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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

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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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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

In the general population, there is overwhelming evidence supporting blood pressure (BP) control to reduce target organ damage and prolong survival.[1] Hypertension is common in dialysis patients with prevalence estimates ranging from 60%–90%.[2,3] 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.[4] 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).[5–7] In the absence of randomized controlled trial data, there remains skepticism about BP lowering in dialysis [8,9] 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.[5]

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).[10,11] 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.[7] 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.[12] N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP) is a marker of left ventricular stretch and volume overload.[13] 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[14–16] 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.[17] 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 pre-dialysis 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°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.[14,16] Those with either TNI 0.1 ng/mL or NT-proBNP 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.[18] 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.[18]

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.[19,20] 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 χ^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 10th, 50th and 90th 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).[21] 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). 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 10th, 50th and 90th 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 forinteraction 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.[10,22] As a result of these studies, there remains skepticism about the goals for treatment of hypertension in dialysis patients.[8,9] 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.[23,24] 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.[25] 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.[26] 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.[27] Home BPs are better correlated with left ventricular mass and mortality in dialysis patients but are not routinely recorded.[28,29] 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.[7] 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.[30] 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.[12,13] 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.[14,16,31] 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.[32] 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.[13] Elevated NT-proBNP in dialysis patients is associated with mortality and cardiovascular events.[14] 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.

Acknowledgments

References

1. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. Dec; 2003 42(6):1206–1252. [PubMed: 14656957]

2. Agarwal R, Nissenson AR, Batlle D, Coyne DW, Trout JR, Warnock DG. Prevalence, treatment, and control of hypertension in chronic hemodialysis patients in the United States. Am J Med. Sep; 2003 115(4):291–297. [PubMed: 12967694]

3. 2010 Annual Report of the Dialysis Outcomes and Practice Patterns Study: Hemodialysis Data. Arbor Research Collaborative for Health; Ann Arbor, MI: 1999–2008. http://www.dopps.org/annualreport/html/MCOMHTN_c_mostrec2010.htm [Accessed September 17, 2013]

4. National Kidney Foundation, K/DOQI Workgroup. K/DOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients. American Journal of Kidney Diseases. 2005; 45(4 Supplement 3):S16–153.

5. Robinson BM, Tong L, Zhang J, et al. Blood pressure levels and mortality risk among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. Kidney Int. Sep; 2012 82(5):570–580. [PubMed: 22718187]

6. Kalantar-Zadeh K, Kilpatrick RD, McAllister CJ, Greenland S, Kopple JD. Reverse epidemiology of hypertension and cardiovascular death in the hemodialysis population: the 58th annual fall conference and scientific sessions. Hypertension. Apr; 2005 45(4):811–817. [PubMed: 15699452]

7. Chang TI, Friedman GD, Cheung AK, Greene T, Desai M, Chertow GM. Systolic blood pressure and mortality in prevalent haemodialysis patients in the HEMO study. J Hum Hypertens. Feb; 2011 25(2):98–105. [PubMed: 20410919]

8. Lacson E Jr, Lazarus JM. The association between blood pressure and mortality in ESRD-not different from the general population? Semin Dial. Nov-Dec;2007 20(6):510–517. [PubMed: 17991196]

9. Weir MR. Debate from the 2012 ASH Annual Scientific Sessions: should blood pressure be reduced in hemodialysis patients? Con position. J Am Soc Hypertens. Nov-Dec;2012 6(6):443–447. [PubMed: 23127361]

10. Levin NW, Kotanko P, Eckardt KU, et al. Blood pressure in chronic kidney disease stage 5D-report from a Kidney Disease: Improving Global Outcomes controversies conference. Kidney Int. Feb; 2010 77(4):273–284. [PubMed: 20016467]

11. Shafi T, Waheed S, Zager PG. Hypertension in Hemodialysis Patients – An Opinion–Based Update. Semin Dial. 2014; 27(2):146–153. [PubMed: 24494716]

12. de Lemos JA. Increasingly sensitive assays for cardiac troponins: a review. JAMA. Jun 5; 2013 309(21):2262–2269. [PubMed: 23736735]

13. Kim H-N, Januzzi JL. Natriuretic Peptide Testing in Heart Failure. Circulation. May 10; 2011 123(18):2015–2019. [PubMed: 21555724]

