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## Does Prehypertension Represent an Increased Risk for Incident Hypertension and Adverse Cardiovascular Outcome?

**Stephen P. Glasser, Jan N. Basile, and Daniel T. Lackland**

Division of Preventive Medicine (S.P.G.), University of Alabama at Birmingham, Birmingham, Ala; Ralph H. Johnson Veterans' Affairs Medical Center (J.N.B.), Medical University of South Carolina, Charleston, S.C.; Department of Medicine, Medical University of South Carolina (D.T.L.), Charleston, S.C

Literature is accumulating that the presence of prehypertension (pre-HTN; defined as a blood pressure [BP] of 120 to 139 mm Hg systolic and/or 80 to 90 mm Hg diastolic) is associated with increased long-term risk. It remains controversial, however, as to whether prehypertensive BP alone or its association with its common risk factor accompaniments is important in determining ultimate risk. In the past, pre-HTN was called transient hypertension (HTN), borderline HTN, and high-normal BP. Although the terminology has changed, what is increasingly agreed on is that pre-HTN is frequently a precursor of HTN and is associated with an excess morbidity and mortality from cardiovascular disease (CVD). In the Framingham Heart Study, 50% of patients age 65 years with a BP of 130 to 139/85 to 89 mm Hg progressed to HTN within 4 years. In those same patients who had a BP of 120 to 129/80 to 84 mm Hg, 26% became hypertensive within 4 years.<sup>1</sup> As observed in the Framingham Heart Study, BPs of 130 to 139/85 to 89 mm Hg impose twice the risk of CV disease compared with those whose BPs are <120/80 mm Hg.<sup>2</sup> Perhaps if pre-HTN was eliminated, almost half of all heart attacks could be prevented. To emphasize the wide variation in risk among prehypertensives, Lee et al<sup>3</sup> combined 3 cross-sectional studies conducted in Singapore (baseline years: 1982–1995), where 5830 subjects were grouped into normotensive, pre-HTN, or HTN cohorts. Follow-up (median: 12 years) was done by linkage to the National Death Register. Outcomes included all-cause and cardiovascular disease (CVD; ischemic heart disease [International Classification of Diseases, 9th Revision, codes 410 to 414]), as well as cerebrovascular accidents (International Classification of Diseases, 9th Revision, codes 430 to 438). After adjustment, pre-HTN was not associated with a statistically significant increased risk of all-cause or CVD mortality. However, an increased risk for all-cause and CVD mortality was found in the presence of diabetes mellitus (adjusted hazard ratio [HR]: 1.8; 95% CI: 1.0 to 2.9 and adjusted HR: 4.4; 95% CI 1.9 to 10.4), smoking (adjusted HR: 2.2; 95% CI: 1.3 to 3.5 and adjusted HR: 4.9; 95% CI: 1.8 to 13.3), and especially preexisting CVD (adjusted HR: 3.1; 95% CI: 1.5 to 6.4 and adjusted HR: 9.3; 95% CI: 3.3 to 25.9).<sup>3</sup>

It has been estimated that the prevalence of pre-HTN among adults in the United States is ≈31%<sup>4</sup> The prevalence is higher among men than women (39% and 23%, respectively). Hsia et al<sup>5</sup> reported on the prevalence of pre-HTN from the Women's Health Initiative. Sex

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Correspondence to Stephen P. Glasser, Division of Preventive Medicine, University of Alabama at Birmingham, 1717 11th Ave S MT 638, Birmingham, AL 35205. sglasser@uab.edu.

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differences were not available from this latter study, and regional differences were not reported; however, ethnic differences were provided and ranged from 32% to 40%. The Women's Health Initiative also evaluated the CVD risk at 7.7 years of follow-up and found an increased risk of myocardial infarction, stroke, CVD death, and other outcomes in the prehypertensive groups.

