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HYPERTENSION AND THE HEART (BHARATHI UPADHYA, SECTION EDITOR)

Preventing Heart Failure by Treating Systolic Hypertension: What Does the SPRINT Add?

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Abstract

Purpose of Review Previous trials definitively established that lowering systolic blood pressure (BP) to 140 mmHg prevented heart failure (HF) exacerbations, but the potential benefits and risks of further BP reduction remain unclear due to a paucity of trial-based data.

Recent Findings A recent secondary analysis of the Systolic Blood Pressure Intervention Trial (SPRINT) found that in older, high-risk, non-diabetic participants with systolic hypertension, a BP treatment target < 120 mmHg resulted in a 36% lower rate of acute decompensated HF as compared with a BP target < 140 mmHg. Those participants with incident HF had a 26-fold increased risk of subsequent cardiovascular events and death. Based in part on the SPRINT results, the 2017 American Heart Association/American College of Cardiology/HF Society Guideline for the Management of HF acknowledged that targeting a significant reduction in BP in those at increased risk for cardiovascular disease is a novel risk-based strategy to prevent HF.

Summary SPRINT redefines systolic BP target goals in older, high-risk patients and provides a key opportunity for preventing HF in this patient group.

Keywords Heart failure · Systolic hypertension · Prevention · Systolic blood pressure · SPRINT

Introduction

Hypertension (HTN) remains a major public health problem associated with considerable morbidity and mortality. HTN continues to be the most prevalent risk factor for heart failure (HF) and precedes the diagnosis of HF in 75–85% of persons who develop HF [1, 2]. Higher systolic blood pressure (SBP) increases the risk of developing HF, and BP reduction prevents incident HF, but the optimal BP target for prevention of HF remains uncertain [3]. Further, in the elderly, aggressive BP-lowering strategies may potentially lead to complications, such as mechanical falls with injury and renal failure, as well as adverse effects associated with polypharmacy. This article aims to review current BP targets to prevent HF among older patients with HTN.

Case Histories

Patient 1: an 84-year-old African American man (body mass index (BMI) of 34) who is followed routinely at his cardiologist's clinic subsequent to a coronary revascularization performed 5 years ago. He remains asymptomatic without diabetes mellitus (DM), but continues to smoke half-a-pack of cigarettes per day. His last echocardiogram showed a normal left ventricular ejection fraction (LVEF) 1 year ago. His routine laboratory tests showed an estimated creatinine clearance of 35 ml/min. His BP was 140/90 mmHg after 5 min in a seated position.

Patient 2: an 84-year-old Caucasian woman (BMI, 24) was examined at a routine annual visit with her primary care physician. She was asymptomatic. Her BP was 140/90 mmHg after 5 min in a seated position. She did not have DM or history of cardiovascular disease (CVD). Her routine laboratory tests were unremarkable, including normal renal function.

To reduce the risk of HF, should both patients be treated to a BP reduction target of < 120/80 mmHg?

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Hypertension and HF Risk—Pathophysiology

The progression from HTN to structural cardiac changes and eventually systolic and diastolic left ventricular (LV) dysfunction is demonstrated in Fig. 1. Although LV hypertrophy (LVH) can precede the development of HTN, the progression from HTN to concentric LVH is an important step in the pathway toward HF. Along with mechanical stress resulting from pressure overload, neurohormonal abnormalities also play an important role in LVH. Neurohormones can directly promote myocyte hypertrophy and matrix deposition independently of their effects on BP [4]. There is a considerable inter-individual variability in how the LV hypertrophies in response to HTN. For example, compared to Caucasians, African Americans have higher LV mass, are more likely to develop concentric hypertrophy, and experience more severe diastolic dysfunction [5–7]. Similarly, those with higher SBP develop concentric hypertrophy much more frequently than eccentric hypertrophy [8]. Women with isolated systolic HTN also develop concentric LVH [9]. Increasing age has also been associated with a concentric as opposed to an eccentric hypertrophic response [1]. Along with afterload excess and LVH with its associated cardiac fibrosis and increased arterial stiffness, HTN also induces inflammation, oxidative stress, and endothelial dysfunction—all predispositions to HF [10]. Further, HTN may progress directly to HF in the absence of LVH or myocardial ischemia or infarction. However, contrary to conventional belief, BP may account for only 25% of the variability of LV mass in a population [11]. Indeed, the majority of patients with HF with preserved EF did not have significant LVH at baseline [12]. A recent report by Soliman et al. showed that changes in electrocardiographic LVH explained only 1% of the reduction in CVD events in the Systolic Blood Pressure Intervention Trial (SPRINT) [13]. Thus, there is uncertainty regarding the relationships between BP lowering, LV mass reduction, and improved CVD outcomes in hypertensive patients, particularly at the lower ranges of target BP.

