Troponin and B-type Natriuretic Peptides Biomarkers in the Management of Hypertension

Aliza Hussain¹, Matthew Deshotels¹, Preethi V. Nambi², Kamna Bansal², Hani Jneid¹,³, Vijay Nambi³

¹Department of Medicine, Baylor College of Medicine, Houston, Texas, United States, ²Department of Family and Community Medicine, Baylor College of Medicine, Houston, Texas, United States, ³Department of Medicine, Michael E. DeBakey VA Medical Center, Houston, Texas, United States

Abstract

The American Heart Association/American College of Cardiology (AHA/ACC) Guidelines for the management of high blood pressure (BP) recommend intensive BP goals in high-risk individuals. However, intensive BP therapy comes with a higher risk of side effects. It is, therefore, important to identify individuals with higher cardiovascular risk who will in turn derive the greatest absolute benefit from BP reduction. In line with this, both ACC/AHA and European guidelines on the management of hypertension recommend the use of risk assessment using traditional risk factors. The European guidelines also recommend complementing risk estimation using additional markers of hypertension-mediated organ damage. Cardiac biomarkers such as natriuretic peptide and high sensitivity cardiac troponins (hs-cTn) reflect structural and/or functional changes in end organs (i.e., myocardium, vasculature) and have been associated with increased cardiovascular risk. These cardiac biomarkers may supplement risk assessment of patients with elevated BP and help personalize treatment strategies. Both NT-pro B type Natriuretic Peptide (NT-proBNP) and hs-cTn have been shown to predict cardiovascular events across different systolic and diastolic BP categories. Furthermore, observational data suggest that individuals with elevated levels of NT-proBNP and/or high-sensitivity troponin have lower numbers needed to treat to prevent cardiovascular events with intensive BP therapy, with the lowest NNT seen in those with elevated levels of both. While the data related to biomarkers in hypertension are encouraging, future randomized clinical trials are needed to further characterize the clinical utility of biomarker-based evaluation and treatment strategies in patients with hypertension.

Key words: Hypertension, biomarkers, cardiovascular risk assessment, NT-pro B type natriuretic peptide, high sensitivity cardiac troponins

Introduction

Cardiovascular disease (CVD) remains a leading cause of death in the world over.¹ Hypertension is an important risk factor for CVD and its treatment can substantially reduce cardiovascular morbidity and mortality.²⁻⁴ Large observational studies have shown a continuous association between elevated blood pressure (BP) and incident coronary heart disease (CHD), stroke, heart failure (HF), and vascular mortality, with the association noted from BPs above 115/75 mmHg.⁴ Meta-analyses of randomized controlled trial (RCTs) including several hundred thousand patients have shown that a 10-mmHg reduction in systolic BP (SBP) or a 5-mmHg reduction in diastolic BP (DBP) is associated with significant reductions of ~20% for all major CV events, 10–15% for all-cause mortality, ~35% for stroke, ~20% for coronary events, and ~40% for HF.⁵,⁶

In clinical practice, guidelines recommend BP thresholds to simplify the diagnosis of and guide treatment decisions in the management of hypertension. The American Heart Association/American College of Cardiology (AHA/ACC) Guidelines for the Prevention, Detection, Evaluation, and Management of High BP⁷ recommend cardiovascular risk assessment in the management of hypertension and advocate for intensive BP control for high-risk adults with BPs >130/80 given clinical trials have shown mixed results for intensive BP therapy. The landmark SBP Intervention Trial (SPRINT) showed that intensive BP lowering in high-risk individuals...
resulted in a significant reduction in combined primary outcomes of myocardial infarction, acute coronary syndrome, stroke, HF events, and cardiovascular mortality compared to routine management over a median follow-up of 3.26 years (5.2% vs. 6.8%, hazard ratio [HR] 0.75, 95% confidence interval [CI] 0.64–0.89). Furthermore, there was reductions see with intensive BP control compared to routine management in the event rates of HF hospitalizations (1.3% vs. 2.1%, P = 0.002), cardiovascular mortality (0.8% vs. 1.4%, P = 0.0005), and all-cause mortality (3.3% vs. 4.5%, P = 0.0003). However, the Heart Outcomes Prevention Evaluation 3 trial, which had individuals with lower risk compared to SPRINT, did not show similar benefit with intensive BP lowering. Moreover, in both these trials, there were increased side effects from intensive therapy, including acute kidney injury, hypotension, and electrolyte abnormalities. For example, in SPRINT, among individuals without chronic kidney disease, 3.8% of participants in the intensive treatment arm versus 1.1% in placebo had a ≥30% decline in Glomerular filtration rate (GFR) to <60 ml/min (P < 0.001), while 2.4% versus 1.4% had hypotension (P = 0.001), 2.3% versus 1.7% had syncope (P = 0.05) and 3.8% versus 2.1% had hyponatremia (P < 0.001), respectively. [Table 1]

