

Prehypertension: An Opportunity for a New Public Health Paradigm

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From 2005 to 2006, approximately 3 of 8 adults in the United States had blood pressure (BP) in the prehypertensive range of 120 to 139/80 to 89 mm Hg and roughly 1 in 8 adults had BP in the range of 130 to 139/85 to 89 mm Hg referred to as high normal BP or stage 2 prehypertension. The term stage 2 prehypertension may serve to more fully convey the actual risk of progression to hypertension and cardiovascular disease (CVD). Stage 2 prehypertension progresses to hypertension at a rate of about 8% to 14% annually, which is 2- to 3-fold higher than normotension (BP <120/80 mm Hg). Adults with stage 2 prehypertension are also roughly twice as likely as adults with normotension to suffer CVD. The Seventh Report of the Joint National Committee on Hypertension (JNC 7) recommended only lifestyle changes for most prehypertensive patients. Although hygienic measures are efficacious in controlled clinical trials, evidence for community-wide effectiveness is limited. BP in the range of 120 to 129/80 to 84 mm Hg is also associated with increased risk but roughly half of that of stage 2 prehypertension.

Most individuals with stage 2 prehypertension have 1 or more concomitant conditions associated with increased cardiovascular risk. These include, but are not limited to dyslipidemias, an early family history of CVD, cigarette use and abdominal obesity, hyperinsulinemia and insulin resistance, impaired fasting glucose, a prothrombotic state, endothelial

dysfunction, and impaired vascular distensibility. The combination of multiple risk factors magnifies absolute risk. In fact, clinical epidemiology suggests that the benefits of treating stage 2 prehypertension and stage 1 hypertension are similar when both groups have additional risk factors.

This review examines evidence indicating that (1) prehypertension is a major contributor to incident hypertension and CVD, (2) although current public health and hygienic strategies are efficacious, they are largely ineffective in reducing prehypertension-related risk, and (3) a new public health paradigm for the prevention and management of prehypertension is needed and should include expanding the evidence base through comparative effectiveness research.

JNC 7 departed from previous reports by defining BP in the range of 120 to 139/80 to 89 mm Hg as prehypertension.¹ Although controversial, the designation for prehypertension was intended to strengthen the recommendation for therapeutic lifestyle changes among a group of individuals at significantly greater risk for progression to hypertension and clinical CVD when compared with normotensive individuals with BP less than 120/80 mm Hg.¹⁻⁷

JNC 7 was not the original source for the term prehypertension or the BP range that defines it. In 1939, Robinson and Brucer² defined BP in the range of 120 to 139/80 to 89 mm Hg as prehypertensive. They observed that most hypertension

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originated from prehypertension in individuals who also had roughly double the mortality of people with a normal BP less than 120/80 mm Hg.

When compared with normotensive individuals, prehypertensive individuals are more likely to be overweight and obese, to have other cardiovascular risk factors, to progress to established hypertension, and to experience premature clinical CVD.^{1–7} Given these considerations, the American Society of Hypertension Writing Group⁸ defined a subset of individuals with BP in the range of 120 to 139/80 to 89 mm Hg as hypertensive based on concomitant risk factors and vascular disease. The scientific evidence and expert opinion that BP in the range of 120 to 139/80 to 89 mm Hg and especially 130 to 139/85 to 89 mm Hg (stage 2 prehypertension) are not optimal for health are longstanding, impressive, and growing.

CLINICAL EPIDEMIOLOGY OF PREHYPERTENSION

A preliminary report from the National Health and Nutrition Examination Survey (NHANES) in 2005 to 2006 estimated that approximately 37% of US adults had prehypertension.⁹ The number of adults with prehypertension was estimated to be approximately 83 million based on extrapolations from NHANES 2005–2006 and information from prior surveys.^{9–12} Among this group, roughly 3 of 8, or approximately 31 million, US adults have stage 2 prehypertension. Prehypertension is associated not only with concomitant cardiovascular risk factors but also with several adverse health outcomes including new-onset diabetes and hypertension, cognitive impairment, and increased CVD events.

Prehypertension and Concomitant Cardiovascular-Metabolic Abnormalities

Individuals with stage 2 prehypertension are more likely than individuals with normotension to be overweight, hyperinsulinemic, insulin resistant^{3,7} and to exhibit a complex dyslipidemia characterized by hypertriglyceridemia, low level of high-density lipoprotein cholesterol, and greater numbers of small low-density lipoprotein cholesterol particles. Stage 2 prehypertensive individuals frequently display other risk factors or markers, which include high levels of fibrinogen, plasminogen activator inhibitor 1, adipokines including leptin and tumor necrosis factor α , and inflammatory cytokines including C-reactive protein as well as endothelial dysfunction, greater vascular stiffness, left ventricular hypertrophy, diastolic dysfunction, decreased coronary flow reserve, and cognitive dysfunction.^{13–20}

New-Onset Diabetes

A representative sample of 11,001 German men and women between the ages of 25 and 74 years and free of diabetes at baseline were followed up for a mean of 12.5 years.²¹ Hypertension was associated with approximately 2-fold higher incident diabetes in men and women after adjusting for multiple covariates including age, family history of diabetes, physical activity, education, and body mass index. Stage 2 prehypertension was linked to a multivariate-adjusted approximately 1.8-fold (hazard ratio [HR], 1.76; 95% confidence interval [CI], 1.24–2.51) higher incidence of diabetes in men, whereas the adjusted risk was not significant in stage 2 prehypertensive women (HR, 1.07; 95% CI, 0.67–1.73). Although it is important to extend these observations to other racial or ethnic groups, the findings suggest that stage 2 prehypertension is associated with diabetes risk in men.

New-Onset Hypertension

Patients with prehypertension are at greater risk for developing hypertension than patients with normotension.^{2,5,22–24} In the Framingham Heart Study, approximately 37% of patients younger than 65 years with stage 2 prehypertension (high normal BP) and 50% of patients older than 65 years progressed to hypertension in 4 years compared with 5% and 16% of patients with a normal BP less than 120/80 mm Hg, respectively.²⁵ In the Trial of Preventing Hypertension (TROPHY), around 52% of placebo-treated patients with stage 2 prehypertension progressed to clinical hypertension within 4 years with the conventional definition of 2 successive visits and a BP of 140/90 mm Hg or more.²⁶ The German Hypertension League Study on hypertension prevention reported a 43% incidence over 3 years of de novo hypertension among patients with stage 2 prehypertension randomized to placebo, which is similar to the rates observed in TROPHY and Framingham Study.²⁷

Prehypertension and CVD Risk

Given the spectrum of risk factors associated with stage 2 prehypertension, this group has a higher incidence of CVD.^{4,6,7,28–35} At least 7 cohort studies documented a significant contribution of stage 2 prehypertension to CVD risk (**Table 1**).^{4,28–30,32–35} The adjusted hazard ratios in these studies ranged from approximately 1.4 to 2.3, with several studies documenting risk independent of progression to hypertension and other major risk factors. Given an estimated number of 31 million people with stage 2 prehypertension in

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