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Reassessment of blood pressure goals: Should a single value or range be the goal?

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ABSTRACT

Previous hypertension guidelines recommended a single blood pressure (BP) goal or value as a treatment target. For years, there has been contentious debate on the ideal BP threshold, and this continues to be a moving target. The lack of a recommended lower limit of efficacy and safety may offset the intended incremental cardiovascular risk reduction proposed by some due to treatment-related adverse events and discontinuation, especially in older and frail people. Evidence from randomized controlled trials, post hoc analyses, and meta-analyses have brought to light that a specific target range of BP appears more pragmatic and clinically relevant than reliance on a single BP threshold value. A risk-based blood pressure target range should maximize incremental benefits in the appropriate patient population while avoiding over- and under-treatment. This evidence-based approach can maximize the time-in-target BP control rate, which has significant prognostic importance. BP treatment should be focused on time in the target range contingent on age, comorbidities including vascular stiffness, and level of cardiovascular risk rather than a single target value. This should be the future of guideline goals and analytical assessments.

Key-words: *Hypertension, guidelines, targets, outcomes, variability*

The approach to hypertension management has been refined through the years and is still evolving, albeit slower. Blood pressure (BP) guidelines from their inception have focused on a single cut-off value to be the goal for diagnosis and treatment. Over the past 40 years, the BP target goal has been reduced from less than 140/90 mmHg to less than 130/80 mmHg.[1] All previous cardiovascular and renal outcomes studies support this revision based on reduced cardiovascular event rates and slowing kidney disease progression.[2] Two notable exceptions are the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and the Systolic Blood Pressure Intervention Trial (SPRINT)[3,4]. Both these trials proport a BP of <120/80 mmHg. However, this needs to be taken into context of the trial cohorts and how BP was measured and thus, can't be compared to other trials using different BP measurement methodology[5] but even then, the overall average BP for the intensively treated group was above 120 mmHg over most of the study duration. Thus, static values as goals, regardless of the methodology used, do not reflect dynamic lifestyle changes that occur daily in people. Moreover, they do not consider physiological changes with aging, progressive stiffness of arteries over

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time, and the presence of concomitant diseases.

The importance of vascular stiffness is also not accounted for when assessing BP goals and the validity of measurements, especially in those with pulse pressures over 70 who are generally older. It is well known that increased vascular stiffness is associated with isolated systolic hypertension, increased BP variability, and a greater likelihood of masked hypertension field[6,7]. These factors contribute to increased cardiovascular morbidity and mortality that a single BP measurement cannot accurately assess. Moreover, these are individuals where lowering BP to <120 mmHg is impossible due to reduced cognitive functioning, dizziness, and somnolence[8]. These factors are better characterized by ambulatory blood pressure monitoring (ABPM).[9] However, what cannot be practically evaluated on a day-to-day basis is the time-in-target range (TTR).

Recent studies have examined TTR and indicate that those with a higher percentage of time within the BP range have reduced all-cause mortality and lower cardiovascular events[10,11]. However, TTR relies on a specific BP range rather than a single threshold value. One primary reason for the absence of a BP range to describe a goal is that there are no outcome trials that delineate a range and validate the cardiovascular outcomes. However, based on available data, it can be argued that BP ranges around the central value within one standard deviation are consistent with lower event rates than a single value.

We highlight the similarities and differences between the American and European hypertension guidelines and review the evidence to support using a BP range within one standard deviation of the mean rather than a single threshold goal for better assessment of cardiovascular and kidney disease outcomes.

The American College of Cardiology / American Heart Association (ACC/AHA) and European Society of Cardiology / European Society of Hypertension (ESC/ESH) guidelines share a common ground in tangible ways[12]. The importance of a standardized BP measurement technique and the utility of home BP monitoring and ABPM are emphasized across the guidelines. The recommendation for using beta-blockers specifically for those with compelling indications such as angina, post-myocardial infarction, heart failure, and atrial fibrillation is consistent with the guidelines. Lifestyle modification remains emphasized by various professional societies involved in the guideline development as the base of all BP-lowering therapy.[12] The similarities between the guidelines focus on a compelling body of evidence supporting such recommendations based on the strength of scientific studies. Nonetheless, there are discordant points between the policies where the respective expert panels interpreted the same data differently.