Physiologically, at a certain lower limit of SBP, autoregulation, and perfusion of vital organs may become impaired and result in worsening outcomes. Moreover, lowering SBP is accompanied by lowering of DBP as well which may impair myocardial perfusion which is dependent on diastolic blood flow.

Hence, although there is a consistent relative risk reduction per unit decrease in SBP, the net benefit versus harm has to be considered. Individuals with higher cardiovascular risk will derive greater absolute risk reduction from BP treatment. Therefore, different thresholds of cardiovascular risk have been explored where the benefit-to-harm ratio favors initiation of pharmacotherapy.

Hence, based on the available evidence, the 2017 ACC/AHA BP guidelines classified patients into 3 categories based on BP levels and indication for anti-hypertensive therapy. The two categories in which anti-hypertensive therapy was not recommended included: (1) Normal BP (<120/80 mm Hg); and (2) elevated BP (120–129/<80 mm Hg) or low-risk stage 1 hypertension (130–139/80–89 mmHg) (note: Appropriate lifestyle changes should be pursued in these categories). For the others, that is, the third category, anti-hypertensive medications are recommended and include patients with high-risk stage 1 hypertension (130–139/80–89 mmHg) or stage 2 hypertension (≥140/90 mm Hg) [9]. “High-risk stage 1 hypertension” was defined by the presence of any of the following: An estimated 10-year atherosclerotic CVD (ASCVD) risk ≥10% by the pooled cohort equation (PCE), diabetes mellitus, estimated GFR <60 ml/min/1.73 m², or age ≥65 years with SBP ≥ 130 mm Hg.

Similarly, the 2018 European Society of Cardiology/European Society of Hypertension Clinical Practice Guidelines for the Management of Arterial Hypertension also recommends the use of risk assessment by the Systematic CROnary Risk Evaluation (SCORE) tool which also uses traditional risk factors to evaluate the risk of fatal atherosclerotic events. However, both PCE and SCORE do not include HF among the CV outcomes predicted. Given that HF has the highest hazards among all CV outcomes resulting from HTN and given that HF is projected to becoming the most frequent CVD outcome in the coming decades, consideration of HF risk will be of immense value in the management of HTN.

The European guidelines additionally recommend complementing risk estimation by assessment of hypertension-mediated organ damage (HMOD). Circulating biomarkers and imaging of HMOD including kidney disease (e.g. cystatin, microalbuminuria), arterial stiffening (e.g. carotid-femoral pulse wave velocity), left ventricular hypertrophy (LVH) by electrocardiography or echocardiography, and subclinical atherosclerosis (e.g., ankle-brachial index [ABI], coronary artery calcium score [CACs], carotid plaque/carotid intimamedia thickness) may help identify individuals at higher risk and prove helpful in the individualized definition of hypertension and associated risk. However, imaging testing

Table 1: Comparison of incident adverse events among participants in three major intensive blood pressure clinical trials

| Adverse event     | SPRINT[7] | ACCORD[8] | HOPE-3[9] |
|-------------------|-----------|-----------|-----------|
|                   | Intensive therapy (%) | Standard therapy (%) | HR (P-value) | Intensive therapy (%) | Standard therapy (%) | p-value | Treatment (%) | Placebo (%) | P-value |
| Hypotension       | 2.4       | 1.4       | 1.67 (0.001) | 3.3       | 1.27       | <0.001 | 3.4       | 2.0       | <0.0001 |
| Syncope           | 2.3       | 1.7       | 1.33 (0.05)  | 0.5       | 0.21       | 0.10  | 0.1       | 0.1       | 0.55    |
| AKI or ARF        | 4.1       | 2.5       | 1.66 (<0.001) | 0.2       | 0.04       | 0.12  | 0        | 0        |        |
| Electrolyte          | 3.1      | 2.3       | 1.35 (0.02)  | 0.4       | 0.04       | 0.01  | 0.5       | 0.3       | 0.13    |
| Injurious falls     | 2.2       | 2.3       | 0.95 (0.71)   | 0.4       | 0.5        | 0.61  |
| Bradycardia        | 1.9       | 1.6       | 1.19 (0.28)   | 0.5       | 0.13       | 0.02  |

