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HYPERTENSION AND CARDIOVASCULAR DISEASE

Blood Pressure, Troponin, and Cardiovascular Function

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ABSTRACT

Hypertension (HTN) is a well-known risk factor for cardiovascular (CV) morbidity and mortality and has been associated with more CV events, including coronary heart disease (CHD), stroke, and heart failure (HF). Although lowering blood pressure (BP) has been associated with improved CV outcomes, there is an epidemiological-clinical trial discordance. Patients at highest risk for CV events benefit the most from BP reduction, but these patients are not easily identified on the basis of a single BP measurement. Earlier identification of high-risk phenotypes may assist in identifying subjects who may benefit from an increased intensity of therapy. Recently, high-sensitivity troponin (hsTn) assays have been developed (available for research in the United States and commercially in Europe), and evidence shows that elevated hsTn levels are predictive of incident HTN, left ventricular hypertrophy (LVH), CV events (including HF), and mortality. This article will review the evidence for and suggest possible future approaches in incorporating cardiac biomarkers in the management of HTN.

Keywords: Biomarkers, Blood pressure, Cardiovascular disease, Coronary artery disease, Heart failure, High-sensitivity troponin, Hypertension, Prevention, Risk factors.

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INTRODUCTION

Hypertension (HTN) is a well-known risk factor for cardiovascular (CV) morbidity and mortality and has been associated with more CV events, including coronary heart disease (CHD), stroke, atrial fibrillation, and heart failure (HF). Presence of risk factors such as HTN and diabetes has been classified as "Stage A HF" in order to identify those at risk for future development of clinical HF.[1] Although lowering blood pressure (BP) has been associated with fewer CV outcomes, there is an epidemiological-clinical trial discordance in that epidemiologically progressively increased risk for adverse CV events begins at systolic BP (SBP) of 115 to 120 mm Hg, but clinically the benefit of treating SBP to values less than 140 mm Hg has been mixed.[2,3] It is evident that individuals at highest risk for CV events benefit the most from BP reduction, but these individuals are not easily identified based on a single BP measurement.

Furthermore, the CV systems of different individuals express different phenotypic responses to elevated BP; for example, some individuals develop significant left ventricular hypertrophy (LVH) and increased LV mass, while others have minimal or no LVH. Hence, earlier identification of individuals with phenotypes associated with increased CV risk could lead to targeting those subjects with more intensive therapy. Recently, high-sensitivity troponin (hsTn) assays have been developed and are available for research in the United States and commercially in Europe. Evidence shows that elevated hsTn levels are associated with CV outcomes (including HF) and mortality. Elevated hsTn may also identify patients with HTN or LVH who are at a high risk of adverse CV events and death. This article will review the evidence for and suggest possible future approaches to incorporating cardiac biomarkers in the management of HTN.

Hypertension: A Traditional CV Disease Risk Factor

Blood pressure is a continuous variable, with HTN defined as a systolic (SBP) or diastolic BP (DBP) above an arbitrary number where treatment is likely to be beneficial. Hypertension has been defined in different ways over the past several decades. The 2003 JNC 7 report[4] and the 2013 European Society of Cardiology guideline[5] defined HTN as SBP >140 or DBP >90 mm Hg, due to randomized trial data demonstrating clinical benefit after reducing BP below these values. In addition, the JNC 7 report defined other BP stages: normal (<120/80 mm Hg), pre-HTN (SBP 120–139 or DBP 80–89 mm Hg), stage I HTN

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(SBP 140–159 or DBP 90–99 mm Hg), and stage II HTN (≥160 or ≥100 mm Hg). The 2014 JNC report did not define HTN *per se*, but rather focused on treatment targets.[6]

