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# Troponin I and NT-proBNP and the Association of Systolic Blood Pressure With Outcomes in Incident Hemodialysis Patients: The Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study

Tariq Shafi, MBBS, MHS<sup>1,2</sup>, Philip G. Zager, MD<sup>3</sup>, Stephen M. Sozio, MD, MHS<sup>1,2</sup>, Morgan E. Grams, MD, PhD<sup>1,2</sup>, Bernard G. Jaar, MD, MPH<sup>1,2,4</sup>, Robert H. Christenson, PhD<sup>5</sup>, L. Ebony Boulware, MD, MPH<sup>6</sup>, Rulan R. Parekh, MD, MS<sup>7</sup>, Neil R. Powe, MD, MPH, MBA<sup>8</sup>, and Josef Coresh, MD, PhD<sup>2,9,10</sup>

<sup>1</sup>Division of Nephrology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland <sup>2</sup>Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Medical Institutions, Baltimore, Maryland <sup>3</sup>Division of Nephrology, University of New Mexico, Albuquerque, New Mexico <sup>4</sup>Nephrology Center of Maryland, Baltimore, Maryland <sup>5</sup>Department of Pathology, University of Maryland School of Medicine, Baltimore, Maryland <sup>6</sup>Division of General Internal Medicine, Duke University School of Medicine, Chapel Hill, North Carolina <sup>7</sup>Departments of Pediatrics, Hospital for Sick Children and Medicine, University Health Network, and University of Toronto, Ontario, Canada <sup>8</sup>Department of Medicine, San Francisco General Hospital and University of California, San Francisco, California <sup>9</sup>Department of Epidemiology and Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland <sup>10</sup>Division of General Internal Medicine, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland

## Abstract

**Background**—There is uncertainty regarding treatment of hypertension in hemodialysis patients due to the observed J-shaped association between blood pressure (BP) and death. We hypothesized that this association reflects confounding by cardiovascular disease (CVD) and that stratification by CVD biomarkers, cardiac troponin I (cTnI) and N-terminal fragment of prohormone brain natriuretic peptide (NT-proBNP), might change this association.

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Corresponding Author: Tariq Shafi, MBBS, MHS, Division of Nephrology, Johns Hopkins University School of Medicine, 301 Mason Lord Drive, Suite 2500, Baltimore, MD 21224-2780, (410) 550-2820 (Ph), (410) 550-7950 (Fax), tshafi@jhmi.edu.

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Supplementary Material

**Note:** The supplementary material accompanying this article (doi: \_\_\_\_\_) is available at [www.ajkd.org](http://www.ajkd.org)

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**Study Design**—National prospective cohort study.

**Setting & Participants**—446 incident hemodialysis patients.

**Predictor**—Predialysis systolic BP.

**Outcomes**—Mortality (all-cause and CVD) and first CVD event assessed using Cox regression adjusted for demographics, comorbidities and clinical factors.

**Measurements**—Participants with cTnI 0.1 ng/mL or NT-proBNP 9,252 pg/mL classified as the high biomarker group; remaining participants included in the low biomarker group.

**Results**—Participants in the high biomarker group (n=138 [31%]) were older (61 versus 57 years) and had higher prevalence of CVD (67% versus 23%) but similar baseline BP (152 versus 153 mm Hg). There were 323 deaths (143 from CVD) and 271 CVD events. The high-biomarker group had higher risk of mortality than low biomarker group (HR, 1.75; 95% CI, 1.37–2.24). The association between BP and outcomes differed among the two biomarker groups (p for interaction of 0.01, 0.16 and 0.07 for all-cause mortality, CVD mortality and first CVD event, respectively). In the low biomarker group, BP was associated with a greater risk: HR per 10-mm Hg higher BP of 1.07 [95% CI, 1.01–1.14], 1.10 [95% CI, 0.96–1.25], and 1.04 [95% CI, 0.96–1.13] for all-cause mortality, CVD mortality, and first CVD event, respectively. Importantly, lower BP was not associated with an increased risk of outcomes in stratified models including among those with high biomarkers.

**Limitations**—BP measurements not standardized.

**Conclusions**—The observed J-shaped association between BP and outcomes in hemodialysis patients is due to confounding by subclinical CVD. A stratification approach based on cTnI and NT-proBNP has the potential to inform BP treatment in hemodialysis patients.

