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Commentary

Taking a step back: Making sense of evidence on diastolic blood pressure in the context of targets for older adults

Vincent D. Salvador, George L. Bakris *

AHA Comprehensive Hypertension Center, Department of Medicine, University of Chicago Medicine, Chicago, IL, USA

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Attaining an optimal blood pressure (BP) goal for older adults remains a highly relevant yet contentious issue that has generated diverging viewpoints. Suffice it to say; there is still a lack of consensus on the ideal BP goal for the senior population. The current review by Filippone and colleagues sheds a bright light on this area. The authors review a variety of studies and make appropriate points about the limitations of data extrapolation [1]. Two issues of note however, the authors very appropriately focus on pulse pressure which is critical in assessing a valid and safe reduction in systolic BP. No recent trial including SPRINT and ACCORD had pulse pressures much above the 70's [2]. In contrast, the one trial not mentioned, the Systolic Hypertension in the Elderly Program (SHEP) did have very wide pulse pressure into the 90 mmHg range [3]. One of the conclusions of this trial was that if BP could not be reduced below 140 mmHg due to symptoms, a reduction below 160 mmHg is associated with reduction in cardiovascular events.

As we grapple with the dilemma regarding the risk/benefit ratio between intensive and standard BP goals, the recently published STEP trial by Zhang and colleagues [4] helps to close this gap. The study contributes valuable insights amidst a limited number of appropriately powered randomized controlled trials (RCTs) explicitly dealing with randomized blood pressure levels in older patients. However, the present trial raises inevitable questions such as the generalizability of its findings given the study design and analysis. Why because like previous trials the patients had relatively normal to mildly elevated pulse pressures. Therefore, a clear understanding of the study results must view in the context of previous observational cohort studies and RCTs to have a more holistic grasp of the issues.

A careful analysis of the STEP trial demonstrates that study participants were not representative of the broader older population who are beleaguered with varying concerns of comorbidities, frailty, and polypharmacy. The restrictive eligibility criteria excluded patients with extremes of BP, specifically diastolic BP < 60 mmHg, and high pulse pressures. By excluding substantial patient subgroups, it limits a meaningful stratified assessment of potential differential treatment effects across various baseline comorbidities that are clinically significant in clinical practice. More importantly, the study's highly selective criterion compromises the study's generalizability to a broader older population across time and setting. Thus, the trial design precludes an accurate depiction of a real-world clinical practice involving geriatric patients with varying comorbidities.

Given that the STEP cohort is limited to the Han Chinese population with considerable burden of uncontrolled hypertension and stroke [5], it is interesting to note that the risk reduction in the incidence of stroke in the intensive BP group in the STEP trial was comparable with that of SPRINT [6]. Yet, there was no significant difference in incident stroke rates between intensive and standard BP groups in SPRINT. Additionally, unlike SPRINT, the STEP trial had very few participants with Stage 3 chronic kidney disease (CKD) (i.e., ~2% in each group eGFR<60 ml/min/1.73 m^2). The data for patients with underlying chronic kidney disease are different, so that should be considered [7,8]. For instance, among patients greater than age 70 years with Stage 3 CKD, systolic BP <130 mmHg was found to be associated with higher risk of death

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* Corresponding author at: University of Chicago Medicine, Department of Medicine, AHA Comprehensive Hypertension Center, Section of Endocrinology, Diabetes & Metabolism, 5841 S Maryland Ave. MC 1027, Chicago, IL 60637, USA.
E-mail address: gbakris@uchicago.edu (G.L. Bakris).

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compared to attaining systolic BP at 131–140 mmHg [9]. Moreover, this cohort, like SPRINT did not have people with wide pulse pressures or diastolic BP below 60 mmHg. Hence, not generalizable to this subgroup.

Attaining an optimal systolic BP is more nuanced for older adults. When systolic BP is lowered, the diastolic BP could also be reduced inadvertently - to critically low levels, i.e., <45 mmHg- which can compromise coronary perfusion. This concern emanates from an established physiologic rationale of the J-shaped association between diastolic BP and coronary events verified by multiple large observational studies [10]. This exemplified in a prospective cohort study involving 11,565 adults that demonstrated a diastolic BP < 60 mmHg was consistently linked to greater risk of both subclinical progressive myocardial damage, coronary heart disease and mortality [11]. In the STEP trial, the mean achieved diastolic BP was above 70 mmHg in both intensive and standard treatment groups – a finding that does not apply to some elderly patients whose diastolic BP could be much lower levels that meet the hypotension criteria. Though sensitivity analysis was performed on a limited subset of patients to examine heterogeneity in treatment effect when diastolic BP was <60 mmHg and/or pulse pressure > 60 mmHg, there was no statistically significant difference in the incidence of primary outcomes in both treatment groups. What is evident is the significantly higher risk of developing hypotension in the intensive treatment group (3.4% vs 2.6%, $P = 0.03$) [4].