However, even at BP levels below the hypertensive range as defined by JNC 7, BP is associated with CV disease. A meta-analysis of >1 million patients showed that CV mortality increases with every 10/5 mm Hg increase in office BP beginning at 115/75 mm Hg.[7] This pattern was demonstrated for all-cause CV mortality and individually for mortality from stroke, ischemic heart disease (IHD), and other adverse CV events including HF. These increased CV risks occurred in both men and women, and was demonstrated at every decade of life after age 40. Similarly, subjects enrolled in the physicians' health study with SBP 130 to 139 mm Hg had an increased incidence of HF compared with patients with SBP <120 [adjusted hazard ratio (HR) 1.35; 95% confidence interval (95% CI), 1.09–1.68)].[8] A review by Kalaitzidis and Bakris[9] describes multiple observational studies that show an increased risk of chronic kidney disease (CKD) and end-stage renal disease in patients with pre-HTN compared with normotension. In fact, in the more recent American College of Cardiology and American Heart Association CV risk assessment guidelines, an untreated BP <120/<80 mm Hg has been identified as optimal.[10] While the ideal BP is not well-defined, it is evident that CV risk begins well-below SBP <140 mm Hg.

Multiple mechanisms including indirect (*via* inflammation) and direct mechanisms (*via* increased myocardial workload) have been proposed to explain the role of HTN in promoting cardiac disease. These models overlap and are not mutually exclusive. Endothelial dysfunction may be precipitated by renin-angiotensin system dysregulation, leading to increased levels of angiotensin II, downregulation of endothelial nitric oxide synthase, decreased nitric oxide production, and increased oxidative stress.[11] This dysfunction leads to inflammation and platelet activation causing thrombotic complications. Endothelial dysfunction is also associated with increased arterial stiffness, leading to cardiac hypertrophy and myocardial ischemia.[12]

Nadruz[13] described how selected pathophysiological processes could lead to LVH in response to HTN. In this model, the heart attempts to reduce LV wall stress induced by high arterial pressures with hypertrophy of cardiac myocytes. Fibrosis and alterations in coronary circulation further contribute to these alterations. Clinically, the link between HTN and onset of clinical LV failure has been demonstrated prospectively in subjects from both the Framingham heart and offspring studies, which found that HTN accounted for 39% of incident HF [both reduced (HFrEF) and preserved (HFpEF) ejection fractions] in men and 59% in women.[14] Recently, a study employed two-dimensional transthoracic echocardiography to compare patients with different levels of BP but no clinical heart disease. When compared with those with normotensive BPs, subjects with pre-hypertensive BPs (SBP 120–139 or DBP 80–89 mm Hg) had increased LV mass index and wall thickness as well as impaired diastolic function parameters.[15] Hypertension (SBP ≥140 or DBP 80–89 mm Hg) was associated with further increased LV mass index and wall thickness compared with pre-HTN, indicating that cardiac remodeling and end-organ damage occur early along the continuum of BP values and worsen as BP increases into the hypertensive range.

Treating Hypertension: the Evidence

Treatment of HTN has come a long way from HTN being considered "essential" to demonstration that reducing BP is associated with improved CV outcomes. One of the first BP trials was the VA cooperative study in 1967, which compared treatment with a combination of hydralazine, hydrochlorothiazide, and reserpine with placebo in patients with diastolic BP 115 to 129 mm Hg. After only 18 months, this trial demonstrated a reduction in mortality and CV complications.[16] In 1977, the first Joint National Committee (JNC) on detection, evaluation and treatment of high blood pressure recommended treatment of DBPs >105 mm Hg.[17] Since that time, as evidence has evolved, numerous guidelines have recommended treating BP to increasingly lower levels. In 2003, the seventh report of the JNC recommended treating all individuals to a target BP <140/90 mm Hg except those who had diabetes mellitus (DM) or CKD. In these high-risk groups, a goal BP of <130/80 mm Hg was recommended, based primarily on epidemiological study data rather than evidence of improved outcomes from randomized clinical trials.[4] In 2014, however, the JNC guideline relaxed the target for patients with DM or CKD, recommending that those with DM or CKD, and all persons aged <60 years, be treated to a target BP <140/90 mm Hg, while all other individuals aged >60 years be treated to a target BP <150/90 mm Hg.[6] These targets were liberalized due to a lack of randomized controlled trial data supporting lower BP targets, highlighting the clinical-epidemiological dissociation: epidemiologic studies show an increased risk of CV events with SBPs above 120 mm Hg, but clinical outcome trials have not shown consistent benefit when SBPs are treated to targets below 140 mm Hg.