Systolic Blood Pressure Target and HF Risk

Risk for HF rises continuously with increasing BP [3]. The lifetime risk for HF doubles in those with BP > 160/100 versus

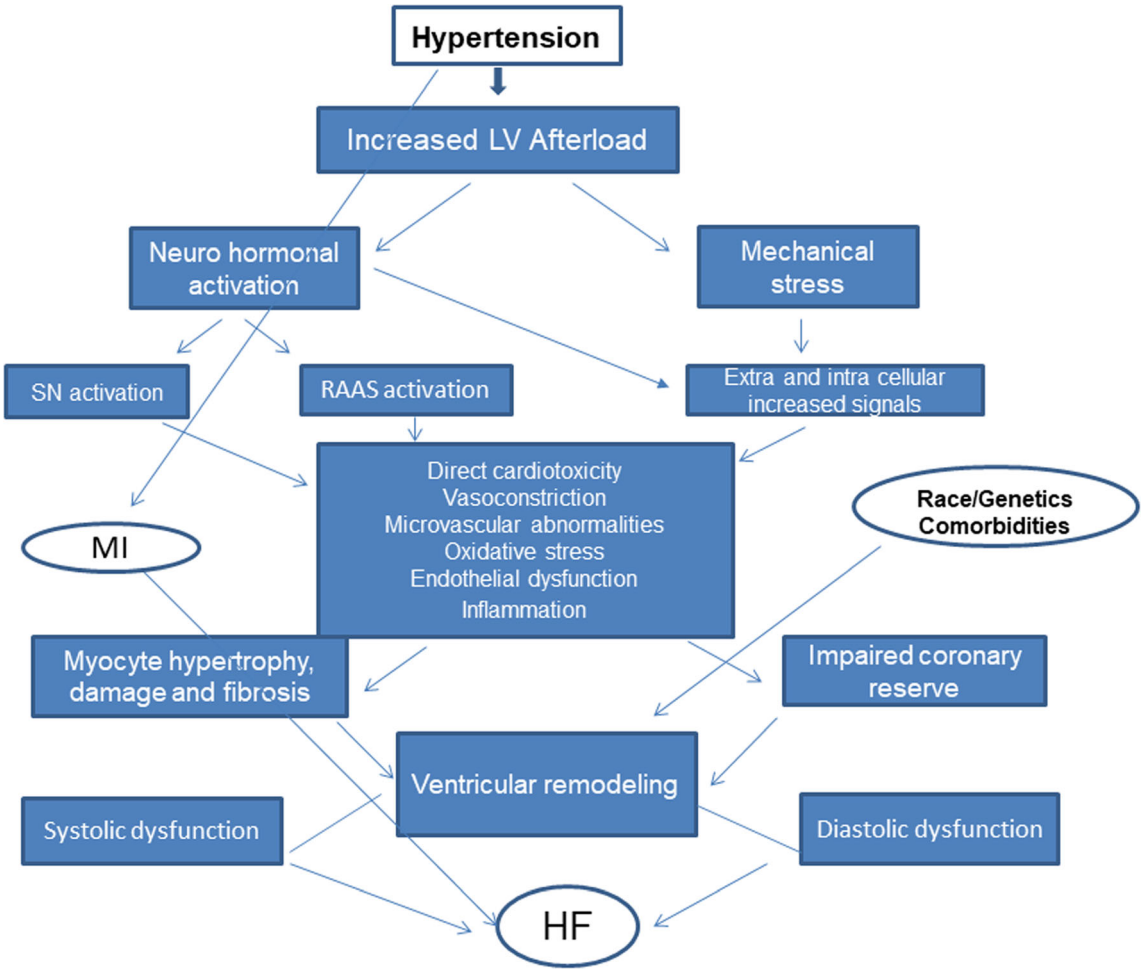

Fig. 1 Hypertension and heart failure risk—pathophysiology. LV, left ventricle; SN, sympathetic nervous system; RAAS, renin-angiotensin-aldosterone system; HF, heart failure; MI, myocardial infarction

< 140/90 mmHg [14]. Several prior trials in older patients with systolic HTN showed large reductions in new HF events resulting from SBP reductions to 140–145 mmHg [15–18] (Table 1). The particularly large reduction in HF events in the Hypertension in the Very Elderly Trial (HYVET) likely reflects the older age of the participants compared to the other three trials [15]. Similarly, a larger benefit was also observed in participants aged > 80 years in the Systolic Hypertension in the Elderly Program (SHEP) trial [16]. Although the benefit of lowering SBP to 140 mmHg for preventing HF events was well established by previous trials [15–18], there has been a paucity of information regarding the potential benefit and risk of lowering BP further. To address this uncertainty, a propensity score analysis of 7785 patients with mild to moderate HF with reduced or preserved EF followed for 5 years was carried out. The study found that a baseline SBP ≤ 120 mmHg was associated with increased CV and HF mortality and all-cause, CV, and HF hospitalizations, independently of other baseline characteristics [24]. Similarly, BP-lowering therapy among intermediate-risk adults showed a trend for harm among those with