## Index Words

End-Stage Renal Disease (ESRD); Hypertension; Troponin I; N-terminal pro-brain natriuretic peptide (NT-proBNP); Dialysis; Epidemiology; Hemodialysis; Mortality; Outcomes; systolic blood pressure

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In the general population, there is overwhelming evidence supporting blood pressure (BP) control to reduce target organ damage and prolong survival.<sup>1</sup> Hypertension is common in dialysis patients with prevalence estimates ranging from 60%–90%.<sup>2,3</sup> The 2005 National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines recommended predialysis BP below 140/90 mm Hg for all dialysis patients.<sup>4</sup> However, unlike general population studies, many observational studies of BP and outcomes in dialysis patients have showed an increased risk of death with low systolic BP (below 120–130 mm Hg) and either a protective effect or no harm associated with higher BP (above 140–150 mm Hg).<sup>5–7</sup> In the absence of randomized controlled trial data, there remains skepticism about BP lowering in dialysis<sup>8,9</sup> and over 70% of hemodialysis patients in North America 55% in Europe, Australia and New Zealand; and 85% in Japan have predialysis systolic BP above the NKF-KDOQI goal.<sup>5</sup>

It has been postulated that the lack of association between BP and outcomes in observational studies of dialysis patients could be due to confounding from cardiovascular disease (CVD).<sup>10,11</sup> Meticulous adjudication of medical records can improve ascertainment of CVD. However, in a recent report of the Hemodialysis (HEMO) Study, the association between predialysis systolic BP and mortality did not change even after adjustment for adjudicated comorbidities.<sup>7</sup> These findings suggest that undiagnosed or subclinical CVD, particularly coronary atherosclerosis and left ventricular dysfunction, could be a major factor in the observed lack of association between BP and outcomes in dialysis patients.

Serum cardiac troponin I (cTnI) is a sensitive biomarker of myocardial injury.<sup>12</sup> N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP) is a marker of left ventricular stretch and volume overload.<sup>13</sup> High levels of these biomarkers in dialysis patients can identify individuals with undiagnosed or subclinical CVD who are at greater risk of death in the short-term<sup>14–16</sup> and as a result less likely to develop long-term consequences of uncontrolled hypertension.

We hypothesized that stratification by serum TNI and NT-proBNP may change the association between predialysis systolic BP and outcomes in hemodialysis patients. We tested this hypothesis by measuring these markers in stored serum samples from the participants of a prospective cohort study of incident dialysis patients and then comparing the association between BP and outcomes, separately, among those with high and low levels of TNI and NT-proBNP.

## METHODS

### Study Design

The Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study is a national prospective cohort of incident dialysis patients.<sup>17</sup> From October 1995 to June 1998, 1,041 participants (767 on hemodialysis) from 19 US states were enrolled a median of 45 days after initiation of dialysis (95% within 3.5 months). Eligibility criteria were initiation of maintenance dialysis therapy in the preceding 3 months, ability to provide informed consent, aged 18 years or older and ability to speak English or Spanish. A specimen bank was established for all Dialysis Clinic Inc. (DCI) participants of the CHOICE study. Our study population comprised 446 participants on hemodialysis who had stored serum samples and BP measurements available on the same day as the sample. The Johns Hopkins Medicine Institutional Review Board (Baltimore, Maryland) and the clinical centers' review boards approved the study and participants provided written informed consent.

### Data Collection

**Cardiac Biomarkers: Serum cTnI and NT-ProBNP**—We collected non-fasting predialysis blood specimens, centrifuged them within 30–45 minutes of blood collection and sent them overnight on ice to the DCI Central Laboratory. We aliquoted each sample into multiple vials and stored them at  $-80^{\circ}\text{C}$ . We measured serum TNI by homogeneous, sandwich chemiluminescent immunoassay based on LOCI technology (Siemens Healthcare) and measured NT-proBNP using a one-step sandwich chemiluminescent immunoassay also

based on LOCI technology. Both TNI and NT-proBNP were measured on the Dimension Vista System (Siemens Healthcare, Glasgow, DE) at the University of Maryland School of Medicine, Baltimore, Maryland. The coefficient of variation (CV) for TNI was 9.1% at 0.090 ng/mL, 5.9% at 1.08 ng/mL and 1.6% at 4.87 ng/mL. The reliability coefficient for TNI in a 5% sample of masked duplicate specimens was 0.969. The CV for NT-proBNP was 5.0% at 107.2 pg/mL, 1.6% at 275 pg/mL and 1.2% at 3,313 pg/mL. The reliability coefficient for NT-proBNP was 0.998.

We categorized participants into two groups based on TNI and NT-proBNP cutoffs based on published studies.<sup>14,16</sup> Those with either TNI  $\geq$  0.1 ng/mL or NT-proBNP  $\geq$  9,252 pg/mL were categorized as a high biomarker group and the rest were classified as a low biomarker group (TNI <0.1 ng/mL and NT-proBNP <9,252 pg/mL).

