Commentary

Debate: Does it matter how you lower blood pressure?

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Abstract

Whether it matters how pressure is lowered has been debated since antihypertensive drugs proved to prevent cardiovascular events. However, in clinical trials, while the stroke benefit predicted by a given difference in blood pressure was achieved, the results for myocardial infarction were roughly half that expected. This suggested that adverse drug effects of diuretics and β-blockers might have detracted from their hypotensive effects. Trials with newer antihypertensive classes have revealed superior effects on outcomes associated with converting enzyme inhibitor use, and that α-blockers are less cardioprotective than diuretics. These studies establish that simple blood pressure reduction is an inadequate guide to therapy. The challenge now will be to determine the optimal therapy for each hypertensive patient.

Keywords: antihypertensive drugs, antihypertensive therapy, clinical trials, hypertension

Does it matter how blood pressure is lowered? Of course it does, but the focus of concern varies according to one's perspective. Clinicians worry about pharmacologic choices. Public health practitioners worry about interventions to change behavior.

Blood pressure is a physical sign that reflects the pressure exerted on the arterial wall, and is determined by the circulatory volume, the force of cardiac contraction, and the tonic state of the arterial vessels. Genes and environment, operating through a variety of neuronal, hormonal, and cellular mechanisms, together determine the status of each of these components. The integrated product of these multiple factors is a blood pressure level that reflects the sum total of a variety of individual mechanisms. Moreover, many of these mechanisms are also involved both in blood pressure control and in the maintenance of vascular structure and function. Thus, perturbation of these mechanisms may either elevate blood pressure or stimulate vascular disease, or both. Presumably, the strokes and heart attacks that occur with greater frequency in those with elevated blood pressure are most likely to occur when both blood pressure and vasculotoxic mechanisms are affected.

From a clinical perspective, the salient point is that the height of pressure directly relates to cardiovascular disease occurrence. In fact, there is a quantitatively predictable,

ACE = angiotensin-converting enzyme; CCB = calcium channel blocker.

linear relationship between the height of the pressure and the likelihood of both heart attack and stroke. This has perhaps best been described through the meta-analysis of multiple observational studies presented by MacMahon *et al* [1]. Most authorities, but not all, now accept the reality that there is no threshold level by which it is possible to separate persons with normal from those with abnormal pressures, but the observed relationship is best understood as reflecting a continuous risk. Nevertheless, on the basis of clinical trial experience, and by convention, an arbitrary divide has been applied to invent the condition we term 'hypertension'. A growing consensus also supports the view that levels of blood pressure alone should not determine the need for therapy. It is but one component of many that defines absolute risk, which is the appropriate foundation on which to base therapeutic decisions.

Availability of orally effective antihypertensive agents made it possible to test, and ultimately confirm the hypothesis that a reduction in pressure could prevent cardiovascular events [2]. Early trials, almost always comparing treatment with diuretics and/or β-blockers with placebo, consistently showed that the decline in strokes (for a given reduction in either systolic or diastolic blood pressure, expected by virtue of the epidemiologic evidence) was actually achieved. Disappointingly, however, only about half of the epidemiologically predicted benefit with regard to heart attack occurred [3].

To my way of thinking, the failure to realize the reduction in heart attack anticipated by the blood pressure change is important evidence that the treatment of hypertension is about more than simply a change in blood pressure. The fact that, in these trials, the same drugs produced different results in two blood pressure-related outcomes lends further weight to the argument that methods of blood pressure lowering may affect risk.

These clinical trials were not designed to explain these differences, nor can they. Perhaps there are adverse consequences of pharmacologic agents that are unrelated to their blood pressure-lowering effect, which may be observed and/or unrecognized. Virtually all drugs have actions beyond those for which they are designed. Diuretics, for example, have an impact on electrolyte balance, lipid and uric acid metabolism, and glucose economy, in addition to their intended hemodynamic effect [4]. The net effect of any particular class of antihypertensive agents may be the sum of the benefit produced by a lower blood pressure and the harmful consequences of its metabolic disturbances.

There is, however, another possibility. Antihypertensive agents alter blood pressure through different mechanisms. For example, diuretics act in part by depleting blood volume. At the same time, they tend to stimulate the renin–angiotensin system. There is strong experimental and epidemiologic evidence that an activated renin–angiotensin system not only tends to increase blood pressure, but is also vasculotoxic [5]. This undesired hormonal effect increases the risk for myocardial infarction. Thus, a diuretic may simultaneously produce opposing effects. By virtue of its hypotensive property, a diuretic might prevent heart attacks. At the same time, by activating the renin–angiotensin system, there might be an increase in heart attacks. In this case, there would be a dissociation between the blood pressure effect and the vascular effects. The unpredictable net health impact would therefore be the sum of these conflicting effects.