One recent outcome trial that highlights this dissociation was the action to control cardiovascular risk in diabetes blood pressure (ACCORD-BP) trial.[2] The overall ACCORD trial randomized 10,251 patients with type 2 DM to either intensive or standard glycemic control. Subsequently, 5518 participants were randomized

to different lipid treatments, and 4733 were randomized to two different BP treatment targets, that is, SBP <140 mm Hg or <120 mm Hg (ACCORD-BP). The primary outcome was a composite of nonfatal myocardial infarction (MI), nonfatal stroke, or CV death. After achieving BP separation of 13 mm Hg (mean SBP 119.3 *vs* 133.5 mm Hg), the trial found no statistically significant difference in the primary outcome between the two SBP-target groups, though there was a nonsignificant trend toward a reduction in the primary outcome in the intensive-treatment arm (HR 0.88; 95% CI, 0.73–1.06). The rate of stroke was reduced in the intensive-treatment arm (HR 0.59; 95% CI, 0.39–0.89). Achieving the lower BP level required 1.3 extra medications per patient. There was a small but significant increase in adverse events attributed to the intervention in the intensive-treatment arm (3.3 *vs* 1.27%), including hypotension, hyperkalemia, bradycardia, and elevated serum creatinine. However, the trial's authors point out that it may have been underpowered, given a 50% lower-than-expected rates of CV outcomes (1.87% per year in the intensive-treatment arm *vs* 2.09% in the standard-treatment arm). This may have partly been caused by the factorial study design: patients with elevated lipids were randomized into the lipid-treatment arm, which may have reduced the baseline risk of patients randomized to the BP arm. The CI could not exclude a benefit as large as a 27% reduction in the primary outcome due to the intensive treatment.

Conversely, the recently published systolic blood pressure intervention trial (SPRINT) showed significantly lower all-cause mortality and reduction in the composite CV outcome in patients treated to an intensive SBP goal of <120 compared with <140 mm Hg.[3] Systolic blood pressure intervention trial randomized 9361 nondiabetic patients with HTN and one or more additional CV risks to the same SBP targets used in ACCORD-BP. Systolic blood pressure intervention trial also included pre-specified subgroups of patients over the age of 75 years and patients with CKD. The primary outcome was a composite of MI, acute coronary syndrome (ACS) without MI, stroke, acute HF decompensation, and CV death. This trial also achieved good BP separation between treatment groups: mean SBP 121.4 *vs* 136.2 mm Hg. The SPRINT trial was terminated early, due to a significant reduction in the primary outcome (1.65 *vs* 2.19%, HR 0.75; 95% CI, 0.64–0.89) as well as in all-cause mortality (HR 0.73; 95% CI, 0.60–0.90) in the intensive-treatment arm compared with the standard-treatment arm. There was a small but significant increase in intervention-related serious adverse events in the intensive-treatment arm (4.7 *vs* 2.5%, HR 1.88), including hypotension, syncope, and acute kidney injury. When comparing the two studies, subjects enrolled in SPRINT were older, male, of black race, and had higher serum creatinine levels than those enrolled in ACCORD-BP. The event rate was similar to that in ACCORD-BP, but SPRINT contained twice as many participants. The apparent conflict in results may therefore be related to the statistical power issues in ACCORD-BP. However, it is unclear how to apply the SPRINT results to patients with DM, who may be at an increased risk of orthostatic hypotension due to autonomic dysfunction.