**Predialysis Systolic BP**—We obtained predialysis systolic BP from the DCI electronic medical records. Predialysis systolic BP was measured with the participants in the sitting position before each dialysis session as part of routine clinical care in the dialysis unit. For our primary analysis, we used a single predialysis systolic BP measurement from the same day as the serum sample (N=446). For sensitivity analyses, we determined the average predialysis systolic BP in the 30 days preceding the serum sample.

**Outcomes**—We adjudicated all-cause and CVD mortality using information from clinic report, hospital records, National Death Index, Centers for Medicare & Medicaid Services death notification forms, and Social Security records, as previously described.<sup>18</sup> We defined first atherosclerotic CVD event (fatal or nonfatal) as an event due to myocardial infarction, cardiac revascularization procedure, stroke, carotid endarterectomy, extremity gangrene or peripheral revascularization procedure, limb amputation, or abdominal aortic aneurysm repair that occurred after enrolment in the study.<sup>18</sup>

**Other Covariates**—We collected data on participants' age, sex, race and body mass index (BMI). We adjudicated baseline comorbidities including prevalent CVD by abstraction of dialysis unit records, hospital discharge summaries, medication lists, consultation notes, diagnostic imaging, and cardiac imaging reports and scoring of the Index of Coexistent Disease (ICED) by two trained nurses. ICED is a validated medical record–derived index that captures both presence and severity of comorbid conditions.<sup>19,20</sup> ICED scores range from 0 to 3 (highest severity level, 3). We abstracted antihypertensive medication use at baseline from patients' charts and obtained routine laboratory data from medical records. We measured serum albumin (CV, 1.9%) in the same specimen as TNI and NT-proBNP at University of Minnesota, Minneapolis.

## Statistical Analysis

We compared the baseline characteristics of participants across low and high biomarker groups using  $\chi^2$  tests and t-tests for categorical and continuous variables, respectively. We imputed data for the only covariate with missing values (BMI, missing in 26 [5.8%]) with 10 data replicates using multiple imputation by the chained equations method implemented by the ice program in Stata. We used Cox proportional hazards regression to model the risk of

all-cause mortality, CVD mortality, and first CVD event associated with BP. We adjusted our analyses for demographics (age, sex and race) comorbidities (baseline ICED, CVD and diabetes), BMI, baseline antihypertensive medication use and serum albumin. We checked proportional hazards assumptions graphically and by tests of Schoenfeld residuals (estat phtest in Stata). To determine the functional form of the association of BP with outcomes, we modeled BP in three different ways. First, we modeled BP as a restricted cubic spline with knots at 10<sup>th</sup>, 50<sup>th</sup> and 90<sup>th</sup> percentile and 140 mm Hg as the reference point. We selected between 3, 4 or 5 knots based on the most parsimonious model by Akaike's Information Criteria (model with 3 knots).<sup>21</sup> We then constructed visual displays of relative hazard for each outcome with and without stratification by biomarker groups. Second, as coefficients from the restricted cubic spline model are not clinically interpretable, we modeled BP as a linear spline with knots based on percentiles and clinical criteria. Finally, we modeled BP as a continuous variable without splines. We assessed whether the association of BP with outcomes differed by the BP level by inspecting the relative hazard plots and by testing for change in slope of relative hazard before and after spline points. We assessed whether the association between BP and outcomes differed by biomarker groups by inspecting the relative hazard plots and by testing for interaction between BP and biomarker group using Wald test after Cox proportional hazard regression.

We performed a number of sensitivity analyses to test the robustness of our findings. First, instead of BP on the same day as serum sample, we used average BP for the preceding 30-days. Second, we added a 30 day lag between the day of BP measurement and outcome ascertainment to prevent the influence of acute illness on outcomes. Third, we defined biomarker groups based on either TNI or NT-proBNP levels (not both). In other analyses, we explored the effect of stratification by baseline CVD status instead of biomarkers on the association between BP and outcomes.

Statistical analyses were performed using Stata software, version 12.1 (Stata Corp LP [www.stata.com](http://www.stata.com)). Statistical significance was defined as  $p < 0.05$  using two-tailed tests.

## RESULTS

### Baseline Characteristics

Participants included in the cohort versus excluded (Table S1, available as online supplementary material) were likely to be younger (58 versus 61 years), non-white (36% versus 26%), and have diabetes (59% versus 50%) and higher serum creatinine (7.5 versus 6.9 mg/dL). Baseline characteristics of the 446 participants by categories of biomarkers are presented in Table 1. Those with high biomarker levels were likely to be older; had more comorbidities including CVD, congestive heart failure and coronary heart disease; had lower BMI; and had lower use of angiotensin-converting enzyme inhibitors. Mean predialysis systolic BP was similar in both groups (Figure 1) but the high biomarker group had more people with lower BP than the low biomarker group. Participant characteristics by high or low level of TNI or NT-proBNP are presented in Table S2. Those with high TNI ( 0.1 ng/mL) compared with a lower level were more likely to be older, have a history of smoking, have lower systolic BP and more likely to be on ACE-inhibitors. Those with high NT-proBNP levels ( 9252 pg/mL) compared with a lower level were more likely to be

older, White, and have CVD, CHF, and CHD, and had lower BMI, creatinine, albumin and hemoglobin levels and higher CRP levels.