These clinical studies are consistent with emerging understanding of the biology of vascular disease. Diuretics provide but one example of how disparate the actions of these pharmacologic probes may be. New and anticipated classes of antihypertensive agents are now characterized according to their unique and vastly differing effects on vascular structure and function, as well as according to their hypotensive potential. It seems almost inevitable that clinical outcomes will also differ in response to these agents.

Recognition that equal blood pressure reduction may not always deliver equal cardioprotection has led to formal comparisons of individual antihypertensive agents. The largest of these, the National Heart, Lung, and Blood Institute-sponsored ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) [6], began in 1993 and has recruited 42 000 persons over 55 years. That study compares three new antihypertensive drug classes with traditional chlorothalidone. The outcome of interest is not blood pressure control, but the effect on stroke and heart attack. Recently, the doxazosin arm of that study was prematurely terminated because patients randomized to receive doxazosin experienced significantly and substantially more cardiovascular disease events than did chlorothalidone-treated subjects [7]. This result, unanticipated by many, particularly in view of the apparently favorable profile of metabolic effects associated with this α-blocker, confirms that equal blood pressure response does not ensure equal cardiovascular benefit.

To this important experience can be added the results of several other recently completed trials. The STOP (Swedish Trial in Old Patients with Hypertension)-2 study [8] was a comparison of conventional diuretic-based therapy with angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers (CCBs). Overall, there were no differences in cardiovascular disease event rates between the conventional and newer therapies. However, there were significant differences between CCBs and ACE inhibitors. The latter produced greater prevention against total cardiovascular events, and particularly against congestive heart failure, than did CCBs. A

similar advantage of ACE inhibitors over CCBs has been demonstrated in the ABCD (Trial of Antihypertensive Therapy in Diabetic Subjects) trial [9]. Finally, there is the recently reported HOPE (Heart Outcomes Prevention Evaluation) trial [10]. In that study, it was found that, in older persons at high risk for cardiovascular events, the addition of an ACE inhibitor to suitable conventional therapy generated substantially greater cardioprotection than did the comparison placebo treatment. Again, the increment in protection against cardiovascular events could not be explained by difference in blood pressure. An attractive candidate to explain the observed outcome might be vasculoprotection produced by ACE inhibitor-induced blockade of the renin–angiotensin system. Regardless of the explanation, it is clear that ACE inhibition in HOPE resulted in benefits that were independent of blood pressure. Together, the results of these studies add up to overpowering evidence that it does matter which drugs are used to treat hypertension.

At risk of over-simplification, an analogy can be drawn to the story of fever. At first, an elevated temperature was itself a disease. It later became clear that fever occurred in multiple circumstances, including infection. Ultimately, advances in microbiology and pharmacology made it possible to match individual therapies with specific infections. In short, the physical sign of blood pressure no more defines a homogeneous subgroup than does a particular level of temperature. Ultimately, however, it seems reasonable to expect that biomedical science will someday be able to identify the biologic heterogeneity that is obscured behind a blood pressure level. This will ultimately lead to specific disease-preventing therapies.

There are several practical consequences of the realization that it matters how pressure is reduced. First of all, it will be difficult for physicians and patients to adopt any antihypertensive agent simply on the premise that blood pressure reduction will inevitably translate into cardioprotection. There will also have to be evidence of cardioprotection. Second, in clinical trials, it can be expected that active antihypertensive controls will replace placebo control.

Nevertheless, although the realization that it matters how pressure is reduced is important, it will probably not revolutionize clinical practice. Instead, this awareness is more likely to signal the beginning of simply another, but more productive chapter in story of blood pressure management. Superiority of one pharmacologic approach over another in an aggregate study tells us the average affect. However, patients are a heterogeneous group of nonaverage individuals. Within this group, not only will individuals differ, but so too will the causes of their cardiovascular events. That is why there can be no single universal translation of clinical trial results. In fact, the physician's task will remain very much the same. Therapeutic decisions will still be based on a wise application of an amalgam of knowledge gained from physiology and vascular biology, experimentation, and clinical trial results. Ultimately, ability to both phenotype and genotype, coupled with a growing armamentarium of functionally distinct drugs, will make the match of treatment to patient both more precise, and more effective.

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