baseline SBP levels < 130 mmHg in the Heart Outcomes Prevention Evaluation (HOPE-3) trial [25]. Achieving intensive SBP reductions will inevitably also lower diastolic BP (DBP). Since myocardial perfusion requirements are increased in HTN, and myocardial perfusion pressure depends on adequate DBP, a drop in DBP could result in myocardial ischemia and increase LV dilation with subsequent HF with reduced LVEF [26]. A recent study demonstrated that among adults with a systolic BP ≥ 120 mmHg, a low DBP, particularly < 60 mmHg, was associated with subclinical myocardial damage and coronary artery disease events [27].

Intensive Systolic Blood Pressure Target (< 130 mmHg) and HF

Based on data to this point, the outcomes from large clinical trials have not successfully addressed the question of whether lowering SBP < 130 mmHg is an effective strategy to prevent HF. The Studio Italiano Sugli Effetti CARDIOvascolari del Controllo della Pressione Arteriosa SIStolica (Cardio-Sis) trial showed that lowering systolic BP to < 130 mmHg in non-diabetic patients decreased composite CV outcomes compared with a SBP < 140 mmHg [20]. However, HF event reduction was not significantly different between treatment arms (hazard ratio (HR), 0.42; 95% confidence interval (CI), 0.11–1.63) (Table 1). The results of the Cardio-Sis trial have to be interpreted within the context of its potential limitations. First of all, they powered their study on LVH as the primary outcome. Few clinical events, short clinical follow-up time with a fairly

Table 1 Randomized systolic hypertension trials that used heart failure as outcomes

