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HYPERTENSION AND THE HEART (BHARATHI UPADHYA, SECTION EDITOR)

Unanswered Questions Regarding Blood Pressure Management for HF Prevention

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Abstract

Purpose of Review Evaluate the relevant new findings regarding hypertension treatment and heart failure prevention published in the past 3 years.

Recent Findings In a recent secondary analysis of Systolic Blood Pressure Intervention Trial (SPRINT), randomization of more than 9000 patients > 50 years old with high cardiovascular risk but without diabetes to intensive treatment targeting blood pressure < 120/80 mmHg compared to standard treatment targeting < 140/90 mmHg significantly reduced incident heart failure. While such benefits outweighed potential harm, adverse events including renal dysfunction, hypotension, and syncope occurred more frequently with intensive treatment. Following SPRINT, existing guidelines differ in their recommendations and controversies still exist. Key persistent questions include the role of intensive treatment in younger adults and those at lower cardiovascular risk and optimal approaches to translate clinical trial findings into clinical practice in a sustainable fashion.

Summary Aggressively treating hypertension to targets below 120/80 mmHg prevents heart failure in high-risk patients. However, evidence is lacking to younger patients and those at lower cardiovascular risk.

Keywords Systolic heart failure · Diastolic heart failure · Prevention · Systolic blood pressure · Diastolic blood pressure · Treatment · Prevention

Introduction

Heart failure (HF) is a critical public health problem worldwide [1]. In the USA alone, HF affects 5.7 million Americans, costs $30.7 billion annually, and is associated with a 50% 5-year mortality [2]. The Framingham Heart Study established hypertension as one of the earliest "factors of risk" for coronary heart disease [3] and subsequently also for incident HF [4]. Indeed, among known HF risk factors, an elevated blood pressure (BP) (≥ 140/90 mmHg) demonstrated the greatest population attributable risk for incident HF in the Framingham Heart Study, such that HF prevalence would be expected to decrease 39% in men and 59% in women if hypertension (by this definition) could be eliminated [5].

Despite remarkable advances in the treatment of HF with reduced ejection fraction (HFrEF) since that time, morbidity and mortality remain high. Furthermore, HF with preserved ejection fraction (HFpEF)—for which no evidence-based therapy exists—accounts for the majority of HF in late life, when HF incidence is highest [6]. Prevention is therefore essential to reduce HF burden, with aggressive treatment of hypertension a key component of such efforts. Recent evidence from the Systolic Blood Pressure Intervention Trial (SPRINT) [7••] demonstrated that, in a non-diabetic high-risk population, targeting a lower BP is an effective strategy to prevent adverse cardiovascular (CV) outcomes, including HF. However, controversies regarding the optimal approach to treating hypertension to prevent HF—particularly in the elderly—persist, as evidenced by differing guidelines recommendations by different professional societies, often based on the same source references [8]. In this review, we will explore important recent findings in hypertension treatment for HF prevention published in the last 3 years.

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Epidemiology

The global burden related to high blood pressure (HBP) has increased over the past several decades and remains a leading risk factor for death and disability, primarily due to CV and cerebrovascular diseases. Between 1990 and 2015, the estimated global mortality rate of persons with a systolic BP (SBP) of ≥ 140 mmHg increased from 98 to 106 deaths/100,000 persons, and disability-adjusted life years increased from 96 million to 143 million [9]. The burden of hypertension differs by age [10] and gender [9]. For example, disability adjusted life-years related to an SBP ≥ 140 mmHg increase substantially from 2.1 million in men aged 25–29 years to 8.3 million in men aged ≥ 80 years but increase from 0.6 million in women aged 25–29 years to 12.6 million in women aged ≥ 80 years [9]. In a large study of 1.25 million persons, hypertension—defined based on SBP ≥ 140 mmHg or diastolic BP (DBP) ≥ 90 mmHg, physician diagnosis, or BP-lowering therapies—was associated with a 50% higher lifetime risk of HF [11]. Thus, even with modern treatment approaches, lifetime burden of hypertension is considerable, as is the associated likelihood of incident HF in patients with hypertension.