### Biomarker Groups and Outcomes

Participants were censored at transplantation or end of study period (all-cause mortality through 12/31/2008 and CVD mortality through 12/31/2004). During a median follow-up of 3.1 years, there were 323 deaths, of which 143 (44%) were due to atherosclerotic CVD. There were 271 atherosclerotic CVD events. Median survival time was significantly shorter in the high biomarker group (2.4 years) than in the low biomarker group (3.5 years; log-rank  $p < 0.001$  for all outcomes). The high biomarker group was associated with significantly increased risk of all-cause and CVD mortality and first CVD event (Table 2 and Table S3).

### Predialysis Systolic BP and All-Cause Mortality

Figure 2a presents the unadjusted and adjusted hazard ratio (HR) for all-cause mortality with predialysis systolic BP overall and by biomarker groups. Among all participants, full adjustment including adjustment for the biomarkers category changed the shape of association and lower BP was no longer associated with increased risk of death ( $p$  for interaction = 0.01). In stratified analyses, there was a nearly linear increase in the risk of death with systolic BP above 140 mm Hg in the low biomarker group but there was no association with BP and mortality in the high biomarker group.

In linear spline models with a knot at 140 mm Hg, the change in slope did not differ above or below the spline after adjusting for biomarkers and other covariates. (Table S4) Similarly, in overall and stratified analyses, models for BP with splines at the 10<sup>th</sup>, 50<sup>th</sup> and 90<sup>th</sup> percentiles as well as models with spline at 140 mm Hg were not statistically significantly different from models with BP as a linear term ( $p$  for likelihood ratio test  $> 0.05$ ). Table 3 and Table S5 show the results of the fully adjusted models for the risk of all-cause mortality per 10-mm Hg higher BP. Among those in the low biomarker group, there was a 7% higher risk of death per 10-mm Hg higher BP (HR, 1.07; 95% confidence interval [CI], 1.01–1.14). BP was not associated with mortality in the high biomarker group.

### Predialysis Systolic BP, CVD Mortality and CVD Events

Figure 2b and 2c present the unadjusted and adjusted HR plots for CVD mortality and first CVD event. The association between BP and outcomes was similar in direction and magnitude to all-cause mortality ( $p$  for interaction for biomarker groups and BP, 0.16 for CVD mortality and 0.07 for first CVD event). Among those in the low biomarker group, per 10-mm Hg higher BP, there was a 10% higher risk of CVD death (HR, 1.10; 95% CI, 0.96–1.25) and 4% higher risk of CVD events (HR, 1.04; 95% CI, 0.96–1.13), though these values were not statistically significant. BP was not associated with mortality in the high biomarker group.

### Sensitivity and Other Analyses

Analyses incorporating systolic BP averaged over the previous 30 day period, adding a lag of 30 days between measurement of biomarkers and outcome as well as alternate definitions of biomarker groups yielded findings similar to the primary analysis (Table S6). Alternate



models for imputation of missing BMI that included outcome and time to outcome were similar to primary analysis (data not shown). In analyses stratified by baseline CVD status instead of the biomarker categories, the -J-shaped association between BP and outcomes persisted among those with prevalent CVD despite multivariate adjustment (Figure S1 and Tables S7 & S8).

## DISCUSSION

In this report from a national prospective cohort study of incident dialysis patients, we found that a stratification strategy using TNI and NT-proBNP has the potential to identify hemodialysis patients who are at increased risk of morbidity and mortality due to higher predialysis systolic BP. Those with low biomarkers (TNI below 0.1 ng/mL or NT-proBNP below 9,252 pg/mL) had longer survival, and, in these patients, predialysis systolic BP above 140 mm Hg was associated with a 7% increased risk of all-cause death and nominally increased risk of CVD death (by 10%) and CVD events (by 4%), per 10-mm Hg higher BP. Those with elevated biomarkers had a shorter survival (median difference, 1.1 year) with a 75% higher risk of death compared with those without elevated levels. There was no association between BP and outcomes in the high biomarker group. Importantly, in contrast to previous observational studies, after stratification by biomarker levels, there was no evidence of a protective effect of higher systolic BP or harmful effect of lower systolic BP.