It has been previously argued - based on a post-hoc secondary analysis of SPRINT involving the elderly group 75 years or older without diabetes - that the group randomized to intensive BP goal (SBP <120 mmHg) had a lower rate of primary cardiovascular disease outcome (hazard ratio, 0.66; 95% CI, 0.51–0.85, $P = 0.001$) which appeared to be consistent irrespective of frailty status [12]. However, the study was merely exploratory in intent, and not conclusive. The results are, at best, hypothesis-generating. In that same study, there was a greater incidence of hypotension, in absolute rate, for the intensive group (2.4% vs. 1.4%) [12]. Consideration of adverse events in BP management is of utmost clinical relevance, especially for frail older adults who will bear the consequences of hospitalization and impaired quality of life – a hefty price to pay for trying to lower BP goal to thresholds that defy the altered physiologic state of the patients.

Previous landmark hypertension trials involving older adults offer some guidance that warrants recapitulation in the post-SPRINT era. In the Systolic Hypertension in the Elderly Program (SHEP) trial involving patients 60 years of age or older, there was a significant reduction in the incidence of stroke, i.e., 36% risk reduction, on lowering systolic BP < 150 mmHg [13]. For the octogenarians and beyond, the Hypertension in the Very Elderly Trial (HYVET) demonstrated the benefit of achieving target BP of 150/80 mmHg in reducing the risks of fatal and non-fatal stroke (30% risk reduction), death from stroke (39% risk reduction), death from cardiovascular causes (23% risk reduction) and heart failure (64% risk reduction) [14]. Both trials attest to cardiovascular benefits of conservative BP lowering but up to a certain degree.

What could be gleaned from the real-world data when it comes to targeting BP for the elderly population? In a recently published prospective observational study of 415,980 primary care patients 75 years and older, with up to 10 years of follow-up data, BP < 130/80 mmHg was found to be consistently associated with excess mortality, independent of frailty status [15].

When one looks at the totality of the data — the STEP study and a post-hoc analysis of SPRINT, put together with the older trials — the following can be said: For people who do not have diabetes and a greater than or equal to a 15% 10-year CV Framingham Risk Score [16], and diastolic BP >60 mmHg, there is no question that a systolic BP, less than 130 mmHg, reduces cardiovascular risk.

There are, however, exceptions. Suppose a patient has significant vascular stiffness, with a pulse pressure greater than 70 mmHg. In that case, a BP that like in the STEP trial, will likely cause a person to be symptomatic, i.e., lightheadedness, memory problems, falls, which some trial participants experienced and should be avoided. If a person has diabetes, you want the systolic level to be at 125 mmHg or higher, as there are good data supporting increased risk at levels below this value [17,18].

The notion *lower is better* is an oversimplification at its best misleading at its worst. Less than 130 mmHg is where you should be if you are older, do not have a widened pulse pressure, and tolerate it. Otherwise, we must follow the mandate of the SHEP trial [13] in 1991, that if you reduce systolic BP to less than 140 mmHg, you derive significant cardiovascular benefits. If you cannot lower systolic BP to less than 140 mmHg due to tolerability and falls etc., at least get it to well below 160 mmHg. Management of hypertension for older adults must take into context of the patient's overall risk profile rather than over-reliance on a rigid BP target alone.

In summary, the STEP trial findings must be interpreted with a "grain of salt" before directly applying to routine clinical decision-making. The results may not be applicable to specific underrepresented patient subpopulations, such as those with multimorbidity, greater polypharmacy burden, and significant frailty. Weighing the merits of a specific BP target requires a balancing act of the relative benefits and risks. Establishing an algorithm-based BP goal management, based on limited evidence is likewise counterintuitive without due cognizance of everyone's comorbidities, well-being, and functional status. Extending patients' longevity is one thing but, preserving their quality of life is another consideration that cannot be ignored.

Duality of interests

Vince Salvador-Nothing.

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