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EDITORIAL COMMENT

Hypertension Guidelines

The Threads That Bind Them*

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Viewing the hypertension guidelines that have been issued in the past 2 years by various national and international societies, at first blush it would appear that there is a fracturing of the world medical order with regard to diagnostic criteria for the definition of hypertension, as well as goals for treatment. However, a deeper and perhaps more nuanced reading of these guidelines reveals 3 common threads. First, although some guidelines suggest a systolic blood pressure (SBP) target <120 mm Hg for persons at high cardiovascular disease (CVD) risk, no guideline suggests an SBP target ≥150 mm Hg, even for persons older than 80 years of age (thread 1). Second, the concept that an individual's risk of a future CVD event should be considered when determining an SBP treatment goal is widely recognized in the guidelines (thread 2). The third and final thread is recognition that there exists a nadir, particularly in persons with coronary artery disease (CAD), of achieved blood pressure (BP) below which there is an increase in adverse events (thread 3).

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It is in this context that we can view 2 publications in this issue of the *Journal*. Addressing all 3 threads, Kim et al. (1) conclude that in patients with atrial fibrillation (AF), a goal of 120 to 129/<80 mm Hg is optimal (thread 1), this goal may be independent of future CVD risk (thread 2), and 120/80 mm Hg may represent the nadir of targeted BP for patients with AF (thread 3). Addressing thread 3, Peri-Okonny et al. (2), in a clever approach that used angina as an intermediate endpoint, found that in patients with CAD, there was more angina in patients whose diastolic BP (DBP) was lower than ~70 to 80 mm Hg than in those whose DBP was >80 mm Hg.

The main evidence supporting thread 1 comes from the SHEP (Systolic Hypertension in the Elderly Program) (3), Syst-Eur (Systolic Hypertension in Europe) (4), and HYVET (Hypertension in the Very Elderly Trial) (5) trials, which compared active treatment with placebo in patients 60 years old or older with predominantly systolic hypertension. Achieved SBP in the placebo arm of each of the trials was ≥155 mm Hg, whereas in the active treatment arm it was 143/68 mm Hg, 151/80 mm Hg, and 145/77 mm Hg, respectively (3-5). Compared with placebo, the treatment arms of all 3 trials had significantly lower CVD events, as well as even lower mortality and fewer serious adverse events in SHEP and HYVET.

The evidence that an individual's CVD risk should be incorporated into decisions regarding intensity of BP management has been growing over the past decade (thread 2). This concept is well ensconced in the management of lipids. Analysis of lipid trials revealed that although relative risk reduction is similar regardless of baseline future CVD risk, absolute risk reduction increases as baseline CVD risk increases. Therefore, the Expert Panel of the American College of Cardiology and American Heart Association (ACC/AHA) Task Force on Practice Guidelines recommended "moderate" statin therapy starting at 10-year atherosclerotic CVD (ASCVD) risk >5% and "moderate or intensive" statin therapy starting at risk

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>7.5% (6). Incorporating risk into decision making affects physicians' behavior (6). Armed with 10-year CVD risk data, Sekaran et al. (7) found that physicians are "nudged" to more appropriately initiate statin therapy. Analysis of multiple datasets suggests that risk-guided therapy would be beneficial in hypertension as well (8–10). If treatment of hypertension were based solely on BP level, a large group of patients at risk for cardiovascular (CV) events would not receive antihypertensive therapy (11). Similar to the lipid data, several analyses have shown that although BP lowering yields similar relative risk reduction irrespective of baseline CVD risk, patients with the greatest baseline CVD risk have the greatest absolute risk reduction (9,12).

