Elevated blood pressure (BP) is one of the most common preventable causes of premature death worldwide. Approximately 8 million deaths/year (i.e., 14% of all deaths worldwide) are directly attributable to an elevated BP, and with the worldwide prevalence of hypertension predicted to increase by more than 50% by 2025, the magnitude of BP-related death is set to increase further (1). Abundant data from randomized clinical trials have confirmed that the therapeutic lowering of BP in hypertensive people substantially reduces the risk of cardiovascular morbidity and mortality, and as a consequence, the routine treatment of hypertension is one of the most common interventions in medicine. BP treatment guidelines have progressively reduced the BP threshold at which treatment should begin and the BP target to which BP should be lowered. This has led to a legitimate debate as to how low BP can safely be lowered to achieve optimal benefit from treatment and concern from some that the therapeutic “harm/benefit” equation might shift toward harm in some patients in whom BP is lowered too much. Over many years, this concern has fueled a seemingly eternal “J-curve” debate about the safety of what some deem to be excessive BP lowering (2–4). The “J-curve” describes the shape of the relationship between BP and the risk of cardiovascular morbidity and/or mortality. The J shape reflects increased risk at high levels of BP, with risk falling in parallel to BP reduction until a nadir is reached, below which further BP reduction begins to increase risk. That there is a J-curve relationship between the level of BP and risk is not in doubt, because there must come a point at which BP becomes too low to sustain adequate perfusion to vital organs and life itself. Thus, the essence of the debate is whether this J-curve exists in the range of BP at which patients might be exposed to further BP lowering by treatment. How low can BP be lowered and remain both safe and beneficial? What is the lower level of BP at which potential harm offsets the benefit of treatment? Other important aspects of this debate are whether the J-curve relationship is more significant for systolic blood pressure (SBP) or diastolic blood pressure (DBP) and whether its impact is more relevant for specific clinical outcomes and in patients with different comorbidities, especially coronary heart disease.

In this issue of the Journal, Messerli and Panjrath (5) add fuel to the J-curve fire by using post hoc analyses of clinical trials to examine the association between in-trial SBP and DBP and various clinical cardiovascular end points. They conclude that a J-curve exists for DBP for patients with coronary artery disease (CAD) but were not convinced that there was a J-curve phenomenon with BP-lowering therapy for renal disease or stroke prevention (5). They reason that patients with CAD might be especially vulnerable to risk from a low DBP because the coronary circulation is critically dependent on perfusion during diastole and requires an adequate pressure. The data as presented seem compelling and are persuasively argued—but are they right?

This is a hugely important clinical dilemma, worthy of closer inspection and debate, not least of all because these analyses create the impression that therapeutic lowering of DBP, within a range frequently encountered in routine clinical practice, could be harmful to many millions of treated patients. I would add a note of caution before accepting this as fact. There is huge potential for confounding in this kind of analysis that I fear cannot be overcome by any amount of multivariate statistical adjustment. Modern medicine struggles to reverse the powerful impact of aging and comorbidities on cardiovascular disease risk, and yet we accept that statistical adjustment can do so at a stroke?

It is most important to recognize that data showing associations between low in-trial DBP and risk do not prove that the therapeutic lowering of DBP caused that risk. On the contrary, it is most likely that patients with low in-trial DBP in the various studies cited had a low DBP at baseline, at entry into the study. Moreover, a low baseline DBP would automatically identify a cohort of patients at high cardiovascular disease risk. Such patients are more likely to experience clinical events in the trials not necessarily because lowering of their DBP has caused the events but rather because a low baseline DBP predicts their events. This latter point is important because a low DBP tracks with a number of confounders.