First author/trial (ref. no.)	Mean basal SBP	Between-group difference in mean SBP at the end of follow-up	Patient type	Relative risk reduction for HF	Average follow-up
HYVET [15] $n = 3845$	173 mmHg	15 mmHg	Mean age, 84 years; women, 61%; h/o CVD, 12%; DM, 7%; h/o stroke, 7%; h/o HF, 3%.	64%	1.8 years
SHEP [16] $n = 4736$	171 mmHg	12 mmHg	Mean age, 72 years; 57%, women; African Americans, 14%; h/o CVD, 5%; h/o HF, 0.3%; h/o stroke, 1.4%; h/o DM, 10%.	50%	4.5 years
Syst-Eur [17] $n = 4695$	174 mmHg	10 mmHg	Mean age, 70 years; women, 67%; CVD, 30%; h/o stroke, 4%	36%	2.0 years
ALLHAT [18] $n = 33,357$	146 mmHg	11 mmHg	Mean age, 67 years; women 47%; African Americans, 35%; DM, 36%; h/o CVD, 52%; h/o HF excluded	26%	4.9 years
ACCORD [19] $n = 4733$	139 mmHg	14 mmHg	Mean age, 62 years; women, 48%; African Americans, 24%; h/o CVD, 34%, h/o HF, 4.3%; all with type II DM	8%	4.7 years
Cardio-Sis [20] $n = 1111$	163 mmHg	4 mmHg	Mean age, 67 years; 59%, women; h/o CVD, 13%; h/o stroke, 9%	62%	2.0 years
SPRINT [21•] $n = 9361$	140 mmHg	13 mmHg	Mean age, 68 years (28% were aged 75 years and older); women, 36%; African Americans, 30%; h/o CVD, 20%; h/o CKD, 28%; h/o stroke and HF excluded	38%	3.3 years
Upadhya et al. [22•] $n = 9361$	140 mmHg	13 mmHg	The same as above	36%	3.3 years
SPRINT SENIOR—Williamson et al. [23•] $n = 2636$	142 mmHg	11.4 mmHg	Mean age, 80 years; women, 38%; African Americans; 17%, h/o CVD, 24%; h/o stroke and HF excluded	36%	3.1 years

SBP—measured in sitting position

SBP, systolic blood pressure; *HF*, heart failure; *CVD*, cardiovascular disease; *DM*, diabetes mellitus; *CKD*, chronic kidney disease

small sample size might have affected the power to examine HF outcomes. Cardio-Sis excluded people with DM and chronic kidney disease (CKD). In addition, the study included only Caucasian patients, so extrapolation to other racial/ethnic groups might not be justified. The study was not double-blind; thus, awareness of the randomization code could have affected the clinical decisions related to admission for HF events [20].

In ACCORD (Action to Control Cardiovascular Risk in Diabetes), a large randomized trial that specifically addressed the potential benefit of lowering SBP to < 130 mmHg (the target was 120 mmHg) in patients with DM, the HF event reduction was smaller and not statistically significant (HR, 0.94; 95% CI, 0.70–1.26) [19] (Table 1). This lower event rate in ACCORD was likely because of several factors. ACCORD recruited patients with DM and excluded people with CKD and those aged > 79 years. In addition, inclusion criteria directed participants with dyslipidemia into the ACCORD lipid trial, leaving participants who were at lower risk for CV events to be enrolled into the BP trial. ACCORD also used a factorial design that included comparisons of standard and intensive glycemic and lipid treatment targets in the same trial. Furthermore, the event rate in the standard therapy group in ACCORD was almost 50% lower than expected; thus, the trial may not have been adequately powered to examine HF events. In a recent meta-analysis, every 10-mmHg reduction in SBP reduced the risk of HF by an average of 28% (HR, 0.72; 95% CI, 0.67–0.78; $p < 0.001$). The proportional reductions per 10-mmHg decrease in SBP were greater for stroke and HF than for coronary heart disease, and there was a trend toward decreased HF events even with baseline SBP < 130 mmHg [28]. Similarly, meta-analysis of 35 HTN treatment trials with HF events showed a strong, significant correlation between the extent of SBP and DBP reduction and the reduction in HF events [29].