SPRINT trial: Intensive therapy: BP target <120 mm Hg. Standard therapy: BP target <140 mm Hg. ACCORD trial: Intensive therapy: BP target <120 mm Hg. Standard therapy: BP target <140 mm Hg. Electrolyte abnormalities were listed as isolated hyperkalemia in the ACCORD trial. HOPE3: Treatment group: Daily fixed-dose combination candesartan 16 mg and hydrochlorothiazide 12.5 mg. Hypotension, syncope, AKI, and electrolyte abnormalities were listed as adverse events leading to permanent discontinuation of study drugs, whereas injuries were reported as reasons for hospitalization. AKI: Acute kidney injury; ARF: Acute renal failure; HR: Hazard ratio
such as CACs, ABI, carotid ultrasound, or echocardiography has limitations when applied to a population due to cost, throughput, and in the case of CACs risk of radiation (albeit minimal). Circulating biomarkers on the other hand may be more convenient as they are in general cheaper and repeatable and hence may prove useful. In this review, we will focus on the role of select circulating biomarkers NT-pro B type natriuretic peptide (NT-proBNP) and high sensitivity cardiac troponins (hs-cTn) and explore their potential role in the management of hypertension.

Natriuretic peptide (NT-proBNP and brain natriuretic peptide [BNP]) and hs-cTn reflect neurohormonal stress, structural, and/or functional changes in end organs (i.e., myocardium, vasculature) from various causes, including hypertension. NT-proBNP and BNP are validated for use in diagnosis and prognostication of HF; hs-cTn T and I are routinely used in the diagnosis of acute coronary syndrome. Over the last decade, these biomarkers have been shown to have value in the prediction and stratification of risk of future CVD in populations with and without CVD. Their role in the risk assessment of patients with elevated BP has recently been explored. They are attractive markers for several reasons; first, they are not included in either SCORE or PCE; second, they have important prognostic significance irrespective of the presence of CVD risk factors and third, these are important predictors of HF, a major cardiovascular outcome of HTN which is not captured in the PCE or SCORE. Hence, the inclusion of these biomarkers in the assessment of cardiovascular risk was explored to identify high-risk patients with hypertension.

High-sensitivity Troponins

The troponin complex regulates contraction in striated muscles and consists of three subunits: troponin C, troponin I, and troponin T. Cardiac troponin I (cTnI) and troponin T (cTnT) have become the standard biomarker for the detection of myocardial injury, diagnosis of acute myocardial infarction, and risk stratification of patients with acute coronary syndrome. Most of the cardiac troponin is present in the contractile apparatus within myocardial cells, with a small fraction (approximately 6-8%) found as a free cytosolic component. While the majority of evidence suggests that cardiac troponin release occurs as a result of irreversible cell death, the release of cytosolic troponin has been reported to occur with ischemia.

New generation hs-cTn assays measure the same protein as traditional troponin assays but allow detection of troponin at concentrations 10–100 times lower than assays currently in clinical use. The term “high-sensitivity” is defined by 2 assay criteria: (1) The total imprecision at the 99th percentile value is ≤10% and (2) measurable concentrations below the 99th percentile are attainable at a concentration value above the assay’s limit of detection for at least 50% of healthy individuals.