Data from randomized controlled trials to determine BP goals for hemodialysis patients are lacking. Recent KDIGO guidelines for BP management in CKD patients did not recommend BP goals for dialysis patients due to paucity of evidence.<sup>10,22</sup> As a result of these studies, there remains skepticism about the goals for treatment of hypertension in dialysis patients.<sup>8,9</sup> In this context, our study provides important data to inform decisions regarding treatment of hypertension in hemodialysis patients. After adjustment for confounders and stratification by cardiac biomarkers, we did not find that lower BP was associated with a higher risk of adverse outcomes. Even in the high biomarker group with overall shorter survival, lower BP was not associated with a higher risk of adverse events. On the other hand, in the low biomarker group, higher BP was associated with a higher risk of outcomes. These findings should provide reassurance to the clinicians treating uncontrolled hypertension in hemodialysis patients, because they do not suggest harm associated with lower BP goals as suggested by NKF-KDOQI guidelines.

The lack of association between higher BP and morbidity and mortality in previous observational studies of dialysis patients are in direct contrast to the observational studies of BP in the general population that showed a linear relationship between higher BP and adverse outcomes.<sup>23,24</sup> These divergent results in dialysis studies could be due to selection bias (incidence-prevalence bias), information bias (BP measurement), incomplete assessment of confounders (CVD, coronary atherosclerosis and left ventricular dysfunction) and misclassification of outcomes using registry data. The presence of these biases can threaten the internal validity of the study and affect the assessment of the direction of causality.<sup>25</sup> Most previous studies of outcomes associated with BP in dialysis patients were conducted using point-prevalent cohorts that are highly susceptible to incidence-prevalence bias due to the higher risk of death in incident patients immediately after initiation of

dialysis.<sup>26</sup> In most dialysis studies, BP measurements available are obtained as part of routine care. These routine BP measurements can be markedly different from standardized BP measurements and could result in misclassification of the exposure.<sup>27</sup> Home BPs are better correlated with left ventricular mass and mortality in dialysis patients but are not routinely recorded.<sup>28,29</sup> Unmeasured confounders could also bias the association between BP and outcomes in dialysis patients. However, a recent post hoc analysis of the HEMO Study, adjustment for CVD using the ICED score, obtained from chart review by trained nurses, did not demonstrate an association between BP and outcomes.<sup>7</sup> Incomplete ascertainment of outcomes can represent a significant problem with registry data and claims-based data can systematically underestimate the prevalence of CVD and CVD events.<sup>30</sup> Similar to the results from the HEMO Study, stratification by CVD in our cohort did not eliminate the J-shaped association between BP and outcome but stratification by biomarker categories allowed us to account for effect modification from subclinical or undiagnosed CVD.

Both TNI and NT-proBNP are widely available and used in routine clinical practice for risk stratification of patients with chest pain and congestive heart failure.<sup>12,13</sup> TNI is a sensitive marker of myocardial ischemia and injury and elevated TNI levels in dialysis patients are associated with 2-fold risk of death.<sup>14,16,31</sup> Myocardial stunning during and after dialysis has been well described in hemodialysis patients and reflects decreased myocardial perfusion due to macro- and microvascular coronary disease.<sup>32</sup> It is quite likely that elevated TNI levels in dialysis patients represent a residual effect of this recurrent ischemia and injury combined with decreased or absent renal clearance. As a response to left ventricular stretch, NT-proBNP is released from cardiac myocytes, and elevated levels in dialysis patients occur as a result of increased left ventricular filling pressures combined with decreased or absent renal clearance.<sup>13</sup> Elevated NT-proBNP in dialysis patients is associated with mortality and cardiovascular events.<sup>14</sup> Elevated levels of TNI and NT-proBNP in dialysis patients can potentially identify patients with ischemic and non-ischemic cardiomyopathies.

Our study has some limitations. First, we had a single measurement of TNI and NT-proBNP and the levels of these markers may change as a result of ongoing illness or volume changes. Second, BP measurements were not standardized and we did not have interdialytic or home BP measurements. Our study also has several strengths, including the prospective design; inclusion of only incident dialysis patients; thorough information on demographic, clinical and treatment factors; and systematic adjudication of baseline comorbid conditions as well as incident events.