Pathophysiology

It is well recognized that mechanical stress from increased left ventricular (LV) afterload leads to chronic myocardial adaptations. Greater wall stress and compensatory increases in ventricular wall thickness ultimately lead to increases in myocardial muscle mass and hypertrophy. Microstructural alterations in myocardial structure in hypertrophy, including fibrotic tissue deposition and microvascular impairment, further contribute to myocardial remodeling and progressive LV diastolic dysfunction. Concomitant neurohormonal activation and autonomic imbalance also play central roles in mediating myocardial tissue and vascular damage, as well as volume and electrolyte dysregulation [12–14]. This widely accepted model is consistent with the observation that antihypertensive therapies show effectiveness in preventing LV remodeling and LV function decline [15]. However, several additional factors can influence the myocardial response to elevated BP, including its severity, chronicity, and rapidity of onset, patient characteristics (e.g., age, race/ethnicity, gender) and clinical comorbidities (e.g., coronary artery disease, diabetes mellitus, obesity, valvular heart disease), associated neurohormonal and inflammatory responses, and genetic factors [12, 13].

Blood Pressure Treatment Targets

The potential benefit of targeting an SBP goal below 140 mmHg was first tested in diabetic patients with high CV risk in the Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial (ACCORD BP) [16]. No significant reduction in the study's primary composite outcome of non-fatal myocardial infarction, non-fatal stroke, or death from CV causes was observed with the more aggressive BP target (SBP < 120 mmHg) compared to standard target (< 140 mmHg) nor was a significant effect on incident HF observed. No large randomized clinical trials assessed the impact of more intensive BP treatment targets high-risk hypertensive patients without diabetes until the Systolic Blood Pressure Intervention Trial (SPRINT). Published approximately 5 years after ACCORD BP, SPRINT demonstrated significant risk reduction with intensive BP treatment targets in non-diabetic patients at elevated CV risk [7••].

The SPRINT trial was a large multicenter (102 sites), randomized open-label trial designed to test the hypothesis that treating hypertension to an SBP goal of < 120 mmHg would be more effective in reducing the primary composite end point compared to a standard goal of < 140 mmHg (Table 1). The primary end point was a composite of first occurrence of myocardial infarction, acute coronary syndrome, stroke, HF, or CV death. Inclusion criteria included SBP 130–180 mmHg, > 50 years old, and at least on additional marker of increased CV disease risk: age ≥ 75 years, clinical CV disease (coronary, peripheral or cerebrovascular), subclinical CV disease (high coronary calcium score, LV hypertrophy, ankle-brachial index < 0.9), estimated glomerular filtration rate 20–59 mL/min/1.73 m^2, or Framingham risk score of ≥ 15% at 10 years. Patients with diabetes, prevalent HF, stroke, and proteinuria were excluded. Notably, BP was measured using the automated oscillometric method and was assessed as the mean of three measures, after 5 min of seated quiet rest. Drug classes with evidence for improvement in CV outcomes (not only thiazide-type, encouraged as a first-line agent, but also angiotensin-converting enzyme inhibitors, angiotensin II antagonists, calcium channel blockers, beta-blockers) were used to achieve the target BP, adding or withdrawing agents as needed. The 9361 participants enrolled had a mean age of 68 years, with 28% ≥ 75 years old, and a mean BP 140/78 mmHg. The study was terminated early because for efficacy. At a median follow-up of 3.26 years (of a planned 5 years), the intensive treatment group experienced a significantly lower risk of the primary outcome compared to standard treatment group (incident rate 5.2 versus 6.8% per year respectively; hazard ratio (HR) 0.75; 95% confidence interval (CI) 0.64–0.89).

Intensive treatment was also associated with a lower incidence of HF compared to conventional treatment (HR 0.62; 95% CI 0.45–0.84). A subsequent SPRINT analysis using updated adjudicated events specifically investigated HF

Table 1 Summary of key studies of hypertension management and HF risk from last 3 years

