COMMENTARY

Blood Pressure Limbo—How Low Can You Go?

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Hypertension is one of the leading causes of death worldwide (1). In 2019, 20.3% of all adult female deaths and 18.2% of all adult male deaths were attributed to high systolic blood pressure (SBP) globally (1). Population-based surveys from diverse settings have shown that many adults with high blood pressure (BP) are not appropriately diagnosed (2). This represents a failure of health systems, particularly when it is known that BP-lowering medications significantly reduce cardiovascular disease (CVD) events among hypertensive patients (3). Furthermore, those patients who are diagnosed are nonetheless often undertreated and not at the recommended BP target. Recent guidelines recommend lower BP targets than ever before, resulting in an increasingly urgent need to address the widespread undertreatment of hypertension.

For people on BP-lowering medication, the 2017 American College of Cardiology/American Heart Association guidelines for hypertension recommend targeting a BP goal of <130/80 mmHg for all hypertensive patients including patients with diabetes (4). The 2018 European Society of Cardiology guidelines recommend targeting a BP of <130/80 mmHg in most treated patients, as long as such treatment is well tolerated, and targeting an SBP in the range of 120–129 mmHg in patients <65 years of age (5). These more intensive treatment recommendations were informed by randomized clinical trial (RCT) data (6) but also by a wealth of epidemiologic data (7). However, the data informing BP targets for patients with diabetes are somewhat mixed, which contributed to the 2021 American Diabetes Association recommendation to use a CVD risk calculator prior to determining the appropriate BP target for individuals with diabetes. A target of <130/80 mmHg is reserved for patients with a 10-year CVD risk of ≥15%, while a target of <140/90 mmHg is advised for individuals at lower risk (8).

These different guideline recommendations reflect the ongoing uncertainty in the balance of benefit/harm in consideration of more intensive BP targets (9,10). Indeed, from a purely epidemiologic perspective, it is well established that risk for CVD starts to increase at BP levels > 115/75 mmHg (7). However, clinical guidelines do not recommend targeting a BP level of 115/75 mmHg with drug treatment because there are no clinical trial data to support this approach. In other words, it is not enough to simply demonstrate an epidemiologic risk above a certain BP threshold in deciding on targets for pharmacologic treatment; one must also have evidence from RCTs that drug treatment to this threshold can actually reduce CVD events.

In the current issue of *Diabetes Care*, Yamada et al. (11) report on a prospective epidemiologic cohort analysis that included 593,196 adults without a history of CVD from a nationwide Japanese database. The authors examined the risk of incident coronary artery disease or CVD events among three subgroups of participants based on glycemic status: normoglycemic patients, patients with prediabetes, and patients with diabetes. Each glycemic subgroup was further subdivided into five categories according to either SBP or diastolic BP (DBP) readings, respectively. One weakness of the study is the use of hospitalization claims data to record events during follow-up, which is less reliable than formal adjudication. Another is the routine and nonstandardized collection of BP measurements in this large clinical registry. Nonetheless, the study showed a linear relationship between the risk of developing coronary artery disease/CVD and the level of SBP and DBP. Importantly, this risk was evident regardless of glycemia status. Specifically, the relative risk of developing cardiovascular and cerebrovascular complications started to increase at a SBP of ≥120 mmHg and at a DBP of ≥75 mmHg in all three categories of glycemic status. Most of the current study population were young, with a mean age of 44, 48, and 52 years for normoglycemic patients, patients with prediabetes, and patients with diabetes, respectively.

This study is of some interest because it provides epidemiologic BP data in a Japanese cohort. Most of the historical data we have on the epidemiology and risk of hypertension come from studies of Caucasians. For example, in one of the largest hypertension data sets of 61 observational studies and more than one million patients, 90% of participants were from Europe and North America and only 10% were from Japan and China (7). Having data from diverse geographies has value in

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demonstrating epidemiologic risk in specific populations and may help in guiding future research in these populations. However, in our opinion, the results reported by Yamada et al. are consistent with numerous prior reports, even when considered on the basis on race/ethnicity and on glycemic status, and so the authors' findings were expected.