In summary, our findings suggest that the lack of association between BP and mortality in previous observational studies of dialysis patients is due to confounding by CVD. Higher systolic BP in dialysis patients is a risk factor for all-cause and CVD mortality and CVD events, particularly among those with low levels of cardiac biomarkers TNI and NT-proBNP. A stratification approach based on serum TNI and NT-proBNP has the potential to identify patients who may benefit from the long-term effects of BP lowering. Validation of our findings in other prospective studies of dialysis patients and particularly studies of risk



prediction may allow these routinely available biomarkers to be used for clinical decision making and risk stratification in clinical trials.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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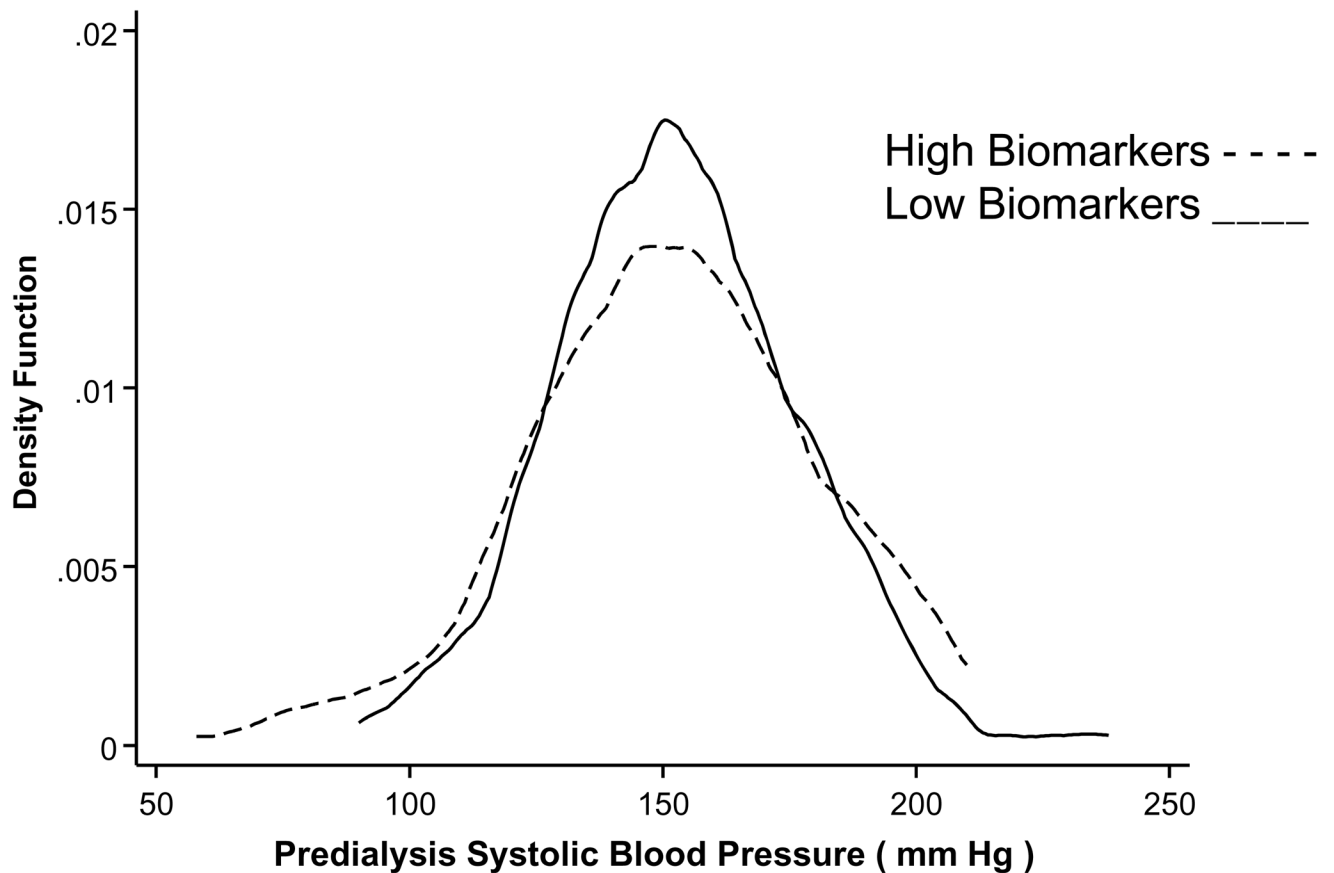
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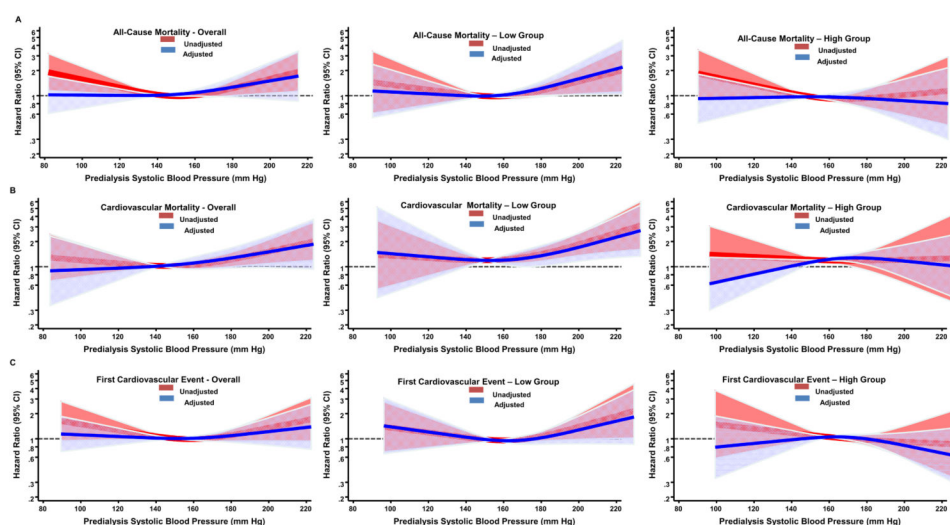
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**Figure 1.**