The development of hs-cTn assays has provided the ability to detect subclinical myocardial injury in asymptomatic patients without known ASCVD. Elevations in cardiac troponins have been shown to predict all-cause and cardiovascular mortality and the development of CHD, stroke, and HF in the general population without CVD. Moreover, hs-cTnT has been shown to predict the development of hypertension and be an independent determinant of pre-hypertension. In a study of 6516 Atherosclerosis Risk in Communities (ARIC) participants without baseline hypertension or CVD, compared to patient with hs-cTnT <5 ng/L, patients with higher categories of hs-cTnT had a higher risk of developing incident hypertension, with HR 1.16 (95% CI 1.08–1.25) for hs-cTnT 5–8 ng/L, HR 1.29 (95% CI 1.14–1.47) for hs-cTnT 9–13 ng/L, and HR 1.31 (95% CI 1.07–1.61) for hs-cTnT ≥14 ng/L (p-for-trend <0.001) after a median follow-up of 12 years. hs-cTnT are associated with greater cardiac structural and functional abnormalities, including LVH in patients with hypertension. This suggests that elevated baseline hs-cTnT levels can identify patients who are at risk for the development of hypertension and/or LVH and in turn trigger closer monitoring and initiation of prevention strategies.

Hypertension has been shown to cause myocardial injury even in the absence of atherosclerosis. Several analyses from studies, including the ARIC, Cardiovascular Health Study (CHS), and Dallas Health Study, have clearly demonstrated a diagnostic and prognostic role for hs-cTnT as a biomarker of subclinical myocardial damage in hypertensive heart disease. For example, in 8571 ARIC Study participants without CVD, patients with baseline hypertension had a significant increase in hs-cTnT over a 6-year period with a linear association between increasing baseline SBP and a 6-year increase in hs-cTnT. Similarly, in the CHS among 2219 adults, those with an increase in hs-cTnT over 2–3 years had a higher CVD risk despite either stable SBP (HR: 1.28 [1.04–1.57], P = 0.02) or decreased SBP (HR: 1.57 [1.08–2.28], P = 0.02) compared to those within the same SBP group but a stable hs-cTnT. Moreover, in both the Jackson Heart Study and Dallas Heart Study, participants with elevations in cardiac troponin and presence of LVH had a significantly higher risk for HF compared to those with LVH but undetectable troponin levels which suggested that troponin identified a malignant phenotype of patients that showed higher risk for progression to HF and CVD death.

Elevated hs-cTnT was also shown to be associated with increased risk of CV events across a spectrum of systolic and diastolic categories. In a study of 11,191 ARIC study participants, hs-cTnT was associated with increased adverse CV events (new-onset HF, CHD, and stroke) in each range of SBP in increments of 10 mm Hg. Interestingly, patients with elevated hs-cTnT >14 nl/L and SBP 130–139 mm Hg had a higher risk of incident HF (HR 3.7, 95% CI 2.3–6.1) and CHD (HR 1.7, 95% CI 1.1–2.6) compared to patients with SBP 140–159 mm H and hs-cTnT <3 ng/L. In contrast, participants with low DBPs of 60–69 mmHg and <60 mmHg had higher odds of elevated hs-cTnT (reflecting lower coronary perfusion) and higher incidence of cardiovascular events compared to those with DBP between 80 and 89 mmHg.
These data suggest that for individuals with hypertension, the risk of cardiovascular events may vary at different SBP or DBP level, and biomarkers such as hs-cTnT by identifying myocardial injury can help identify those at higher risk for subsequent cardiovascular events across a wide range of systolic and DBP who would benefit from more aggressive BP management.

**Natriuretic Peptides**

Atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are hormones/peptides secreted by organs including the heart that have a positive physiological role in natriuresis, vasodilation, suppression of hypertrophy and fibrosis, and inhibition of the renin-angiotensin-aldosterone system. Their respective precursor prohormones proANP and proBNP are released from the heart in response to myocardial stretch and other hemodynamic stimuli. These prohormones are then processed to their biologically active forms ANP and BNP, and biologically inactive NT-proBNP. BNP and NT-proBNP have shown sufficient value to be recommended for use by the guidelines for the diagnosis, prognostication, and management of HF. As natriuretic peptides reflect vascular re-modeling and volume homeostasis, they may also prove clinically useful in the assessment of an even wider range of CVD outcomes than HF. Correspondingly, NT-proBNP has been shown to be strongly associated with increased risk of CHD, stroke, and atrial fibrillation outcomes.