This discord between trials such as ACCORD-BP and SPRINT, and between observational and trial data, has led to confusion among clinicians about the most appropriate application of guidelines for individual patients. For example, a healthcare provider may be faced with the dilemma of which BP goal to target in the patient who has become diabetic after being started on anti-HTN drugs. It is also important to note that these trials enrolled only patients who were hypertensive at baseline, and the results therefore cannot be extrapolated to patients at an increased CV risk but with pre-hypertensive levels of BP at baseline. In the absence of clear guidelines, practitioners will be forced to use their best clinical judgment in the management of an individual patient.

It is possible that stratification using published risk calculators may help clinicians guide BP therapy. A meta-analysis from the blood pressure lowering treatment trialists' collaboration showed that the greatest absolute risk reduction from BP-lowering treatment came for the patients at the highest risk levels.[18] In this analysis, the risk assessment was done using a fitted risk equation that included the patient's age, sex, BMI, SBP, DBP, smoking, diabetes, and history of CV disease; the equation however did not include lipids. There is also currently no validated calculator for assessing the spectrum of CV risk in hypertensive patients, in order to guide intensity of antihypertensive therapy.[19] However, even if there were HTN-specific risk scores, their use may be suboptimal, as clinicians already have many different risk equations (such as the Framingham CV risk score) available to them, and even these risk scores are not adequately utilized in practice. Also, clinicians may not think to apply such a risk calculator to a patient with "pre-hypertensive" BPs, therefore potentially overlooking patients with an increased CV risk. Therefore, it is unlikely for additional risk scores such as a "HTN risk score" to be adapted to clinical practice when selecting BP targets.

Another consideration may be to evaluate patients for early subclinical end-organ damage. This approach has been taken by the ESC/ESH 2013 guidelines on HTN,[5] which recommend using four diagnostic test markers of end-organ damage: LVH, urine microalbumin, carotid artery assessment, and pulse wave velocity (PWV). Electrocardiography is readily available and can be used to screen for LVH; testing for microalbuminuria is

similarly easy. However, carotid artery ultrasound with evaluation of intima media thickness and atherosclerotic plaque may not be available in all settings. Pulse wave velocity is not yet widely available or used and hence will therefore not be helpful for the majority of clinicians in assessing risk. Limitations of PWV measurements include the need for special equipment and training of operators of that equipment, inability to obtain accurate measurements in patients with arrhythmias, and the absence of robust data in selected patient groups such as those with peripheral arterial disease. Therefore, these factors could be of value, but we need additional studies to determine whether treating HTN to targets based on these markers will reduce adverse clinical events. Furthermore, another question is whether the manifestation of these abnormalities (LVH, microalbuminuria, *etc*.), though subclinical, may already be advanced enough that one may have lost some opportunity *vis-à-vis* prevention of adverse events. Herein is where, based on recent accumulating evidence, the value of the newer biomarkers such as troponin could also come to the fore.

Cardiac Troponins for Risk Stratification

The troponin complex is a functional part of the myocyte thin filament and consists of three subunits: troponin C (TnC), troponin I (TnI), and troponin T (TnT).[20] Each of the three subunits has a different function and is coded for by a different gene. TnI and TnT have distinct cardiac versus skeletal isoforms, allowing for measurement of specific cardiac TnI (cTnI) and cardiac TnT (cTnT). Serial measurement of cTnI or cTnT is recommended in diagnosis and risk stratification of acute non-ST elevation myocardial infarction (NSTEMI), as the level will rise within several hours of myocardial injury.[21] However, it has been well recognized that troponin levels may be elevated in several situations not associated with ACS including other forms of myocardial injury (arrhythmia, HF, myocarditis, etc.) or noncardiac illnesses with a potential for myocardial injury such as pulmonary embolism, sepsis, renal failure and stroke.[22] In fact, patients with non-ACS causes of elevated cTnI were shown to have higher long-term mortality than ACS patients in a recent prospective study.[23] The Dallas Heart Study (DHS) demonstrated a low prevalence of cTnT elevation in the general population (0.7%), but such elevation was independently associated with CHF, LVH, DM, and CKD in multivariable analysis.[24]

