EDITORIAL

High Blood Pressure in Young Adulthood and Risk of Premature Cardiovascular Disease
Calibrating Treatment Benefits to Potential Harm

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High blood pressure poses a major public health problem worldwide, including in the United States.[1] Today, an estimated 1.13 billion people worldwide have hypertension (at the cut points of either ≥140 mm Hg for systolic or ≥90 mm Hg for diastolic blood pressure).[2] The prevalence of hypertension has been forecast to escalate to about 1.56 billion people by 2025.[3] These statistics provoke major concern because numerous observational studies have demonstrated a continuous and graded relationship of systolic and diastolic blood pressure with the risk of cardiovascular disease (CVD) and chronic kidney disease. The vascular risk starts at measures as low as 115 mm Hg for systolic and 75 mm Hg for diastolic blood pressure, which are considered optimal levels,[4] and is consistent across sexes, age groups, race/ethnic categories, and countries.[5] It is estimated that about half the risk of CVD that is associated with suboptimal systolic blood pressure is attributable to values in the 130 to 150 mm Hg range.[6]

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Recognizing the CVD-risk continuum across the range of escalating blood pressure values, Rose defined high blood pressure aptly as "the level of blood pressure at which investigation and management does more good than harm."[5] Large-scale randomized clinical trials conducted over the last 4 decades have firmly established the benefits of blood pressure–lowering treatment in hypertension across groups defined by age, sex, race, and geography.[7] Relative risk reductions are consistent across the range of higher blood pressure values, although absolute risk reductions are greater for values at the upper end of the blood pressure distribution. In parallel, treatment thresholds for initiating blood pressure–lowering treatment and establishing targets for patients taking medication have both progressively moved to lower systolic and diastolic blood pressure values as data have accumulated to demonstrate the continuous gradient of risk across the blood pressure spectrum; clinical trials have treated elevated blood pressure to lower thresholds with demonstrable clinical benefits; and the safety profile of available blood pressure–lowering agents has enhanced substantially.

It is not surprising, therefore, that classification systems that indicate relative deviance from optimal levels (blood pressure elevation or hypertension) and associated treatment recommendations have changed over time and are somewhat discrepant across different sets of national and international guidelines (**Figure**).[8-11] These differences arise because judgments regarding blood pressure levels at which intervention is associated with "more good than harm" can vary among experts even when they interpret the same body of scientific evidence.[12,13] Furthermore, in a world of finite resources, greater societal good with blood pressure–lowering treatment accrues to a larger number of people with high blood pressure when the absolute CVD risk is higher, a choice that is influenced as much by health economics as it is by scientific evidence. Thus, estimates of absolute CVD risk can skew management decisions toward favoring treatment of older individuals who manifest greater vascular risk. Therefore, for the same numerical level of blood pressure, the interpretation of good vs harm can change over time (as evidence grows); with increasing age of the patient; with the presence of comorbidities; and by the influence of both expert opinion and the availability of national, regional, and local health care resources. To refine Rose's concept, when a level of blood pressure is associated with a favorable benefit-to-risk ratio to qualify as elevated and requiring treatment may be influenced by context.

In this issue of the *JAMA*, 2 reports[14,15] provide evidence about a less well-studied area—the association of higher blood pressure with the risk of premature CVD in adults younger than 40 years, using the 2017 American College of Cardiology/American Heart Association (ACC/AHA) blood pressure classification system.[11] Yano and colleagues[14] evaluated nearly 5000 black and white participants (mean age, 35 years) in the Coronary Artery Risk Development in Young Adults (CARDIA) study, and categorized each participant as having normal blood pressure (n = 2574); elevated blood pressure (n = 445); stage 1 hypertension (n = 1194); or stage 2 hypertension or by whether they were taking antihypertensive medication (n = 638). Over a median follow-up of 18.8 years, 228 incident CVD events occurred (109 coronary heart disease, 63 stroke, 48 heart failure, and 8 peripheral arterial disease). Cardiovascular disease incidence rates for normal blood pressure were 1.37; for elevated blood pressure, 2.74; for stage 1 hypertension, 3.15; and for stage 2 hypertension, 8.04 per 1000 person-years. The investigators observed a stepwise increase in the multivariable-adjusted CVD risk across increasing blood pressure categories. Compared with normal blood pressure, the hazard ratio for CVD events for elevated blood pressure stage was 1.67 (95% CI, 1.01-2.77); for stage 1 hypertension, 1.75 (95% CI,