Distribution of predialysis systolic blood pressure (BP) in 446 CHOICE Study participants stratified by cardiac troponin I (cTnI) and N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP). Lines represent the kernel density estimates. Broken line shows the distribution of predialysis systolic BP in 138 participants with cTnI  $\geq 0.1$  ng/mL or NT-proBNP  $\geq 9,252$  pg/mL. Solid line shows the distribution of predialysis systolic BP in 308 participants with cTnI below 0.1 ng/mL and NT-proBNP below 9,252 pg/mL.



**Figure 2.**

Adjusted relative hazards of all-cause mortality associated with predialysis systolic blood pressure in 446 incident hemodialysis participants of the CHOICE Study. Those with cardiac troponin I (cTnI)  $\geq 0.1$  ng/mL or N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP)  $\geq 9,252$  pg/mL are classified as high biomarker group and the remaining participants as low biomarker group. Figure 2a presents the relative hazard of all-cause mortality, Figure 2b presents the relative hazard of cardiovascular mortality and Figure 2c presents the relative hazard of first cardiovascular disease event. Top panel for each figure presents the unadjusted and adjusted results for the full cohort, the middle panel for those in the low biomarker group and the lower panel for those in the high biomarker groups. Model adjusted for demographics (age, sex and race) comorbidities [baseline Index of Coexistent Disease (ICED) score, CVD and diabetes], body mass index, baseline antihypertensive medication use and serum albumin. Overall model also includes an interaction between blood pressure and biomarker group. Relative hazard predicted using Cox proportional hazards regression. Predialysis systolic blood pressure is modeled as a restricted cubic spline with knots at 10<sup>th</sup>, 50<sup>th</sup> and 90<sup>th</sup> percentile. The solid line is the adjusted hazard ratio of mortality; systolic blood pressure = 140 mm Hg was used as the reference (hazard ratio =1). The shaded area represents the 95% confidence interval. Red color represents the hazard before adjustment and blue color represents the hazard after adjustment.

**Table 1**

Baseline Characteristics by cTnI and NT-proBNP Categories

	Low Biomarker Group	High Biomarker Group	p
No. of Participants	308	138	
Biomarkers			
cTnI (ng/mL)			
Mean	0.013 ±0.016	0.113 ±0.315	
Median	<0.015 [ $<0.015 - <0.015$ ]	0.026 [ $<0.015 - 0.094$ ]	
No. with 0.1 ng/mL	0 (0)	34 (25)	
NT-proBNP (pg/mL)			
Mean	2,737 ±2,378	28,915 ±40,223	
Median	1,950 [942–3,727]	15,831 [10,843–25,633]	
No. with 9,252 pg/mL	0 (0)	123 (89)	
Demographic			
Age (y)	57 ± 15	61 ± 13	0.01
Female Sex	45%	44%	0.9
White Race	62%	70%	0.1
High school graduate	33%	36%	0.5
Clinical			
Smoking status, ever smoker	58%	63%	0.3
ICED score			0.02
1	32%	21%	
2	42%	43%	
3	26%	37%	
Diabetes	56%	64%	0.1
CVD	23%	67%	0.007
CHF	43%	68%	<0.001
CHD	39%	57%	<0.001
MI	23%	30%	0.2
BMI (kg/m <sup>2</sup> )	28.4 ±7.7	26.1 ±6.2	0.004