A secondary analysis of the Systolic Blood Pressure Intervention Trial (SPRINT), a large multicenter (102 sites), racially diverse randomized open-label trial, showed that treatment that targets a SBP of < 120 mmHg, compared with < 140 mmHg, resulted in a 36% lower rate of acute decompensated HF events [22•] (Table 1). Persons with DM, those with a history of stroke, and institutionalized people were excluded from the study. Symptomatic HF within the past 6 months, a LVEF of less than 35%, and an estimated glomerular filtration rate less than 20 ml/min/1.73 were also exclusions [21•]. All HF events were new (incident) events and were adjudicated based on a manual of operations that had been validated in the Atherosclerosis Risk in Communities (ARIC) study [30]. The beneficial effect of the intervention on the HF event rate became apparent early, at 6-month follow-up, and increased with duration of follow-up [22•]. The beneficial effect was consistent across all the key prespecified subgroups, including age ≥ 75 years or < 75 years, with or without prior CVD, with or without CKD, women or men, black race or non-black race, and the tertiles of baseline SBP [22•]. Participants who had an initial HF event had markedly increased risk of subsequent events, including recurrent HF (Fig. 2) [22•]. Similar results were also seen in the SPRINT SENIORS cohort (participants' age ≥ 75 years) [23•].

Clinical Implications of Lowering SBP to < 130 mmHg: Feasibility, Safety, and Patient Burden

While the efficacy of the SPRINT strategy is clear, given that the trial was stopped early due to benefit, some have questioned the feasibility, safety, and patient burden of lowering SBP to < 130 mmHg, particularly in older, frail patients. However, in both the main SPRINT and in the SPRINT SENIORS cohort, HF events were lower in the intensive arm compared with those of the standard arm, despite significantly lower DBPs (SPRINT, 69 versus 76 mmHg; SPRINT SENIORS, 62 versus 67 mmHg) [21•, 23•]. The benefit of intensive BP control was consistent among elderly persons (≥ 75 years) who were frail or had reduced gait speed [23•]. An analysis of the HYVET population showed similar treatment benefits, even in the frailest participants [31]. Furthermore, the overall serious adverse event rate was comparable in both treatment groups, including among the frailest participants in the SPRINT SENIORS cohort [23•]. There were no differences between treatment groups in injurious falls or orthostatic hypotension [23•]. Similarly, the ACCORD trial showed that intensive treatment (mean SBP < 120 mmHg) was not associated with an increased risk of falls or non-spine fractures in patients with type II DM [32]. Further, the Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly of Boston (MOBILIZE Boston Study) showed that improved BP control (< 140/90 mmHg) reduces risk for orthostatic hypotension in older community-dwelling adults (mean age of 78 years; female, 65%) and has no effect on risk for injurious falls [33]. A recent meta-analysis of existing randomized trials suggested that in patients with HTN, an on-treatment SBP target of < 130 mmHg achieved optimal balance between efficacy and safety [34]. Although there is no evidence of permanent kidney injury associated with the lower BP goal in SPRINT SENIORS, mild acute kidney injury occurred more frequently in the intensive treatment group [23•]. Similarly, hypotension, electrolyte abnormalities, and syncope were more frequent in the intensive group, though infrequent in the study overall [21•]. In the SPRINT intensive treatment group, an average of 2.8 antihypertensive drugs was required to reach SBP goal. Some healthcare providers have expressed reluctance to prescribe more than two antihypertensive drugs to a given patient, and adherence is generally lower with increasing complexity of clinical regimens. However, these disadvantages must be balanced with the clear benefit of substantially reduced mortality and CVD events from adopting the SPRINT intensive BP treatment strategy.