Although, the incidence of HTN approaches 90% by the age of 70 years, the etiology of HTN remains elusive for the vast majority. The complications of long-standing HTN are well known and relate to arterial disease with clinical manifestations in the heart, brain, and kidney. However, the paradigm of elevated BP resulting in vasculopathy continues to be debated. Rather than HTN resulting in altered vascular structure and function, it appears that changes in vascular integrity (structure) precede (and may be causal) in the development of elevated BP with resultant HTN that ultimately leads to clinical events.

Alterations in cardiovascular structure and function that have been shown to precede the finding of elevated BP include the occurrence of left ventricular hypertrophy in children and young adults of hypertensive parents (although one cannot rule out the role of BP in causing cardiovascular remodeling in studies where only resting, occasional measurements of BP are made), diastolic filling abnormalities in normotensive individuals predisposed to HTN, endothelial dysfunction as a precursor to the finding of HTN, and increased arterial stiffness in normotensive subjects predisposed to develop HTN.<sup>6</sup> It has been reported recently that, in confirmed prehypertensive subjects, intimal-medial thickness is increased in the common carotid artery when compared with subjects who remain normotensive.<sup>6</sup> In addition, Lackland<sup>7</sup> has demonstrated an association between low birth weight and the subsequent development of HTN, with the greatest risk of HTN occurring among those with low birth weight and accelerated "catch-up weight." How the role of pre-HTN fits into this paradigm remains to be answered, but if changes in vascular integrity precede the development of HTN, pre-HTN could well fit into the continuum of HTN, with pre-HTN being the first manifestation and isolated systolic HTN being the late manifestation of the natural history of vascular disease.

The Trial of Preventing Hypertension supports the view that the treatment of pre-HTN can reduce the occurrence of the development of HTN.<sup>8</sup> The Framingham Offspring Study recently evaluated predictors of developing HTN in those with pre-HTN and found that an algorithm incorporating body mass index, age, systolic and diastolic BPs, sex, smoking history, and a parental history of HTN predicted the 4-year risk of HTN.<sup>9</sup>

In this issue of *Hypertension*, De Marco et al<sup>10</sup> address the question of whether "... metabolic and/or cardiac characteristics favor development of HTN in prehypertensive subjects." They base their observations on participants of the Strong Heart Study, a population-based cohort of American Indians from 3 communities in Arizona, 7 in southwestern Oklahoma, and 3 in North and South Dakota, a population with a high prevalence of diabetes mellitus, CVD risk factors, and incident HTN. In fact, 22% of the Strong population had diabetes mellitus, 55% were obese, 33% were current smokers, and 17% had left ventricular hypertrophy. The Strong Heart Study provides a valuable resource for the assessment of CVD progression among a high-risk cohort, but the study population represents a high-risk group that may not be easily generalized to other populations. American Indians are reported to have high cardiovascular and HTN risks, incidence rates at younger ages, and a more progressive disease process, as suggested by this current work.<sup>11-13</sup> Thus, the authors correctly point out that their findings may not be generalizable to other populations. On the other hand, De Marco et al<sup>10</sup> have provided useful information for populations with excess risks from HTN, such as blacks, with similar great disease burden. The current data provide valuable insight for HTN disease progression in these

high-risk individuals. Also, the authors did not find that their measure of arterial stiffness predicted incident HTN. In fact, a number of studies have suggested that baseline measures of arterial stiffness do predict incident HTN. The authors do provide some insight into why their estimate of arterial stiffness did not predict incident HTN, but it is still curious that they did not find that association.

Thus, the question of whether pre-HTN alone or only in combination with other CVD risk factors is necessary to accurately predict incident HTN needs additional assessment. On the basis of the available evidence and lifetime risk of HTN, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommended that, in prehypertensive individuals, lifestyle modifications to prevent the progressive increase in BP and CVD should be considered.<sup>4</sup> Studies like that of De Marco et al<sup>10</sup> help refine to whom the most aggressive approaches should be directed.

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