	Low Biomarker Group	High Biomarker Group	p
Predialysis systolic BP (mm Hg)	153 ±24	152 ±29	0.7
ESRD-Related			
Assigned primary cause of kidney failure			0.04
Diabetes	152 (49)	72 (52)	
Hypertension	47 (15)	32 (23)	
Glomerulonephritis	53 (17)	11 (8)	
Other	56 (18)	23 (17)	
Average Kt/V	1.36 ±0.27	1.16 ±0.27	0.7
Average dialysis session duration (min)	218.3 ±22.3	217.2 ±23.7	0.7
Laboratory			
Predialysis SUN (mg/dL)	58.11 (14.78)	59.22 (14.12)	0.5
Predialysis creatinine (mg/dL)	8.29 (2.95)	7.81 (2.64)	0.1
Potassium (mEq/L)	4.70 (0.59)	4.81 (0.64)	0.06
Albumin (g/dL)	3.6 (0.5)	3.5 (0.6)	0.008
Calcium (mg/dL)	9.79 (0.80)	9.79 (0.84)	0.9
Phosphorus (mg/dL)	5.55 (1.56)	5.66 (1.46)	0.5
Hemoglobin (g/dL)	11.1 (1.1)	10.8 (1.1)	0.006
C-Reactive Protein (mg/dL)	0.60 [0.28–1.23]	0.72 [0.28–2.19]	0.1
Antihypertensive Medication Use			
ACE Inhibitors	78%	49%	0.03
Calcium Channel Blockers	63%	54%	0.07
β-Blockers	23%	28%	0.2

*Note:* Unless otherwise indicated, values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation or median [interquartile range]. For cTnI, 0.015 is the lower limit of detection. *Conversion factors for units:* calcium in mg/dL to mmol/L, x0.2495; phosphorus in mg/dL to mmol/L, x0.357; creatinine in mg/dL to μmol/L, x88.4.

*Abbreviations:* cTnI, cardiac troponin I; ICED, Index of Coexistent Disease; NT-proBNP, N-terminal fragment of prohormone brain natriuretic peptide; CVD, cardiovascular disease; CHF, congestive heart failure; CHD, coronary heart disease; MI, myocardial infarction; SUN, serum urea nitrogen; BMI, body mass index; BP, blood pressure; ESRD, end-stage renal disease; ACE, angiotensin converting enzyme.

Table 2

cTnI and NT-proBNP groups and their association with outcomes

Outcome by Biomarker Group	No. of Events	HR <sup>J</sup> (95% CI)
<b>All-Cause Mortality</b>		
Low cTnI and NT-proBNP	203	1.00 (reference)
High cTnI or NT-proBNP	120	1.75 (1.37–2.24)
<b>CVD Mortality</b>		
Low cTnI and NT-proBNP	76	1.00 (reference)
High cTnI or NT-proBNP	67	2.29 (1.55–3.38)
<b>First CVD Event</b>		
Low cTnI and NT-proBNP	167	1.00 (reference)
High cTnI or NT-proBNP	104	1.67 (1.32–2.10)

Note: N=446. P for all <0.001. Low cTnI and NT-proBNP group are those with cTnI < 0.1 ng/mL and NT-proBNP < 9252 pg/mL. High cTnI or NT-proBNP group are those with either cTnI 0.1 ng/mL or NT-proBNP 9252 pg/mL

Abbreviations: cTnI, cardiac troponin I; NT-proBNP, N-terminal fragment of prohormone brain natriuretic peptide; CVD, Cardiovascular Disease; HR, Hazard Ratio; CI, Confidence Interval.

<sup>J</sup>HR adjusted for demographics (age, sex and race) comorbidities [baseline Index of Coexistent Disease score, CVD and diabetes], body mass index, baseline antihypertensive medication use and serum albumin.

**Table 3**  
Association of Predialysis Systolic BP and Outcomes by cTnI and NT-proBNP Categories

Outcome by Biomarker Group	No. of Events	HR* (95% CI)	p	p-interaction**
All-Cause Mortality				
Low cTnl and NT-proBNP	203	1.07 (1.01–1.14)	0.03	0.01
High cTnl or NT-proBNP	120	0.99 (0.92–1.06)	0.7	
CVD Mortality				
				0.2
Low cTnl and NT-proBNP	76	1.10 (0.96–1.25)	0.2	
High cTnl or NT-proBNP	67	1.04 (0.98–1.11)	0.2	
First CVD Event				
				0.07
Low cTnl and NT-proBNP	167	1.04 (0.96–1.13)	0.4	
High cTnl or NT-proBNP	104	0.98 (0.92–1.04)	0.4	

Note: N=446. Low cTnI and NT-proBNP group are those with cTnI < 0.1 ng/mL and NT-proBNP < 9252 pg/mL. High cTnI or NT-proBNP group are those with either cTnI 0.1 ng/mL or NT-proBNP 9252 pg/mL

Abbreviations: cTnI, cardiac troponin I; NT-proBNP, N-terminal fragment of prohormone brain natriuretic peptide; CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval.

\* HR per 10–mm Hg higher BP, adjusted for demographics (age, sex and race) comorbidities [baseline Index of Coexistent Disease score, CVD and diabetes], body mass index, baseline antihypertensive medication use and serum albumin.

\*\* P-interaction between predialysis systolic BP and biomarker group.