14. Winkler K, Wanner C, Drechsler C, Lilienthal J, Marz W, Krane V. Change in N-terminal-pro-B-type-natriuretic-peptide and the risk of sudden death, stroke, myocardial infarction, and all-cause mortality in diabetic dialysis patients. Eur Heart J. Sep; 2008 29(17):2092–2099. [PubMed: 18617483]

15. Zoccali C, Mallamaci F, Benedetto FA, et al. Cardiac Natriuretic Peptides Are Related to Left Ventricular Mass and Function and Predict Mortality in Dialysis Patients. J Am Soc Nephrol. Jul 1; 2001 12(7):1508–1515. [PubMed: 11423580]

16. Apple FS, Murakami MM, Pearce LA, Herzog CA. Predictive value of cardiac troponin I and T for subsequent death in end-stage renal disease. Circulation. Dec 3; 2002 106(23):2941–2945. [PubMed: 12460876]

17. Powe NR, Klag MJ, Sadler JH, et al. Choices for Healthy Outcomes in Caring for End Stage Renal Disease. Seminars in Dialysis. 1996; 9(1):9–11.

18. Longenecker JC, Klag MJ, Marcovina SM, et al. High lipoprotein(a) levels and small apolipoprotein(a) size prospectively predict cardiovascular events in dialysis patients. J Am Soc Nephrol. Jun; 2005 16(6):1794–1802. [PubMed: 15800123]

19. Miskulin DC, Meyer KB, Athienites NV, et al. Comorbidity and other factors associated with modality selection in incident dialysis patients: the CHOICE Study. Choices for Healthy Outcomes in Caring for End-Stage Renal Disease. Am J Kidney Dis. Feb; 2002 39(2):324–336. [PubMed: 11840373]

20. Nicolaos VA, Dana CM, Gladys F, et al. Comorbidity Assessment in Hemodialysis and Peritoneal Dialysis Using the Index of Coexistent Disease. Seminars in Dialysis. 2000; 13(5):320–326. [PubMed: 11014695]

21. Harrell, FE, Jr. Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis. New York: Springer; 2001.

22. Wheeler DC, Becker GJ. Summary of KDIGO guideline. What do we really know about management of blood pressure in patients with chronic kidney disease? Kidney Int. Mar; 2013 83(3):377–383. [PubMed: 23325075]

23. Klag MJ, Whelton PK, Randall BL, et al. Blood pressure and end-stage renal disease in men. N Engl J Med. Jan 4; 1996 334(1):13–18. [PubMed: 7494564]

24. Vasan RS, Larson MG, Leip EP, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. N Engl J Med. Nov 1; 2001 345(18):1291–1297. [PubMed: 11794147]

25. Rothman, KJ.; Greenland, S. Modern Epidemiology. 2. Philadelphia: Lippincott Williams & Wilkins; 1998.

26. Tripepi G, Jager KJ, Dekker FW, Wanner C, Zoccali C. Bias in clinical research. Kidney Int. Jan; 2008 73(2):148–153. [PubMed: 17978812]

27. Rahman M, Griffin V, Kumar A, Manzoor F, Wright JT Jr, Smith MC. A comparison of standardized versus "usual" blood pressure measurements in hemodialysis patients. Am J Kidney Dis. Jun; 2002 39(6):1226–1230. [PubMed: 12046035]

28. Agarwal R. Managing hypertension using home blood pressure monitoring among haemodialysis patients--a call to action. Nephrol Dial Transplant. Jun; 2010 25(6):1766–1771. [PubMed: 20350928]

29. Agarwal R. Blood pressure and mortality among hemodialysis patients. Hypertension. Mar; 2010 55(3):762–768. [PubMed: 20083728]

30. Longenecker JC, Coresh J, Klag MJ, et al. Validation of comorbid conditions on the end-stage renal disease medical evidence report: the CHOICE study. Choices for Healthy Outcomes in Caring for ESRD. J Am Soc Nephrol. Mar; 2000 11(3):520–529. [PubMed: 10703676]

31. Gutierrez OM, Tamez H, Bhan I, et al. N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations in hemodialysis patients: prognostic value of baseline and follow-up measurements. Clinical chemistry. Aug; 2008 54(8):1339–1348. [PubMed: 18539645]