In a large systematic review and meta-analysis involving 40 studies and 87,474 participants, those in the highest tertile of natriuretic peptides levels (either BNP or NT-proBNP) had a higher risk for CVD (hazard’s ratio [HR]: 2.82; 95% CI: 2.4–3.33); CHD (HR: 2.03; 95% CI: 1.54–2.66); stroke (HR: 1.53; 95% CI: 1.58–2.37); and HF (HR 3.45; 95% CI 2.66–4.46) compared to the lowest tertile. Moreover, NT-proBNP has been shown to strongly improve risk prediction of multiple cardiovascular outcomes, including cardiovascular mortality, suggestive that in diverse patient populations with and without CVD, NT-proBNP could be integrated into the risk assessment of CVD in primary prevention.

NT-proBNP has been investigated as a biomarker to augment risk prediction in the general population and those with hypertension. In a large study of 70-year-old men (n = 907), free of baseline disease, measurement of NT-proBNP, high-sensitivity C-reactive protein, and cystatin C, over a median of 10 years significantly improved the net reclassification (18.7–19.9%; P < 0.01) of incident ASCVD events (defined as fatal or nonfatal myocardial infarction or fatal or nonfatal stroke) when added to traditional risk factors which included ambulatory BP. Moreover, NT-proBNP was a strong predictor of mortality in patients with hypertension, independent of and superior to ECG marker of LVH (the Sokolow index and the RaVL amplitude).

In clinical practice, elevated levels of NT-proBNP may be used to identify patients with the greatest risk for CVD, who would, in turn, derive the highest absolute risk reduction from therapies targeting modifiable cardiac risk factors. For example, in the PONTIAC (NT-proBNP Prevention of Cardiac Events in a Population of Diabetic Patients without a History of Cardiac Disease) trial, NT-proBNP levels were used to identify diabetic patients for aggressive up-titration of neurohumoral therapy (renin-angiotensin system-antagonists, ACE-Is or ARBs, and beta-blockers) in 268 patients with diabetes. After 2 years, randomization to the biomarker-guided “intensified” group was associated with a 65% reduction in risk of the primary endpoint (hospitalization or death due to cardiac disease) without major side effects requiring hospitalization. Similarly, in the STOP-HF (St Vincent’s Screening to Prevent HF Study) trial of 1374 at-risk patients with cardiovascular risk factors, randomization to BNP screening, and collaborative care (including echocardiography and specialist cardiovascular service) reduced the combined rates of asymptomatic LV systolic and/or diastolic dysfunction with or without newly diagnosed HF, compared to usual care (odds ratio [OR], 0.55; 95% CI, 0.37–0.82; P = 0.003) over a mean follow-up 4.2 years. The intervention group underwent significantly more cardiovascular investigations and received more renin-angiotensin-aldosterone system-modification therapy at follow-up.

NT-proBNP may also have value in individualizing intensification of BP therapy by identifying higher-risk individuals, although this will still need to be tested in RCTs as was done in STOP HF and PONTIAC studies. In a study of 9,309 participants without CVD from the ARIC study, patients with NT-proBNP in 100 to 300 pg/ml, >300 pg/ml categories, compared to <100 pg/ml, demonstrated a graded increase in the risk of CVD, HF, CV, and all-cause mortality across increasing categories of systolic blood, diastolic blood, and pulse pressure categories over a median follow-up of 16.3 years. Importantly, patients with stage 1 hypertension (SBP 130–149 mmHg) but elevated NT-proBNP (≥100 pg/ml) had a higher risk for CVD events, CV mortality, and all-cause mortality compared to those with stage 2 hypertension (SBP 140–159 mmHg) and NT-proBNP levels <100 pg/ml.