Trial	Population	Intervention	Main findings
SPRINT—Wright et al. 2015 [7••]	9361 hypertensive persons (SBP ≥ 130 mmHg and < 180 mmHg), ≥ 50 years old, with increased CV risk* but no diabetes	Multicenter, randomized controlled trial comparing an SBP target of < 120 mmHg (intensive treatment—4678 participants) to a target of < 140 mmHg (standard treatment—4683 participants). Primary end point was a composite of MI, other acute coronary syndromes, stroke, heart failure, or CV death.	Mean age was 68 years, 35% female, and black race 31%. At a median follow-up of 3.26 years, incidence of the primary outcome was 1.6%/year in the intensive treatment arm and 2.2%/year in the standard treatment arm, with a relative risk reduction of 25% and an absolute risk reduction of 1.6%. All-cause mortality was also lower in intensive treatment arm, with a relative risk reduction of 27%. Rates of hypotension, syncope, electrolyte disturbances and acute kidney injury were more common in the intensive treatment group.
Upadhya et al. 2017 [17•]	Same as SPRINT	Same as SPRINT. This secondary analysis focused on acute decompensated heart failure events, investigating six prespecified subgroups: age ≥ 75 years, prior cardiovascular disease, chronic kidney disease, women, black race, and three levels of baseline systolic BP (≤ 132, > 132 to < 145, and ≥ 145 mmHg)	In a median follow-up of 3.29 years, 65 incident ADHF (1.4%) occurred in intensive treatment arm, and 103 events (2.2%) in standard treatment arm, with a HR 0.63 (95% CI 0.46–0.85). The benefit was similar to all prespecified subgroups.
SPRINT Senior—Williamson et al. 2016 [18•]	Participants enrolled in SPRINT who were ≥ 75 years of age at enrollment	Same intervention as SPRINT analysis included a total of 2636 participants, 1317 in the intensive treatment arm, and 1319 in the standard treatment arm.	The mean age was 80 years, 38% were female, and 17% were black. At a median follow-up of 3.14 years, the primary outcome occurred in 2.6%/year (102 events) with intensive treatment and in 3.8%/year (148 events) with standard treatment, with a HR of 0.66 (95% CI 0.51–0.85). HF also was less frequent among patients in intensive treatment arm (HR 0.62 [95% CI 0.40–0.95]).
Victor et al. 2018 [19••]	319 black males who were frequent barbershop patrons (≥ 1 haircut every 6 weeks for ≥ 6 months) from 52 black-owned barbershops, as a model of a non-traditional healthcare setting. Participants had hypertension (SBP > 140 mmHg), age 35–79 years	Cluster randomized trial, comparing a barber driven approach (encouragement for lifestyle modification and physician's appointment; control arm) to addition of a pharmacist-driven intervention (drug prescription and adjustments in collaboration to participants' physicians; intervention arm). The primary outcome was reduction in SBP at 6 months. The intervention group had 132 clients from 28 barbershops, and the control group had 171 clients from 24 barbershops.	Mean age was 54 years, with baseline BP of 153 mmHg in the intervention group and 155 mmHg in the control group. At 6 months, mean SBP decreased 27 mmHg in the intervention group versus 9 mmHg in the control group, accounting to a net intervention effect of 22 mmHg reduction ($p < 0.001$). The intervention group also had more participants under 130/80 mmHg (64% versus 12%, $p < 0.001$). The intervention group also used more antihypertensive agents (2.6 ± 0.9, 1.4 ± 1.4, $p < 0.001$).

SBP systolic blood pressure, *CV* cardiovascular, *ADHF* acute decompensated heart failure

*One or more of clinical or subclinical cardiovascular disease, but not stroke; chronic kidney disease (estimated glomerular filtration rate between 20 and 60 mL/min/1.73 m^2 ; a 10-year risk of cardiovascular disease of 15% using Framingham risk score; or ≥ 75 years old)

prevention [17•] (Table 1). Intensive compared to conventional BP treatment targets reduced incident HF by 37%, with separation of HF event curves between groups evident after 6 months. The number needed to treat to prevent one incident HF event was 130 over a median follow-up of 3.29 years. Additional predictors of incident HF were chronic kidney disease, age ≥ 75 years, history of CV disease, increase in SBP and DBP, body mass index, and smoking. Patients that did experience a first event of HF during follow-up also demonstrated a several fold increase in rate of subsequent events including death (CV and all-cause), myocardial infarction, other acute coronary syndromes, and stroke independent of treatment arm, sex, age, chronic kidney disease, and presence of CV disease. Another preplanned analysis of SPRINT studied the 2636 participants who were ≥ 75 years old at enrollment (SPRINT-SENIOR) [18•], the age range when incidence of HF is highest (Table 1). In this subgroup, intensive compared to conventional treatment targets also improved prognosis, including a significant reduction in risk of incident HF (HR 0.62; 95% CI 0.40–0.95).