High-sensitivity versions of assays for cTnI (hs-cTnI) and cTnT (hs-cTnT) have been developed and are available for clinical use in Europe, but are currently available only for research in the United States. These high-sensitivity assays detect lower levels of cardiac troponin (cTn); for example, one higher sensitivity troponin T assay has a 10-fold lower detection ability than the current generation assay used in the United States.[22] The European Society of Cardiology has made recommendations for the use of hs-cTnI and hs-cTnT assays in evaluating ACS, especially with serial measurements to monitor for dynamic changes.[25] These assays have also shown value in stratifying patients with known but stable heart disease. In a subgroup of the Val-HeFT trial, patients with stable HF and elevated hs-cTnT had significantly greater risk of adverse CV events than those without elevated hs-cTnT.[26] Similar results from a subgroup analysis of the PEACE trial showed that patients with stable CAD and elevated hs-cTnT had an increased risk of CV mortality and incident HF, but not new ACS.[27] This suggests that subgroups of patients with stable CV disease have different propensities for developing incident adverse CV outcomes, and that troponin as a marker of ongoing myocardial injury may help identify these individuals. This is conceptually represented in (Fig. 1).

Three large prospective epidemiological studies now suggest that cardiac troponin could be useful at the population level for identifying individuals at a high risk of developing clinical CV disease. Using a hs-cTnT assay in the DHS cohort of 3546 patients aged 30 to 65 years, the prevalence of detectable cTnT increased from 0.7% (conventional) to 25% (high sensitivity).[28] After adjustment for other CV risk factors, renal function and biomarkers such as C-reactive protein (CRP) and N-terminal pro-brain type natriuretic peptide (NT-proBNP), hs-cTnT levels were independently associated with all-cause mortality [adjusted HR 2.8 (95% CI, 1.4–5.2) for the highest category, hs-cTnT >0.014 ng/ml]. The relationship of detectable cTnT levels with adverse CV events persisted even when individuals with high Framingham risk score were excluded. Independent determinants of detectable cTnT levels, using multiple logistic regression, included male sex, older age, black race, heart failure, worse renal function, higher left ventricular (LV) mass index (or LV wall thickness and end-diastolic volume). LV mass and wall thickness both increased with increasing levels of cTnT, and the proportion of patients with LVH increased from 7.5% in the undetectable cTnT group (95% CI, 6.4–8.8) to 48.1% in the highest cTnT group (95% CI, 36.7–58.6).

The atherosclerosis risk in communities (ARIC) study, on the contrary, included 9698 middle to older aged participants (aged 54–74 years) without CV disease.[29] In this study, the prevalence of detectable cTnT with the high sensitivity assay was 66.5%. Values of cTnT in the highest category (>0.014 µg/l) were associated with incident CHD events, including death, MI, and revascularization; the strongest association was with fatal CHD events. Detectable cTnT levels were also significantly associated with HF hospitalization in all groups, from HR 1.48 at