Figure. Changing Blood Pressure Classification Systems Across Guidelines and Prevalence in 2 Reports

Blood Pressure, mm Hg							Patient Blood Pressure, %[d]	
Systolic		Diastolic	JNC 6[a]	JNC 7[a]	ACC/AHA[b]	ESC/ESH[c]	Yano et al[14]	Sun et al[15]
<120	and	<80	Optimal	Normal	Normal	Optimal	53	39.9
120-129	and	<80	Normal	Prehypertension	Elevated	Normal	9.2	10.8
	and/or	80-84			Stage 1 hypertension		24.6	37.7
		85-89	High normal			High normal		
130-139	and/or	85-89						
140-159	and/or	90-99	Stage 1 hypertension	Stage 1 hypertension	Stage 2 hypertension	Grade 1 hypertension	13.2	11.6
≥160-179	and/or	≥100-109	Stage 2 hypertension	Stage 2 hypertension		Grade 2 hypertension		
≥180	and/or	≥110	Stage 3 hypertension			Grade 3 hypertension		

[a] Joint National Committee (JNC) on Detection, Evaluation, and Treatment of High Blood Pressure in Adults 6 guideline, reported in 1997,[8] and 7 guideline, published in 2003.[9]

[b] American College of Cardiology/American Heart Association (ACC/AHA) Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure, published in 2017.[11]

[c] Task Force for the Management of Arterial Hypertension of the European Society of Cardiology/European Society of Hypertension (ESC/ESH) published in 2017.[10] Note its concordance with the JNC 6 guidelines and ESC-ESH.

[d] Blood pressure strata are based on the ACC/AHA 2017 guidelines.

1.22-2.53), and stage 2 hypertension, 3.49 (95% CI, 2.42-5.05), with notable consistency in sensitivity analyses using blood pressure measures at more than 1 time point, across individual CVD end points evaluated, and across race groups.

In the other study, Son and colleagues,[15] also using ACC/AHA 2017 guidelines, assessed a nation-wide Korean database of nearly 2.5 million people (baseline median age, 31 years) including 991 884 participants with normal blood pressure, 267 790 with elevated blood pressure, 938 908 with stage 1 hypertension, and 289 519 with stage 2 hypertension (median age, 31 years [interquartile range, 27-36 years], 31.7% women). Study participants had blood pressure readings obtained at 2 time points (measured approximately 2 years apart). During a median follow-up of 10.0 years, a total of 44 813 CVD events (defined as hospitalization for ≥2 days or death due to coronary heart disease or stroke) were observed. Compared with those with normal blood pressure, those with stage 1 hypertension had higher risk of CVD events (adjusted hazard ratios for men, 1.25; 95% CI, 1.21-1.28 and adjusted hazard ratios for women, 1.27; 95% CI, 1.21-1.34). In addition, a higher blood pressure category at the second time point and an upgrading of blood pressure category from the first to the second time point were both associated with increasing multivariable-adjusted CVD risk.

These 2 observational studies provide several important findings. First, almost half to 60% of the young adults in these reports had nonnormal levels of blood pressure. Second, individuals with a higher blood pressure category often had a concomitant burden of additional CVD risk factors (higher mean body mass index, fasting glucose concentrations, and smoking prevalence) demonstrating that these risk factors cluster, thereby increasing CVD risk synergistically. Third, a higher blood pressure level (starting at levels of >120 mm Hg systolic and >80 mm Hg diastolic) was associated with a greater hazard of premature CVD in both cohorts. Fourth, progression of blood pressure across the stages was associated with greater CVD risk on follow-up in the Korean study. Fifth, most of the individuals with elevated or stage 1 hypertension in both studies did not experience a premature CVD event on follow-up during the period of observation. Although the relative risks for CVD associated with the various blood pressure categories varied somewhat across the 2 studies, the absolute CVD event rates were low, consistent with the age of the samples studied. Sixth, the observation of an elevated risk of premature CVD risk in young adults does not establish causality nor does it necessarily imply that intervention to lower blood pressure in this age group will mitigate CVD risk.