The number needed to treat (NNT) to prevent 1 CVD event over 10 years with BP treatment initiation or intensification (to SBP goal of 120 mm Hg) was calculated for combined SBP and NT-proBNP category and sub-stratified by PCE risk (<10% and ≥10%). Participants with increasing levels of NT-proBNP demonstrated lower NNT across SBP groups and PCE risk. For example, among subjects with SBP 120–139 mmHg and PCE risk <10%, NNT for those with NT-proBNP ≥300 pg/ml versus <100 pg/ml was 21 versus 82 [Table 2]. The results of this study provide more evidence of the interplay between NPs and BP in the prediction of CVD and highlight the importance of measuring NP in addition to BP and pulse pressure ranges in cardiovascular risk assessment in ambulatory patients without CVD.
Following the incorporation of ASCVD risk estimation into the ACC/AHA guidelines for the management of hypertension, Pandey et al. analyzed the role of cardiac biomarkers (hs-cTnT and NT-proBNP) in association with the BP categories in assessing CV risk. In this cohort study that pooled 12,987 low-risk participants without prevalent CVD from the ARIC study, Dallas Heart Study, and Multiethnic Study of Atherosclerosis, elevated hs-cTnT and NT-proBNP was observed in 32.3% of participants with elevated BP or stage 1 hypertension (i.e., not recommended for anti-hypertensive medications). Over a follow-up of 10 years, patients with elevated biomarkers achieved the highest absolute risk reduction and corresponding lower NNT with intensive BP therapy for individual HF and mortality outcomes. Hence, a biomarker-based approach using biomarkers such as BNP and troponin may represent an effective strategy to guide intensive BP therapies to lower cardiovascular risk. However, future randomized clinical trials are needed to further characterize the utility of such strategies in selecting patients with hypertension for intensive BP control.

### Table 2: Comparison of incident hazard ratios of cardiovascular events and number needed to treat to prevent 1 cardiovascular event over 10 years (NNT10) across systolic blood pressure ranges and cardiac biomarker levels

| Hazard ratios | SBP, mm Hg | hs-cTnT (ng/L) | NT-proBNP (pg/mL) | Number needed to treat | Number needed to treat |
|---------------|------------|----------------|-------------------|-----------------------|-----------------------|
|               |            | <3 ≤14         | <100 ≥300         |                       |                       |
| CVD           | <120       | (ref)          | 3.01              | 120–139               | 82                    |
|               | 120–129    | 1.08           | 2.59              | 140–159               | 21                    |
|               | 140–149    | 1.22           | 3.35              |                       |                       |
| Heart failure hospitalization | <120       | (ref)          | 5.4               | 120–139               | 300                   |
|               | 120–129    | 1.4            | 5.8               | 140–159               | 123                   |
|               | 140–149    | 1.2            | 4.3               |                       |                       |
| CHD           | <120       | (ref)          | 1.8               | 120–139               | 2.08                  |
|               | 120–129    | 1.1            | 2.5               | 140–149               | 1.65                  |
| Stroke        | <120       | (ref)          | 1.1               | 120–129               | 3.90                  |
|               | 120–129    | 1.2            | 1.4               | 140–149               | 2.84                  |
|               | 140–149    | 1.0            | 3.0               |                       | 4.55                  |

Hazard ratio data for both hs-cTnT and NTproBNP and number needed to treat (NNT10) for NT-proBNP alone obtained from ARIC studies. NT10 data for the combined biomarkers (Hs-cTnT and/or NT-proBNP) were obtained from the pooled cohort study involving the ARIC study, Dallas Heart Study, and Multiethnic Study of Atherosclerosis. Hazard ratios of each SBP and biomarker category are in comparison to participants with SBP<120 mm Hg and Hs-cTnT <3 ng/L or NT-proBNP <100 pg/ml. NNT10 is the number needed to treat to prevent one CVD event when blood pressure is lowered to target systolic blood pressure <120 mmHg where CVD includes CHD, stroke, and heart failure hospitalization. Bolded values are statistically significant (P<0.05). N CHD: Coronary heart disease; CHF: Congestive heart failure; CVD: Cardiovascular disease (composite of CHF, CHD, and stroke).
Conclusion

Hypertension remains a major risk factor for CVDs. There is a disconnect between epidemiological levels of BP at which CVD risk increases and BP treatment targets due to several issues, including the risk of intensive treatment. Hence, reserving intensive treatment for individuals at the highest risk has been proposed. However, the currently used risk scores do not include the prediction of HF and renal disease which are major end-organ complications of hypertension. Natriuretic peptide and high sensitivity cardiac troponins reflect structural and/or functional changes in end organs (i.e., myocardium, vasculature) and have been associated with increased cardiovascular risk. These cardiac biomarkers may play a complementary role in the risk assessment of patients along with other markers of end-organ damage (e.g., coronary calcium score, ankle-brachial index, echocardiographic or electrocardiogram evidence of left ventricular hypertrophy).

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