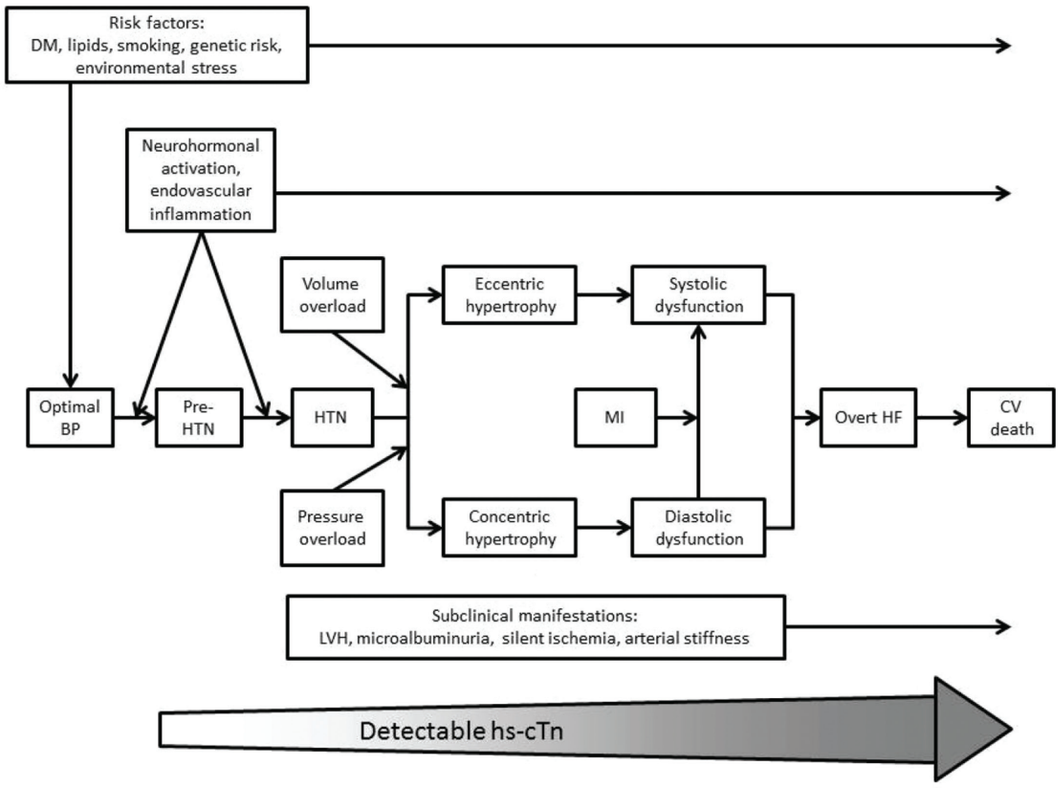

Fig. 1: Graphic representation of cascade of events that could lead from hypertension to heart failure and CV death (*Source:* Drazner[33]; Dzau, Braunwald E,[34]; Nadruz[13]; Vasan, Levy[35])

the lowest measurable levels (0.003–0.005 µg/l, 95% CI, 1.14–1.92) to an HR of 5.95 at the highest level (>0.014 µg/l; 95% CI, 4.47–7.92). Adding hs-cTnT to the CHD risk calculator used in the study reclassified 10.8% of patients to a lower risk group and 7.1% to a higher risk group, indicating that hs-cTnT may be helpful in addition to calculators based on traditional CV risk factors. Using hs-cTnT with the risk calculator produced the strongest associations and improvement in risk prediction for HF hospitalization, showing a particular group of patients with HTN at an increased risk for HF who would not be identified using traditional risk calculations.

The cardiovascular health study (CHS) measured hs-cTnT in 4221 patients over 65 years old without known CV disease.[30] The prevalence of detectable cTnT using a high sensitivity assay was similar to ARIC, 66.2%. After adjustment, participants with the highest cTnT levels had an increased risk of HF (HR 2.48; 95% CI, 2.04–3.00) and CV death (HR 2.91; 95% CI 2.37–3.58) compared with those with undetectable cTnT. The CHS also looked at changes in cTnT levels at a 2 or 3-year follow-up visit, finding that 35.6% of participants with baseline detectable cTnT had >50% increase or decrease in their cTnT level. Within each category of cTnT level, compared with participants with less than 50% change in cTnT levels, participants with >50% increase in cTnT had the highest risk of incident HF and CV mortality, and participants with >50% decrease in cTnT had the lowest risk. This demonstrated that cTnT levels are dynamic and may reflect changing patterns of risk over time. Overall, the DHS, ARIC, and CHS studies demonstrated that detectable cTnT using a high-sensitivity assay was strongly associated with adverse CV events in diverse groups of patients without known CV disease.