Why were so many young adults in these investigations manifesting higher levels of blood pressure? The blood pressure levels reported in these studies may not have been measured as recommended by hypertension guidelines or may not be consistent with usual care in the clinic. In the Korean Study, a large proportion of individuals with a higher blood pressure level at baseline (first time point) regressed to a lower level during the follow-up period of 2 years (second time point), and a moderate proportion progressed to a higher blood pressure category, reflecting the plausible lability of blood pressure classification in this age group. Valuable adjuncts for better blood pressure phenotyping such as ambulatory or home blood pressure monitoring that have been highlighted in contemporary guidelines[10,11] were not used in either study. Improved blood pressure phenotyping may obviate some of the criticisms directed at the ACC/AHA blood pressure classification system.[11] These concerns may be particularly relevant in young adults and include labeling[12] (suddenly sick syndrome due to changing guidelines), anxiety provocation, and the specter of long-term treatment with potential for harm outweighing benefits.

What information do these 2 studies provide about the natural history and the management of elevated blood pressure in young adults? Both studies focused on CVD risk associated with the ACC/AHA blood pressure classification system but did not evaluate specifically the epidemiology of elevated blood pressure in young adults or the underlying pathophysiology in this age group. Neither study evaluated or adjusted for progression of blood pressure categories during

the follow-up period (prior to the occurrence of CVD). Such blood pressure progression to higher levels may antedate CVD incidence. Additionally, these investigations did not report data on blood pressure–mediated target organ damage[10] that could elucidate the potential influence of the individual ACC/AHA blood pressure stages on subclinical and microcirculatory injury to the heart, kidneys, or eyes in young adults.

The pathophysiological basis of higher blood pressure levels in young adults is complex.[16] The broad category of young adults with elevated or higher blood pressure likely includes some individuals with white-coat hypertension, some people with peripheral amplification of blood pressure with normal central blood pressure (often in the context of obesity[17]), others with a hyperadrenergic state (characterized by a hyperkinetic circulation and a faster heart rate), a subset with increased arterial stiffness and pulse wave velocity (isolated systolic hypertension in youth), and a smaller group with secondary hypertension (estimated prevalence of 5%-10% in this age group[10]). These distinct pathophenotypes may have varying natural histories and their management approaches may be distinctive, suggesting the importance and potential role of subphenotyping of elevated blood pressure in young adults to facilitate treatment decisions.

The investigations by Yano et al[14] and Son et al[15] lead to some key questions. Are children born today guaranteed a very high risk of developing nonnormal levels of blood pressure from young adulthood onwards? What can be done during the prenatal, antenatal, and postnatal phases to ensure healthy blood pressure profiles of offspring during infancy, early childhood, adolescence, and youth to mitigate this risk (primary prevention)? Are there modifiable societal factors (environmental, social, behavioral, and cultural factors) that are conducive to the primordial prevention of elevated blood pressure? A substantial body of scientific evidence underscores that higher blood pressure levels evolve over the life course, with environmental (including lifestyle) influences superimposed on innate genetic risks. Some recent data also suggest that longitudinal blood pressure trajectories in youth vary according to sex and by race and may portend future elevations of blood pressure as well as the occurrence of target organ damage.[18,19] Overall, these data emphasize that primary prevention of higher blood pressure levels must begin in childhood.

Yet major gaps exist in current knowledge regarding the epidemiology, diagnosis, risk stratification, and management of higher blood pressure levels in young adults. Studies are needed to elucidate the developmental origins of higher blood pressure levels in children and the impact of social determinants of health, acculturation, and allostatic load on blood pressure trajectories in youth. Greater clarity is needed regarding the potential use of individual characteristics (eg, geographic residence in the stroke belt, black race with apolipoprotein L1 risk alleles, or a positive family history of CVD), long-term CVD risk, and blood pressure–mediated target organ damage to guide treatment decisions for high blood pressure levels in young adults. Optimal blood pressure targets in relation to plausible clinical benefit vs possible harm due to long-term blood pressure–lowering treatments need to be clearly delineated for young adults with nonnormal blood pressure levels according to the ACC/AHA classification. Bridging these critical knowledge gaps may help define how, when, and what measures could be implemented to maintain an optimal blood pressure profile from childhood through young adulthood and beyond. Answers to these questions will be a public health legacy to the current generation of children and young adults and to their future offspring.

ARTICLE INFORMATION

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