Most recent attempts to meta-analyze existing data on the impact of adopting lower BP goals for hypertension treatment are strongly influenced by the results of SPRINT [7••]. A recent meta-analysis of existing randomized control trials (RCTs), which included 613,825 subjects, demonstrated a linear decrease in the risk of incident CV disease with SBP reductions below 140 mmHg. Indeed, using meta-regression approaches, the estimated decreased in incidence of HF and stroke for every 10 mmHg reduction in SBP (28% and 27% respectively) was greater than for coronary heart disease (17%) [20••]. In a second meta-analysis that included data from 35 BP lowering trials with HF assessed as an outcome, the magnitude of reduction in risk of HF was significantly greater than in risk of all-cause mortality for any given degree of BP lowering. The estimated absolute risk reduction was 19 HF cases/1000 patients treated for 5 years with a pooled net difference in BP between treatment and control arms of 7 mmHg for SBP and 3 mmHg for DBP [21].

Generalizability

While an estimated 46% of the US adult population has hypertension, approximately 7.6%—16.9 million—are estimated to meet SPRINT inclusion criteria [22]. Most notably, patients with diabetes were not included in the SPRINT trial, as an intensive SBP target of < 120 mmHg has previously been shown not to add net prognostic benefit in this context [16]. Indeed, newer antidiabetic drugs, such as sodium–glucose cotransporter 2 inhibitors, may have a greater impact on HF risk reduction in these patients [23]. In addition, hypertensive patients with lower CV risk, with resistant hypertension, with age < 50 years old, or who are currently institutionalized were excluded from SPRINT.

Limited randomized trial data is available regarding more intensive treatment targets in patients falling outside the SPRINT inclusion criteria, in particular those of younger age and at lower baseline CV. In an observational study of 1.25 million people followed for a median of 5.2 years, among the subgroup of 1245 individuals aged 30–59 years, the risk of incident HF associated with an SBP of 130–139 mmHg was 57% higher (HR 1.57; 95% CI 1.27–1.94) compared to a reference SBP if 115 mmHg. The risk of incident HF was 69% higher with a DBP of 85–89 mmHg compared to a reference DBP of 75 mmHg (HR 1.69; 1.51–1.88) [11]. Similarly, data from general population studies, such as the Framingham Heart Study, also show that "high-normal" BP (130–139/85–89 mmHg) is associated with an increased risk for CV events, including HF [24]. Given the higher prevalence of the "prehypertension" (120–139/80–89 mmHg) compared to hypertension [25], a large proportion of persons at risk of HF are not addressed by the Seventh Joint National Committee on Hypertension (JNC 7) recommendations. However, RCT support for pharmacologic treatment of the current stage 1 hypertension (BP 130–139/80–90 mmHg) for primary prevention is absent, particularly in young adults [26]. Although randomized data is scarce, there is justified concern that a longer exposure to hypertension, particularly if untreated or undertreated, may increase the lifetime risk of HF and other adverse outcomes in these individuals. Given the lower absolute risk in these populations, one challenge is that longer follow-up will likely be necessary to demonstrate treatment benefits, as suggested by Rapsomaniki et al.'s data [11].

Potential Harm

The potential for harmful side effects with intensive BP treatment is a significant concern, especially in the elderly. While intensive SBP targets improved CV outcomes compared to conventional targets in SPRINT, intensive SBP targets were also associated with a higher incident of certain serious adverse effects. These included renal dysfunction (defined as ≥ 30% reduction in estimated GFR to < 60 ml/min/1.73 m^2), hypotension, syncope, hyponatremia, hypokalemia, and acute kidney injury [7••, 18•]. A recent pooled analysis using a network meta-analysis of existing randomized trials specifically investigated the balance between benefit and harm with intensive SBP targets [27]. Among 55,163 patients from 17 trials, efficacy and safety outcomes were evaluated over 204,103 person-years of follow-up among 5 BP target categories: (1) < 160 mmHg, (2) < 150 mmHg, (3) < 140 mmHg, (4) < 130 mmHg, and (5) < 120 mmHg. SBP targets of < 120 mmHg and < 130 mmHg were found to be most efficacious, while SBP targets of < 140 mmHg and < 150 mmHg were associated with the fewest serious adverse effects. Using cluster plots, an on-treatment systolic BP target of

< 130 mmHg appeared to reach the optimal tradeoff between efficacy and safety [27].