In their discussion, Yamada et al. call for stricter BP control in all patients to prevent CVD. While one might think that establishing an epidemiologic association between high BP above a certain threshold and CVD risk will mean that intervening with medications to reduce BP below that threshold will reduce or reverse the risk of CVD, the data that we have from large hypertension trials paint a more complicated picture. For example, the Systolic Blood Pressure Intervention Trial (SPRINT) (6) showed that more intensive BP control in high–CVD risk hypertensive patients without diabetes (targeting unattended SBP of <120 mmHg) significantly reduced overall and cardiovascular mortality in comparison with less intensive control targeting SBP at <140 mmHg. However, another trial that evaluated intensive BP control (<120/80 mmHg) in Japanese adults with a history of stroke (12) showed that the risk of stroke recurrence was not statistically lower than with a BP target of <140/90 mmHg (hazard ratio 0.73 [95% CI 0.49–1.11]). Similarly, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (13), which exclusively enrolled patients with type 2 diabetes and also compared intensive (SBP <120 mmHg) versus less intensive (SBP <140 mmHg) targets, did not show any significant difference in overall mortality, cardiovascular mortality, risk of nonfatal MI, and nonfatal strokes between the two groups. Furthermore, trials of other patients at lower risk for CVD suggest that there is no added benefit to targeting a BP <130/80 mmHg (14–16).

Indeed, the apparent contradiction between some aspects of BP observational research and therapeutic RCTs should not come as a surprise to clinicians caring for persons with diabetes. A similar contradiction has been found in trials of diabetes therapies targeting HbA_{1c}. Specifically, multiple observational studies have shown a strong linear relationship between HbA_{1c} levels and the risk of CVD outcomes (17,18), which led to the study of more intense HbA_{1c} targets in ACCORD. However, this RCT showed that the primary outcome was not reduced by targeting lower HbA_{1c} (<6%), but mortality was indeed higher (19).

Therefore, despite the observational data presented here by Yamada et al., we cannot agree that the evidence base conflicts with present guideline recommendations for SBP treatment and we feel the results of this study do not justify calls for widespread treatment of SBP to levels 120–130 mmHg, especially since these more intensive BP targets may come with increased risk of falls, acute kidney injury, and hypotension in elderly and may add more burden to patients and health care systems.

What is also notable about the current study is that it showed a linear relationship between DBP readings and cardiovascular/cerebrovascular risk. This finding is interesting because several previous observational studies have described a J-curve association between DBP and adverse cardiovascular events (20,21), i.e., adverse cardiovascular events when the DBP is below a certain point. However, because the J curve is a phenomenon of observational research, there is a lot of uncertainty around this DBP J-curve relationship and whether it represents a confounded association or a true causal one. Recent studies point strongly to reverse causation as the reason for higher cardiovascular event rates in patients with lower DBP (22). Therefore, the higher risk for CVD may not be related directly to lower DBP in these patients; instead, it might reflect the fact that adults with low DBP are typically older and have other comorbidities like underlying vascular stiffness and heart failure (this is supported by the lack of DBP J curve in the randomized treatment data from SPRINT and ACCORD) (6,13,23,24). The lack of J curve in the study by Yamada et al. is likely a result of the study including relatively young patients (of an average age between 44 and 52 years). Indeed, in our opinion, the linear relationship between DBP and risk in this relatively young population adds to the emerging data calling into question the causal validity of the diastolic J curve, and it supports the hypothesis that the J curve found with DBP is secondary to reverse causation rather than a direct association between lower DBP and mortality.

In summary, like the game of limbo, we are going lower and lower with our recommendations for BP treatment targets. For the SBP target of <130 mmHg in current guidelines, we believe the supporting evidence is strong overall and also supports, on balance, the use of this target for patients with diabetes and higher CVD risk. This SBP target should be pursued irrespective of baseline DBP and physicians should not worry about lowering DBP too low. Whether patients have diabetes or do not, to get all eligible hypertensive adults who are on drug treatment to meet this SBP goal of 130 mmHg will require substantial effort and a change in mindset. Finally, despite the wealth of observational data documenting an increased risk of CVD once SBP is >120 mmHg (to which Yamada et al. contribute nicely), we do not think there is sufficient justification to recommend further reducing the diagnostic threshold and treatment target of hypertension to 120 mmHg or lower. Thus, until more trial data demonstrate consistent long-term benefit for treatment of SBP to <120 mmHg (and recognizing that healthy lifestyle and diet are recommended for all), we believe that the therapeutic management of adults with SBP 120–130 mmHg will be in the other form of limbo, that of uncertainty.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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