If high-sensitivity troponin assays can potentially identify high-risk individuals within the general community, or among patients with CHF and CAD, then this invites the question, can these assays be used to risk stratify hypertensive individuals? Two studies suggest possible future application of hsTn in risk assessment of hypertensive individuals. An analysis in the DHS population studied hs-cTnT and NT-proBNP levels in association with LV mass [as measured by cardiac magnetic resonance imaging (MRI)] in a population without HF.[31] Patients with LVH and elevation of either hs-cTnT or NT-proBNP, compared with patients with LVH and no biomarker elevation, had significantly increased incidence of HF and CV mortality (LVH+ cTnT+, adjusted HR 4.3; 95% CI, 1.7–11.1; LVH+ NT-proBNP+, adjusted HR 4.5; 95% CI, 1.7–11.8). These data suggested that elevations of either troponin or NT-proBNP may identify patients with HTN and LVH who were more likely to manifest adverse CV events, that is, a more malignant phenotype.

Pokharel et al[32] used the ARIC cohort to evaluate the value of cTnT in various BP categories. They categorized

the ARIC subjects by cTnT levels and by SBP in 10 mm Hg increases, starting at SBP 120 mm Hg and ending with SBP >160 mm Hg. This study found that within groups with similar levels of BP, cTnT levels were strongly associated with CV outcomes (strongest again for HF hospitalization). This association held true even at levels of SBP below the treatment targets recommended by the 2014 JNC guidelines, and in fact showed that cTnT levels across a range of BP were more predictive of CV risk than BP levels across a range of cTnT. For example, compared with participants with SBP 140 to 159 mm Hg and undetectable cTnT, individuals with SBP 130 to 139 mm Hg and cTnT >14 ng/l had a higher risk for incident HF (HR 3.7; 95% CI, 2.3–6.1) and CHD (HR 1.7; 95% CI, 1.1–2.6).

Taken together, these data suggest that it is not only the actual BP value but also the pathological consequence of that BP (i.e., myocardial injury/adaptation), as marked by elevations in troponin levels in this situation, that may alert us to the seemingly healthy individuals at a greater risk for adverse CV events. It is therefore conceivable that troponin levels could help guide us as to which hypertensive individual could derive a greater benefit from aggressive lowering of BP. However, given that this is based on observational prospective cohorts, it will need to be tested in prospective clinical trials before affecting clinical recommendations (i.e., trials to show that treating individuals to BP targets based on their troponin levels will improve outcomes). We have recently started a trial examining the cardiac effects (as assessed by cardiac strain) of treating individuals with SBPs between 125 and 150 mm Hg who have a detectable troponin and an estimated HF risk >5% with spironolactone, carvedilol or usual care (Clinical Trial #NCT02230891). Until additional data emerge, for now, these markers can only be interpreted as indications of higher risk.

CONCLUSION

Hypertension leads to CV disease *via* mechanisms such as increasing endothelial dysfunction, arterial stiffness, and LVH. The SPRINT trial demonstrated that treating to lower levels of SBP may reduce CV mortality than previously recommended. Not all patients will benefit from a lower SBP target with those at the highest CV risk likely to gain the most from BP reduction. In addition, treating to lower levels of BP is not entirely benign; patients in the SPRINT trial (as in other previous trials) in the lower BP group experienced a small but significant increase in adverse events related to their treatment regimen. Achieving the lower BP target required, on average, one additional BP medication, which was also shown in the ACCORD trial. In order to minimize adverse effects, improve cost-effectiveness, and ensure that the highest-risk patients receive appropriately aggressive therapy, risk stratification could be very helpful. Screening for subclinical end-organ damage is recommended in the 2013 ESC guidelines, but the options given are not always available in clinical practice (such as pulse-wave velocity). High-sensitivity troponin assays could be useful as an easily obtainable/usable biomarker of cardiac dysfunction/injury consequent to HTN. An approach to risk-stratify patients and then tailor interventions to their level of risk should be carefully considered and studied and may ultimately prove more useful than a one-size fits all approach to BP treatment. We hope that future prospective randomized controlled trials will provide more guidance as to the clinical value of these markers.

The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

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