Guideline Recommendations

In 2017, the American Heart Association/American College of Cardiology Hypertension guidelines [28••] changed the definition of hypertension to incorporate the former "prehypertension" as stage 1 hypertension. Thus, normal BP is considered < 120/80 mmHg, elevated BP is ≥ 120/80 mmHg, and stage 1 hypertension is now 130–139/80–90 mmHg. This change resulted in an increase in prevalence of hypertension among US adults > 40 years of age from 32 to 46%. In contrast, the 2018 European Society of Cardiology guidelines [29••] consider a BP of < 130/85 mmHg as "normal," 130/85 to 140/90 mmHg as "high normal," and 140/90 to 160/100 mmHg is "grade 1" hypertension (Table 2).

Antihypertensive Therapy Class and HF Prevention

The majority of patients with hypertension will require more than 1 agent to achieve treatment targets, with more intensive targets requiring a greater number of agents [30]. Indeed, in SPRINT, persons randomized to intensive treatment targets used 2.8 antihypertensive medications on average, compared to 1.8 in those randomized to conventional targets. Furthermore, 56% of persons in intensive group used three or more pharmacologic agents, while 75% of persons in the conventional group used two or less agents [7••].

Findings from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) demonstrated not only that treatment of hypertension prevents HF but also that the type of pharmacologic agent also matters. The doxazosin arm of this trial was terminated prematurely due to a twofold increase in risk of incident HF compared to chlorthalidone [31]. Furthermore, risk of incident HF was lower among those randomized to chlorthalidone compared to lisinopril or amlodipine [32]. The results of a recent large meta-analysis, including data from ALLHAT, confirmed the potential differential impact of individual antihypertensive drug classes on clinical outcomes [20••], with diuretics appearing superior (RR 0.81; 95% CI 0.85–0.95) and calcium channel blockers inferior (1.17; 95% CI 1.11–1.24) to other drug classes. These findings are consistent with those of a previous meta-analysis [21]. This evidence supports the hypothesis that a diuretic should be the first option to HF prevention and calcium blockers should perhaps be avoided as a single agent. However, determining the differential effects of antihypertensive medication classes is particularly challenging [20••]. These previous observations may have been impacted by unaccounted for confounders, including concurrent use of additional drug classes, difference in treatment regimens, or even chance due to multiple comparisons. The primary focus in treating hypertension should be on achieving and maintaining BP control.

Approaches to Improve Antihypertensive Therapy Adherence

Adequate access and adherence to treatment prescriptions are crucial to achieve better hypertension management and HF prevention and to effectively translate randomized clinical trial findings into routine clinical practice. Observational studies support the crucial importance of adherence to an antihypertensive regimen to derive the expected benefit with respect to primary prevention of HF. In a nested case–control study [33], compared to a very low adherence group (proportion of days covered by treatment—PDC ≤ 25%), the intermediate (PDC 51–75%) and high adherence groups (PDC > 75%) demonstrated lower likelihood for HF hospitalization (OR 0.73; 95% CI [0.55–0.98], and OR 0.66 [0.52–0.83] respectively). In a cohort of 155,597 Medicare beneficiaries aged 66–79 years with hypertension who were followed-up for a median of 5.8 years, the most adherent group (PDC ≥ 80%) represented 61% of the sample and had a significantly lower incident of HF compared to the lowest adherence group (PDC < 40%; adjusted HR 0.57; 95% CI 0.54–0.61) [34].