Nearly all guidelines now include a suggestion that in persons at higher risk for CV events, a lower BP goal is desirable (**Table 1**). The 2017 ACC/AHA guidelines firmly recommend an SBP target of <130 mm Hg not only for those with pre-existing ASCVD, diabetes mellitus, or chronic kidney disease (CKD), but also in those individuals with a 10-year CVD risk ≥10%; and for those without "increased CVD risk, a BP target of <130/80 mm Hg may be reasonable" (13). The American College of Physicians and American Academy of Family Physicians guidelines suggest a goal of <150 mm Hg, but a goal of <140 mm Hg if there is significant CVD risk (14). The Canadian guidelines suggest a goal of <140 mm Hg in individuals with low CVD risk, an SBP of <120 mm Hg in those with CVD high risk, and an SBP <130 mm Hg in patients with diabetes (15). The American Diabetes Association guidelines suggest a goal of <140 mm Hg in patients with diabetes, but a goal of <130 mm Hg if there is significant CVD risk (16). The Kidney Disease: Improving Global Outcomes guidelines suggests a goal of <140 mm Hg for patients with CKD, but a goal of <130 mm Hg if there is albuminuria (17). The European Society of Cardiology and European Society of Hypertension guidelines are an outlier. Regardless of comorbidities, these European guidelines suggest a goal of <140 mm Hg, but not <130 mm Hg, in persons >65 years of age, who generally have higher CVD risk, and conversely a more intensive goal of <130 mm Hg, but not <120 mm Hg, in adults <65 years of age, who generally have lower CVD risk (18). For persons <65 years of age with CKD, an SBP target of <140 mm Hg, but not <130 mm Hg, is recommended (18).

There is no dispute that a J- or U-curve relationship exists between BP and CV outcomes, particularly in patients with pre-existing CAD (thread 3) and that it exists somewhere between a DBP of zero and the BP range that is typically achieved with antihypertensive treatment (19). The dispute lies in a number of nuances: whether the lower achieved DBP caused the events or whether the lower DBP is simply a marker of stiffer and more dysfunctional blood vessels (20) (i.e., reverse causation); and where is the inflection point of DBP below which CV events increase.

Evidence for a J-curve has predominantly come from post hoc analyses of the achieved BP in clinical trials that were not explicitly designed to test a level of DBP that could be associated with decreased vascular bed perfusion. In the INVEST (International Verapamil-Trandolapril Study) study (21), which compared efficacy of beta-adrenergic blocker with a calcium-channel blocker treatment strategy, there was a nadir in events at an achieved DBP of 84 mm Hg. Below this level, CV event rates began to increase. In Syst-Eur, in the treatment arm, but not the placebo arm, CV events began to increase significantly at a DBP lower than 70 mm Hg (22).

In contrast to these studies, SPRINT (Systolic Blood Pressure Intervention Trial) (23) intentionally randomized individuals with either pre-existing CVD or high risk for CVD to an SBP goal of <120 mm Hg versus <140 mm Hg. Compared with the standard-treatment arm, participants in the intensive-treatment arm had a 25% lower incidence of the primary outcome events ($p < 0.001$) and a 27% reduction in all-cause mortality ($p = 0.003$) (23). Two-fifths of SPRINT participants had a baseline DBP lower than 75 mm Hg, and one-fifth had a baseline DBP lower than 68 mm Hg (23). In both the standard-treatment and intensive-treatment arms, there was a U-shaped relationship between baseline DBP and primary outcomes, all-cause death, and incident CKD (23). However, the benefits of intensive treatment on the primary outcome and all-cause death were not blunted in participants with low baseline DBP, a finding suggesting that intensive treatment to lower SBP should not be withheld in these patients (23).

Taking these data into account, the Canadian guidelines suggest an SBP of <120 mm Hg in patients with CAD and express caution if DBP is <60 mm Hg, particularly in persons with left ventricular hypertrophy (15). Perhaps because of the findings noted previously from SPRINT, the 2017 ACC/AHA guidelines suggest a goal of <130 mm Hg in hypertensive patients with CAD and do not comment on a DBP level below which caution may be exercised.

Peri-Okonny et al. (2) add a clever twist to the J-curve reports by exploring the relationship between a patient's reported angina and the DBP. Hence, these investigators used a clinically relevant and quantifiable indicator of decreased coronary perfusion. In this cross-sectional, observational, multisite study of 1,259 patients, nearly 80% had hypertension (2).