Hypertension in the Young

Preventing the Evolution of Disease Versus Prevention of Clinical Events*

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Two great dilemmas in the treatment of hypertension are when to treat and how to assess the effectiveness of drug therapy in younger patients. There is very little data about the most effective treatment strategies for younger patients with high blood pressure (BP) (1,2). This is because clinical trials are predicated on showing benefits of drug therapy on “hard clinical outcomes” such as stroke, coronary heart disease, and mortality. To ensure sufficient end points over the typical duration of clinical trials, the patients studied are invariably older and at high cardiovascular risk by virtue of established complications. Indeed most trials have only recruited patients over age 50 years, and typically the mean age of patients in trials is 65 years or more. Moreover, most of these older patients with established vascular damage require multiple drug therapies to control their BP, making it difficult to isolate the potential benefit (or harm) of specific drug therapies, over and above the overwhelming benefit of BP lowering per se in these older populations.

It is conceivable that studies of earlier BP-lowering intervention in younger patients could yield a completely different perception of the effectiveness of specific drug therapies, particularly with regard to both their efficacy at BP-lowering and, perhaps more importantly, their capacity to prevent or regress structural damage.

Hypertension evolves over many years, and this leads to important structural changes in small and large arteries and the heart (3–7). Importantly, these structural changes begin early and often go undetected for many years. With regard to small artery structure, there is a characteristic remodeling which results in thickening of the vascular media and a reduction in lumen size, increasing the wall/lumen ratio. This change dramatically increases vascular resistance, setting up a “pressure-damage-pressure” cycle of further increases in BP and further vascular structural change (8).

With regard to large arteries, increased BP generates vascular wall stress that contributes to progressive damage to the elastic fibers and stiffening of the larger conduit arteries, reducing their compliance, which widens pulse pressure (5). The consequence of large artery damage is the progressive rise in systolic BP observed with aging in Western societies. Once again, a perpetuating cycle ensues whereby the large artery damage results in further widening of pulse pressure that in turn increases wall stress, promoting further damage. Ultimately these changes disturb ventricular–vascular coupling, increasing left ventricular wall stress and promoting left ventricular hypertrophy and dysfunction.

The aforementioned structural changes in hypertensive patients are insidious and evolve over time. They usually go undetected in clinical practice until clinical signs of ischemic heart disease, stroke, or renal disease develop, by which time it is invariably too late to reverse the structural damage, and treatment serves only to delay the further insidious decline in end-organ function (6,7,9–13).

A key question is whether earlier intervention with BP-lowering therapy in younger patients would regress early structural damage and prevent further evolution of vascular structural changes? Such a finding could be important for 2 reasons. First, intuition suggests that preventing cardiovascular structural damage would most likely be beneficial. In support of this, recent studies have demonstrated that regression of left ventricular hypertrophy is associated with substantial improvements in survival (14). A second important but poorly recognized rational for early therapeutic intervention is to prevent or break the aforementioned “pressure-damage-pressure” damage perpetuation cycle in large and small arteries. This damage cycle leads to an inevitable progressive rise in of BP over time that ultimately becomes more resistant to treatment. There has been a complacent acceptance that the age-related rise in systolic BP and pulse pressure are inevitable—they are not, they represent the consequence of progressive vascular structural damage. People are not born with drug-resistant hypertension! Could it be that much earlier treatment of the hypertensive phenotype would arrest the relentless rise in BP that results in the use of multiple drug therapies in the belated struggle to overcome the consequences of large artery damage on systolic pressure and small artery damage on vascular resistance?

There is another important consideration in support of earlier treatment of hypertension. There is a common misconception that delayed treatment will completely reverse the risk associated with progressive structural damage. The evidence from clinical trials suggests that this is certainly not the case and that most people with hypertension-mediated vascular disease will eventually suc-

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cumb prematurely to its consequences. Delayed treatment reduces risk but never recovers the lost years.