These data on the importance of adherence provided the motivation for the barbershop study [19••] (Table 1). This study aimed to leverage barbershops as potential sites of community health promotion, capitalizing on the trusting relationship between barbers and patrons, to assess a BP control program among black men with uncontrolled hypertension (SBP ≥ 140 mmHg). The efficacy of two strategies were compared in a cluster-randomized design: the control group (171 clients) received barber encouragement for lifestyle modification and to arrange visits with their physicians as needed; the intervention group (132 clients) received a health promotion strategy by barbers along with education and drug adjustments by a pharmacist. Pharmacists regularly verified BP, prescribed antihypertensives, and notified treating physicians. At 6 months, the intervention group demonstrated a mean reduction in SBP of 22 mmHg compared to the control group, and 64% of the participants from the intervention group achieved BP goal of ≤130/80 mmHg compared to 12% in the control group. As expected, the number of drugs needed to maintain a goal BP was higher in the intervention compared to control (average number of antihypertensive agent 2.6 versus 1.4 respectively). Ongoing analyses should address the sustainability of such achievements and their impact on incident HF and other outcomes [35]. However, these findings emphasize the importance of implementation studies to optimize patient engagement and adherence using local strategies to ensure that the expected benefits of treating hypertension on HF outcomes are realized.

Table 2 Summary of recent ACC/AHA and ESC/ESH hypertension guideline recommendations

		2017 ACC/AHA [27••]		2018 ESC/ESH [28••]	
	mmHg	Classification	Pharmacologic treatment	Classification	Pharmacologic treatment
Office based blood pressure values	< 120 and < 80	Normal	–	Optimal	–
	120–129 or 80–84	–	–	Normal	–
	120–129 and < 80	Elevated	No. Reassess 3–6 months	–	–
	130–139 or 80–89	Stage 1	If ASCVD or 10-year CVD risk ≥ 10%. Initially with monotherapy but targeting < 130/80.	–	–
	130–139 or 85–89	–	–	High normal	Consider high normal BP if very high-risk patients with CAD
	140–159 or 90–99	Stage 2	Immediate. Initially with 2 first-line drugs from different classes.	Grade 1	For patients with high or very high risk, patients with CVD, renal disease, or hypertension-mediated organ damage. For low/moderate risk patients, without CVD, renal disease, hypertension-mediated organ damage, if BP not controlled after 3–6-month lifestyle intervention.
	160–179 or 100–109			Grade 2	Immediate
	≥ 180 or ≥ 110			Grade 3	Immediate
	≥ 140 and < 90	–	–	Isolated systolic hypertension	Same recommendations, based on SBP.
BP treatment goals		For adults with confirmed hypertension and known CVD or 10-year ASCVD event risk of 10% or higher, a BP target of less than 130/80 mmHg is recommended.		First objective of treatment should be to lower BP to < 140/90 mmHg in all patients and, provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower in most patients. In patients ≥ 65 years, SBP should be targeted to a range of 130–139 mmHg. DBP target of < 80 mmHg should be considered to all patients.	

ACC/AHA American College of Cardiology and American Heart Association, *ESC/ESH* European Society of Cardiology and European Society of Hypertension, *CVD* cardiovascular disease, *ASCVD* atherosclerotic cardiovascular disease, *BP* blood pressure, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

Conclusions

Hypertension is a leading cause of death and disability from CV and cerebrovascular causes and a major risk factor for HF. Treating hypertension is one of the most effective strategies for HF prevention and is one of the only evidence-based interventions to prevent HFpEF, for which evidence of effective treatment is lacking. The most compelling novel evidence regarding hypertension treatment and HF risk from last 3 years come from SPRINT, which demonstrated that in higher risk patients without diabetes, treating hypertension to a more intensive target (< 120/80 mmHg) significantly reduced incident CV events, including incident HF, compared to standard treatment targets (< 140/90 mmHg) (Table 2). Despite these robust benefits, more intensive treatment targets were not surprisingly associated with a higher incidence of renal dysfunction, hypotension, syncope, and electrolyte disturbances. Recent meta-analyses support previous findings that diuretic therapy may be more—and calcium channel blockers may be relatively less—effective at HF prevention. However, effective BP treatment is rarely achieved with a single pharmacologic agent, and no antihypertensive combination has proven to be superior. Several questions remain, including the appropriate BP targets in young adults and those with low-intermediate CV risk, among whom prospective trials will likely need long follow-up time. Additional studies are also necessary to define the best approaches to optimize patient engagement and adherence with antihypertensive therapies to fully realize the potential for HF prevention.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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