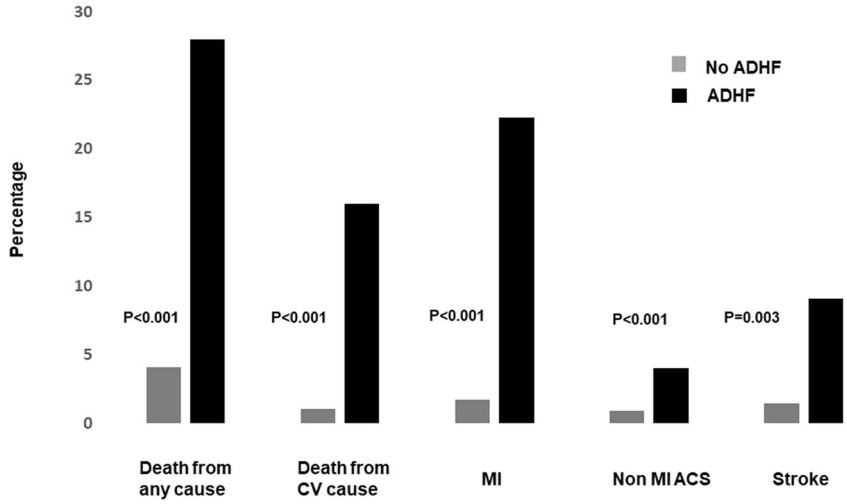

Fig. 2 Subsequent clinical outcomes based on initial acute decompensated heart failure events occurrence. ADHF, acute decompensated heart failure; CV, cardiovascular; MI, myocardial infarction; ACS, acute coronary syndrome

What Does the SPRINT Add?

The SPRINT results have substantial implications for the future of intensive BP therapy in older adults because of this condition's high prevalence, the high absolute risk for CVD complications from elevated BP, and the devastating consequences of such events on the independent function of older people. However, the public health implications are dependent on the generalizability of the SPRINT outcomes to the US population, especially populations excluded from the trial, e.g., younger and lower-risk persons; those with DM, severe kidney disease, prior HF, and stroke; and subgroups of elderly adults (nursing home residents, extremely frail or demented individuals). Using data from the National Health and Nutrition Examination Survey (NHANES), Bress et al. found that 8.2 million adults with treated HTN (17% of the hypertensive population) meet the SPRINT eligibility criteria and thus may benefit from intensive BP treatment [35]. They also predicted that in patients who fit SPRINT eligibility criteria, intensive BP treatment would prevent approximately 46,100 cases of incident HF per year but would cause 56,100 episodes of hypotension, 88,700 cases of AKI, 34,400 episodes of syncope, and 43,400 cases of electrolyte disorders (hyponatremia and hypokalemia) compared to standard care [36].

Blood Pressure Measurement in SPRINT

Knowing how BP is measured is important for guiding clinicians in appropriate management of HTN [37]. Although numerous HTN experts have argued that the BP measurement technique in SPRINT makes it an outlier, SPRINT BP measurements were conducted using methods that were commonly recommended by professional societies and BP guideline committees [38•, 39]. The SPRINT used programmable automated oscillometric devices (Omron Digital BP Monitor) to measure BP [40]. This device could be programed to incorporate the 5-min rest and then initiate the three BP measurements automatically after the 5 min had elapsed. Coordinators were instructed how to program the Omron device during training [40]. The coordinators could have been in or out of the room during the 5-min rest period and/or during the time the Omron was automatically taking the BP measurements. Recent publications have stated that the BP measurement technique used in SPRINT was unattended, and was not comparable with BP readings in other trials where the measurement was attended and that the intensive treatment goal of < 120 mmHg in SPRINT would actually correspond to higher SBP values in other trials [41]. Notably, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines do not comment on the presence or absence of an observer during BP measurement. The recent post hoc SPRINT analysis suggested that there was no compelling evidence in SPRINT that unattended BP measurements led to lower SBP at baseline or during follow-up compared to the attended BP measurements [40]. Importantly, similar BP levels and CVD risk reduction were observed in the intensive treatment group of SPRINT participants whether the measurement technique used was primarily attended or unattended [40]. Similarly, data from the SPRINT Ambulatory BP Ancillary Study also showed that the BP values obtained at the SPRINT study clinic visit, whether attended or unattended, are similar to values obtained during 24-h ambulatory BP monitoring [42].