In this issue of the Journal, Duprez et al. (15) report the results of an intriguing pilot study in which they have evaluated the capacity of BP-lowering with valsartan (an angiotensin receptor blocker [ARB]) to slow the progression of a range of early indicators of vascular disease in a population of patients with hypertension (treated and untreated) whose BP is at goal (<140/90 mm Hg). This study set out to establish proof of principle that it would be feasible to detect early markers of benefit from therapeutic intervention. Various markers of early structural damage or dysfunction were assigned an arbitrary score that was then aggregated to yield a vascular disease score. This score was heavily weighted toward structural abnormalities, which is appropriate, mindful of their importance. It should be emphasized that the disease score has not been formally validated as a robust marker of clinical outcome, but it does provide a plausible and pragmatic index of early vascular damage.

A weakness of the study is its small size and short duration. The former led to inequalities in the baseline scores between groups, and the latter might not have allowed sufficient time for the structural benefits of intervention to fully emerge. Nevertheless, it is worth recalling that this was a population of patients whose BP was considered “controlled” according to current treatment guidance. Treatment with the ARB reduced BP and the vascular damage score by 6 months. The fact that this benefit was also observed with the placebo-associated fall in BP suggests that the benefit was almost certainly driven by the improved BP control, which was predictably better with the ARB. However, the possibility of a specific additional effect of angiotensin receptor blockade to regress structural abnormalities cannot be discounted. In support of the latter, previous studies comparing an ARB (losartan) with a beta-blocker (atenolol) have shown better structural regression and improved compliance of small arteries despite similar BP control after 1 year of treatment (16). This is consistent with an important role for the renin-angiotensin system as a mediator of early structural damage in younger people with a hypertensive phenotype.

It is of interest that the most impressive early benefit seemed to be on the noninvasive assessment of small artery compliance, which is consistent with previous observations suggesting that abnormalities in small artery structure and function might be the earliest manifestation of BP-mediated damage (17). These findings complement those of the TROPHY (Trial of Preventing Hypertension) study, which showed that treatment with an ARB (candesartan) in people with pre-hypertension might delay the development of overt hypertension (18). No vascular structure data have been reported from the TROPHY study. The TROPHY study and that of Duprez et al. (15) are important, perhaps not so much by what they found but more by virtue of what they set out to study. They have challenged the boundaries of current therapeutic approaches to hypertension by highlighting the potential of earlier therapeutic intervention—targeting the early evolution of disease and not just BP values. It is intriguing that both studies have used ARBs, which might ultimately turn out to be the most logical intervention in the context of early therapeutic intervention in younger people, mindful of the importance of the renin-angiotensin system (RAS) in the genesis of hypertension and structural damage in younger patients and the seemingly innocuous adverse effect profile of ARBs.

The challenge for future studies will be to better define clinically important and meaningful markers of therapeutic benefit on structural and functional cardiovascular damage. This is a challenge that will be made easier by the exciting developments in noninvasive imaging techniques to better characterize early damage. Moreover, the opportunities to better define differential drug effects on such markers will be greater in patients treated with monotherapy with clearly defined phenotypes. Indeed it is conceivable that in the early stages of hypertension, structural regression could be more dependent on properties of specific drug treatments and less dependent on the BP-lowering efficacy. In this regard one wonders how many potentially novel therapeutic interventions for early hypertensive disease have already been discarded in early development, because they failed to overcome the crude BP criteria used to define a successful treatment by the regulators.

In summary, for the treatment of hypertension, the current focus is on preventing clinical end points. However, for the insidious destructive process associated with an elevated BP, perhaps the focus would be better directed at preventing the longer-term evolution of disease. Although this strategy would increase the number of patients treated, it could simplify and reduce the number of drugs used to treat the majority of patients and ultimately improve their longer-term outcome. For this radical change to occur, 2 key things need to happen. First, future research and drug development strategies need to be focused on the means to better identify and treat those patients at risk of structural damage. Second, there needs to be a radical change in the drug regulatory environment to recognize the benefits of specific drug therapies on cardiovascular structural change so that appropriate drugs can be licensed for this key indication. Without these developments we will continue to struggle with the consequences of BP-mediated damage in older patients rather than more effectively dealing the cause.

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