DBP tends to decline with age, from approximately the age of 40 to 50 years, due to progressive stiffening and loss of compliance of large conduit arteries, especially the aorta. This aortic stiffening tends to be accelerated in people with diabetes (6). The same mechanism accounts for the progressive rise in SBP with age and the consequent age-related increase in pulse pressure (7). Thus, the cohort of patients with low in-trial DBP are most likely to be older and have diabetes and more
likely to have coronary heart disease and a higher SBP and pulse pressure. Therefore, they are the highest-risk cohort irrespective of subsequent treatment. Indeed, a review of the patient characteristics in a recent analysis of the J-curve phenomenon from a major clinical outcomes study of hypertensive patients clearly shows that those patients with a low in-trial DBP had baseline characteristics identical to those described in the preceding text—therefore, they were, not surprisingly, at higher risk of developing incident coronary events during the trial (8). The cohort of patients with low DBP at baseline would most likely have experienced the highest rate of cardiac events irrespective of whether their DBP was lowered further. This in turn highlights the key question in this debate: if a patient already has a low DBP, will they get benefit or harm from further DBP lowering? Whilst reflecting on this question, it is worth remembering that patients with a low DBP will also most likely be those with a high SBP and pulse pressure. Put simply, would you lower the BP of a patient with isolated systolic hypertension (ISH), (e.g., a BP of 180/70 mm Hg)? Current guidelines recommend that you should. Should this recommendation hold true if the patient also has evidence of coronary disease due to concerns about the impact of further DBP lowering? With regard to the latter, in patients with ISH, the fall in SBP will greatly exceed the fall in DBP. Indeed, with aging, the predominant effect of treatment is to lower SBP, because the ratio of DBP/SBP lowering with antihypertensive therapy progressively declines with age and low baseline DBP (9). This underscores the likelihood that the low in-trial DBP analyzed in the aforementioned analyses (5,8) almost certainly reflects a low baseline DBP rather than a dramatic treatment effect.

The question as to whether patients with ISH should have their BP lowered even if their DBP is already low cannot be addressed by post hoc analyses of the association between in-trial DBP and clinical outcomes without reference to the baseline DBP, because of the aforementioned confounding. This question has been addressed, however, by a number of randomized clinical trials of patients with ISH that have overwhelmingly demonstrated the strong net benefits of BP lowering. In this regard, Wang et al. (9) performed a quantitative overview of trials that tested active antihypertensive drugs against placebo or no treatment in thousands of patients across a spectrum of age and baseline DBP. Crucially, with individual patient data, they also conducted a matched pair analysis to match patients for their baseline BP and other characteristics, and then compared active treatment with placebo. Antihypertensive treatment reduced the risk of all cardiovascular events, stroke, and myocardial infarction across all age and BP strata to a similar extent, and the absolute benefit of treatment increased with age (i.e., in those with the lowest DBP). Moreover, in patients with a larger-than-median reduction in SBP, active treatment consistently reduced the risk of all outcomes irrespective of the associated decrease in DBP or the achieved DBP. These findings remained consistent even if the achieved DBP averaged <70 mm Hg (9). Thus, the danger of advocating a J-curve for DBP on the basis of potentially confounded observational in-trial data is that it risks undermining the treatment of those with a high SBP (i.e., those at highest absolute risk of events and with the greatest absolute benefit from treatment) (10). Moreover, as discussed earlier, those with ISH experience the smallest fall in DBP relative to the change in SBP with treatment.

Since the aforementioned analysis by Wang et al. (9), there have been further patients with low baseline DBP entered into randomized clinical trials of BP-lowering therapy. What is clearly needed are extensive individual patient data analyses of those with a low baseline DBP who have been randomized to active BP-lowering treatment or placebo to determine whether the high baseline risk of these patients is modified by treatment, either in a positive or negative direction. This is the only way to comprehensively address the J-curve question and define the safety of treatment for patients with a low DBP, especially those with established CAD. Clearly, there is a point at which both DBP and SBP become too low to sustain life. The challenge is to better define the limits of intervention and whether there are groups of people who are particularly susceptible to over-aggressive lowering of BP. In the meantime, while post hoc association studies can generate interesting hypotheses and debate, they must never be used to frame treatment recommendations or, worse, alarm physicians into under-treating patients with ISH.

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