mol/L) (15) or, perhaps, microalbuminuria (16). In our experience, only about 12% of low-risk mild hypertensive subjects have at least one of these disease markers. The presence of target organ disease, in addition to signaling high risk for CVD, is a further yardstick to be used in gauging the absolute benefit of treatment. The absence of end-organ disease in otherwise low-risk mildly hypertensive subjects further reduces the likelihood of future CVD, and diminishes the absolute benefit that might be expected from antihypertensive drug therapy.

Although no prospective randomized study has established the clinical wisdom of withholding drug treatment from these low-risk disease-free subjects with mild hypertension, retrospective analysis of the experience of 8000 mildly to moderately hypertensive participants in the British Medical Research Trial confirms the marked difference in absolute benefit—the actual number of subjects avoiding a CVD event—between high- and low-risk subjects. Treatment, overall, produced a small decrease in stroke occurrence but no significant change in heart attack incidence. However, analysis of the experience of the participants of the Medical Research Center trial, segregated by the presence of risk factors similar to those applied in our clinical study, distinguished subgroups with very different expectation of events despite similar entry and in-treatment blood pressure values (10). High-risk subjects had roughly 150 CVD events per 1000 patient years, whereas low-risk subjects had only 2–3 per 1000 patient years (Figure 8). The relative risk reduction by diuretics (the best case) was about 1:3 in both risk categories. However, in absolute terms, that meant that 52 of every 1000 high-risk subjects were benefited, compared with $<1$ of every 1000 low-risk subjects.

The distinction between absolute and relative risk...
reduction, I believe, should be part of the information that is used to determine the value of drug treatment. Although this analysis was based on theoretical multivariate modeling of actual data, it strongly supports the idea that one can identify a group of mild hypertensive subjects for whom treatment offers trivial, if any, benefit, and that this benefit can be purchased only at the price of treating very many more subjects. That is entirely consistent with what might have been expected from the Framingham study.

Taken together, the Framingham study, our own clinical experience, the results of clinical trials, and the ex post facto assessment of the British Medical Research Trial strongly support the proposition that treatment decisions based exclusively on the measurement of blood pressure are no longer tenable. Instead, a clinical staging process is available that can provide useful information in planning the management of individual mildly hypertensive subjects. Figure 9 summarizes a strategy that we believe permits the most effective management of hypertensive subjects. This algorithm provides a useful paradigm for translating prognostic stratification into therapeutic decision making. The first step is to measure the blood pressure. Diastolic pressures \( \geq 105 \) mmHg that are sustained portend an absolute risk that merits drug treatment. Although even these patients might experience a decrease in pressure over time, this possibility can be dealt with by a subsequent trial of drug withdrawal after control of blood pressure has been achieved and maintained with drugs for at least six months (17).

Mildly hypertensive patients (DBP 90–104 mmHg) are next segregated by individual risk-factor status into three categories. Roughly two-thirds have at least one additional risk factor; it is these patients, I believe, who merit pharmacological intervention. However, simply lowering the pressure of these subjects can reduce only those CVD effects attributable to the degree of blood pressure change produced. These subjects clearly need further intervention to maximize CVD prevention. For example, if a high or medium concentration of renin is present, a converting enzyme inhibitor or perhaps a beta blocker may be the appropriate first therapeutic agent. Both epidemiological evidence, and human and animal experimental data, suggest that renin (and presumably angiotensin) is vasculotoxic (18). Thus, although unproven, a drug that reduces angiotensin concentrations might have a cardioprotective effect beyond its capacity for lowering blood pressure. Inhibiting converting enzyme may also be a very effective antihypertensive therapy in such patients.

In addition, one should pay specific attention to the presence of other risk factors. Recent evidence from Sweden, for example, suggests that hypertensive patients whose above-normal cholesterol concentration is reduced during antihypertensive treatment are likely to have a lower incidence of myocardial infarction, whereas similar patients whose cholesterol does not decrease during treatment do not (19). Although no similar evidence exists regarding fasting blood sugar, I nevertheless believe that a weight reduction and (or) exercise program linked to antihypertensive treatment might be helpful in hyperglycemic cases as well.

The guiding principle in this strategy, absent specific experimental evidence to support the belief that some low-risk mild hypertensive patients can best avoid treatment, is to err on the conservative side by searching for excuses to justify using drugs. Thus, in low-risk subjects, we search for any evidence of preclinical end organ disease. Specifically, we assess cardiac status by electrocardiography and echocardiography. An enlarged heart or evidence of previous myocardial infarction would be grounds for initiating antihypertensive therapy. Kidney status can be evaluated by measuring serum creatinine and urinary albumin. In the Hypertension Detection and Follow-up Program, hypertensive subjects with serum creatinine \( \geq 17 \) mg/L (150 \( \mu \)mol/L) had a dramatically increased risk of a subsequent cardiovascular event, despite treatment for high blood pressure. Microalbuminuria appears to be a far more sensitive and early measure of renal damage. Although its predictive significance in hypertensive subjects has not been defined, we believe that either above-normal serum creatinine or \( >30 \) mg of albumin excreted in 24 h would justify drug treatment. Finally, a family history of CVD events at a premature age (<55 years) would also tip the scales toward drug therapy. Despite this extensive search, only a small minority of the low-risk mild hypertensive subjects display evidence justifying immediate drug treatment.

There remain about one-third of all the mild hypertensive subjects who are without other risk factors, or evidence of end organ disease, or adverse family history. In my opinion, these patients can be spared the hazard of immediate antihypertensive drugs. Management of these patients should be rigorous, but conservative. Blood pressure should be measured at three-month intervals and an annual search made for the appearance of disease markers. If cardiac or renal damage is caused by above-normal blood pressure, the appearance of these end organ changes should be preceded by an increase in blood pressure. I believe that a persistent increase in blood pressure—at least 5 mmHg diastolic or 10–20 mmHg systolic—provides a sound basis for initiating therapy. Of course, any evidence of end organ change would provoke immediate drug therapy.

This management strategy, based on data derived from both observational and experimental studies, is designed to improve both efficiency and efficacy of hypertensive patient care. It is a demanding process that depends on rigorous application of modern clinical and laboratory tools well beyond the single measure of blood pressure to support rational clinical decision-making. This staging process also identifies those who might benefit from an intervention that goes beyond simple control of blood pressure. Finally, and perhaps of greatest value, it identifies millions of mildly hypertensive subjects whose absolute risk of disease is so meager...
as to suggest that they can be spared treatment. Instead, such patients can be carefully monitored to detect any change in circumstance that would imply the need for drug therapy.

Adherence to this strategy will free the clinician from exclusive reliance on an artificial threshold value for blood pressure to identify who should be treated. Further, it permits those in whom there is trivial inherent danger and consequently little chance of benefit to avoid the harm of needless therapy, thus conserving scarce resources. Finally, by more-precise characterization of those at greatest hazard and identification of the potential need for interventions that go beyond and complement blood pressure reduction, this strategy is likely to substantially increase cardioprotection in patients with hypertension.

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References