The significant differences between the guidelines are far from trivial to ignore. The areas of contention on the threshold for diagnosis and treatment have far-reaching repercussions in achieving hypertension control and its potential complications. The ACC/AHA defines the diagnosis of hypertension at a lower threshold value of 130/80 mmHg compared to 140/90 mmHg in the ESC/ESH. Meanwhile, the recommended initial treatment strategy involving a single-pill combination is strongly recommended by the ESC/ESH but with the provisional condition by ACC/AHA only for those with 20/10 mmHg above goal. Therapeutic BP target is more nuanced, i.e., considering patients' age and comorbidities, in the ESC/ESH guidelines compared to a "one-size-fits-all" BP target in the ACC/AHA.[1,13] When the guidelines don't meet eye-to-eye, the divergence in the recommendations raises questions on what could have been the underlying justification for such differences.

One distinguishing feature of the ESC/ESH guidelines is the tailored BP target goal based on an individual's cardiovascular risk. Some specific BP ranges have been suggested depending on accompanying cardiovascular risk factors.[13] The underlying concept is that the risk for cardiovascular events is cumulative from the various predisposing factors at play. For instance, patients with high-normal BP, defined by ESC/ESH guidelines as 130/85 to 139/89 mmHg, are recommended to have pharmacologic treatment initiated only if their cardiovascular risk is very high such as those with established coronary artery disease (CAD).[13] This recommendation is supported by meta-analyses of randomized controlled trials (RCTs) that demonstrated risk reduction in stroke in those treated with BP-lowering medications for those with normal and high-normal BP (120-139/80-89 mmHg) accompanied with very high cardiovascular risk only. There were no reduced cardiovascular events in patients with low or moderate cardiovascular risk.[14] Thus, the total cardiovascular risk matters in treatment decisions as the absolute risk reduction is more significant for those at higher baseline risk.[15]

A rigid BP target for hypertension treatment ig-

nores that cardiovascular risk runs a spectrum based on the individual's predisposing conditions. The therapeutic benefit and risk have to be balanced by achieving an "optimal" BP target range that provides more significant risk reduction while minimizing treatment intolerance.[12] One has to be cognizant of identifying the sweet spot for reducing the risk of cardiovascular events in individuals who are also at high risk of adverse events from too aggressive BP lowering. As previously demonstrated in a meta-analysis, reduction in systolic BP (SBP) below 130 mmHg was associated with more significant treatment discontinuation but a minor absolute risk reduction of cardiovascular events.[16]

Aside from the burden of adverse effects in an attempt to achieve a lower target BP threshold, another critical consideration in proposing a target BP range is avoiding wide BP variability. Though BP variability as a therapeutic target remains an open question that warrants clinical outcome studies, emerging evidence has suggested that wide BP variability beyond one standard deviation of a mean between 130 and 140 mmHg could contribute to stroke, cardiovascular mortality, and worsening renal function.[17-19] It has been hypothesized that wide BP variability facilitates oscillatory shear stress in the endothelium, leading to atherosclerosis and loss of glomerular autoregulation.[20]

The concept of "the lower, the better" has reinforced the practice of focusing on a single threshold BP target. This oversimplification ignores the phenomenon of BP variability over time. A single BP threshold does not reflect the actual BP load over time which could be better tracked by monitoring the therapeutic BP range. Rather than adhering to a fixed threshold value, a more prudent and clinically relevant approach targets an optimal therapeutic range between 120 and <140 mmHg. In a multiethnic retrospective study by Gomadam and colleagues, this concept was illustrated where the presence of diabetes changed the CV and renal disease progression risk.