Impact of SPRINT on Guidelines

In 2017, the ACC/AHA HTN guideline changed the definition of HTN to incorporate the former "pre-hypertension" as stage 1 hypertension. Thus, normal BP is considered < 120/80 mmHg, elevated BP is 120–129/80 mmHg, and hypertension is > 130/80 mmHg [38•]. Similarly, they recommended that in adults with

HTN and increased risk of HF, the optimal BP should be < 130/80 mmHg [38•]. The guideline committee concluded that the available randomized controlled trials that provided evidence for their recommendation were efficacy studies in which BP measurements were more consistent with guideline recommendations than is common in clinical practice, resulting in lower absolute values for SBP. However, the Eighth Joint National Committee determined that SBP targets should be below 140 mmHg or below 150 mmHg in those 60 years of age or older [39]. The 2016 Canadian HTN Education Program Guidelines recommend intensive BP treatment with target SBP ≤ 120 mmHg (grade B) for high-risk patients based on automated office BP measurements (grade D) [43•]. Importantly, the 2016 Canadian HTN Education Program Guidelines recommend that BP be measured as in the SPRINT. The 2016 Australian guidelines recommend a SBP target < 120 mmHg (strong recommendation, class II) for high-CV-risk patients without DM, including CKD patients and those aging > 75 years [44]. Finally, the 2017 ACC/AHA HF guideline is one of the first to recommend the lower SBP target of 130 mmHg to prevent HF, based in part on the results of the SPRINT [21•, 22•, 23•, 45•].

Case Resolution

Based on this, considering that the risk for future development of HF differs considerably among these individuals, should their therapeutic targets be different? Would a lower SBP target for patient 1 than current recommendation further decrease the risk of HF? It is self-evident that the patient described in case 1 is at significantly higher risk of development of HF compared with patient 2. The former patient has a history of CVD and renal dysfunction. Patient 1 definitely needs a SBP target of 130 mmHg. If we implement the guideline-recommended BP measurement technique as in SPRINT, patient 1 needs a SBP target of 120 mmHg. However, for patient 2, the SBP target to reduce HF risk remains uncertain. On the basis of the available data, we recommend the SBP target of 2 to 130 mmHg for patient 2 to reduce the risk of HF.

In summary, using the SPRINT intensive treatment algorithm and a SBP goal of < 120 mmHg, along with the BP measurement techniques recommended by HTN guideline committees (staff training to allow for a quiet rest period, proper positioning of the arm and body, use of proper cuff size, and multiple measurements using a validated automated BP device), will reduce the risks of HF in non-diabetic patients at medium–high CVD risk.

Conclusion

Uncontrolled SBP continues to be a highly prevalent and highly modifiable HF risk factor. Targeting only those at the highest end of the BP spectrum does not address most individuals at risk for developing HF. Therefore, treatment decisions should be based on a person's absolute risk. The results of SPRINT are likely to have a major impact on the treatment of HTN. SPRINT results are reflected in changes in recent HTN guidelines regarding treatment goals and BP measurement techniques. SPRINT revisits BP target goals and challenges us to improve BP measurement and management to prevent HF events. In addition, these results suggest that translation of the SPRINT results will require measurement of BP as performed in that trial. After all, BP is a vital sign and should be measured as in the clinical trials so that we can provide evidence-based care to our patients.

Compliance with Ethical Standards

Conflict of Interest Dr. Kitzman declares the following relationships: consultant for Abbvie, Bayer, Merck, Medtronic, GSK, Relypsa, Regeneron, Merck, Corvia Medical, DCRI, and Actavis, research grant funding from Novartis, St. Luke's Medical Center, and stock ownership in Gilead Sciences. Dr. Upadhya has received research funding from Novartis and Corvia.

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