Contrary to previous studies, the benefit of very low BPs, i.e., less than 120 mmHg systolic, was detrimental concerning CV risk in those with diabetes but not those without diabetes.[21] This is corroborated by a longitudinal study using an extensive database of about 700,000 US Veterans with almost 15 million BP readings during 12 years of follow-up. The lowest risk of all-cause mortality was evident in those with SBP maintained within the 120 to <140 mmHg range.[11]

Identifying a target BP range appears to be a more judicious approach in hypertension treatment from an efficacy and safety standpoint. A one-size-fits-all approach to a single BP target goal may inadvertently contribute to the J-curve phenomenon where increased cardiovascular mortality occurs above and below a specific BP range.[22] Thus, it is critical to focus on absolute risk reduction rather than a population approach of relative risk and balance the magnitude of absolute benefits expected for a given cardiovascular risk status and the potential burden of side effects that usually result in treatment termination. As demonstrated in a meta-analysis that quantified the benefits and risks of BP lowering, there was a significant trend in progressively increasing risk of treatment-associated adverse effects when there was lower achieved SBP.[16] This situation supports identifying a well-defined BP range rather than targeting a single BP cut-off value.

After years of adhering to a traditional single BP cut-off value for diagnosis, the quest for an optimal BP target range remains elusive. Nonetheless, the ESC/ESH guidelines are making some giant leaps forward in shifting the treatment paradigm for hypertension in the right direction. While the ACC/AHA has a universal BP threshold, i.e., <130/80 mmHg, irrespective of age and comorbidities, the ESC/ESH provides specific BP ranges contingent on the demographic and clinical conditions of the patient. For instance, among patients older than 65 years or with CKD (defined as eGFR<60 mL/min/1.73 m^2), the recommended target BP goal lies between 130 to <140 / 70 to 79 mmHg.[13] Aiming for a lower BP threshold for very old patients poses significant risks of adverse treatment events that could lead to treatment discontinuation, especially for the frail population excluded from clinical trials. While this has been achieved in individuals over the age of 75, they were generally healthy with good vascular compliance for their age.[23]

Focusing on the older age group with poor vascular compliance, we have excellent data that support this point. Older individuals with a wide pulse pressure of >70 mmHg in the Systolic Hypertension in the Elderly Program (SHEP) who could not tolerate BP reduction to <140 mmHg systolic had a significant risk reduction in CV events if their BP level could be brought below 160 mmHg systolic.[8] Conversely, very old individuals (mean age 82 years) with pulse pressures <70 mmHg in the Hypertension in the Very Elderly Trial (HYVET) showed propor-

tional cardiovascular benefits of reducing SBP to target levels in the 140-150 mmHg range.[24] As a caveat, close BP monitoring for this subgroup of patients is highly recommended.

Incorporating the latest evidence to date, the recently published iteration of the 2021 ESC guidelines on cardiovascular prevention is long-awaited progress. It recommends a stepwise approach of initially lowering BP <140/90 mmHg for all groups with an eventual goal of attaining a lower optimal target BP range, if tolerated, based on the patient's age and presence of diabetes, CKD, CAD, and stroke/TIA. For hypertensive patients (18-69 years), the ultimate target SBP range is 120-130 mmHg in the presence of diabetes, CAD, and stroke, and 130 to less than 140 mmHg if with CKD. Among older individuals (>/= 70 years), the target BP range has been proposed at 130 to less than 140 mmHg for all clinical scenarios if tolerated.[25]

The older paradigm of reducing cardiovascular events by lowering BP to an absolute cut-off value has begun to shift into a risk-based target BP range that considers the patient's context. Regardless of the severity of hypertension, lowering BP to a specific threshold range confers clinical benefits.[26] A review of the totality of evidence based on a trial-level meta-analysis demonstrates a similar proportional reduction in the risk of cardiovascular disease and all-cause mortality across various high-risk patient subgroups with underlying comorbidities, irrespective of baseline BP. The commensurate benefits of BP reduction have remained consistent with baseline SBP <130 mmHg, arguing in favor of target SBP <130 mmHg.[27] However, there was a lack of net benefit for renal outcomes when SBP is lowered to <130 mmHg as described in a previous meta-analysis.[27,28]

Clinicians have debated the critical question of how far to go in lowering BP. In clinical practice, the cost of reducing cardiovascular events aggressively has to be weighed carefully with the potential risks of adverse events that could lead to treatment discontinuation. The optimal threshold range for BP treatment should be based on age, cardiovascular risk, other concomitant medical conditions, tolerability, and, very importantly, how BP is measured. Current practice guidelines are evolving towards a more personalized treatment paradigm. The conventional threshold for BP treatment has been ripe for a change for a long time.

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