32. McIntyre CW, Burton JO, Selby NM, et al. Hemodialysis-Induced Cardiac Dysfunction Is Associated with an Acute Reduction in Global and Segmental Myocardial Blood Flow. Clinical Journal of the American Society of Nephrology. Jan 1; 2008 3(1):19–26. [PubMed: 18003765]
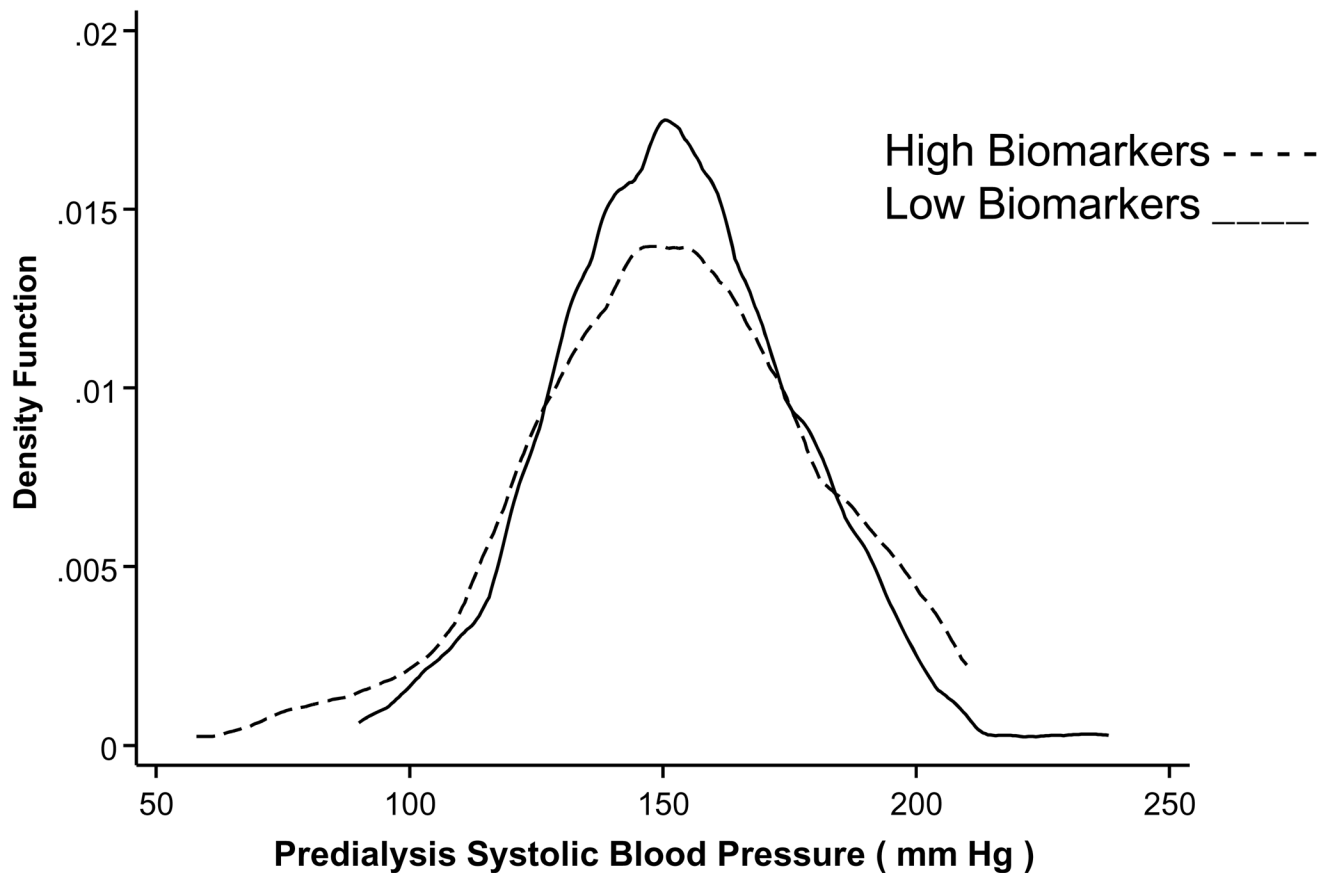
Figure 1.
Distribution of predialysis systolic blood pressure (BP) in 446 CHOICE Study participants stratified by cardiac troponin I (cTnI) and N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP). Lines represent the kernel density estimates. Broken line shows the distribution of predialysis systolic BP in 138 participants with cTnI ≥ 0.1 ng/mL or NT-proBNP ≥ 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.
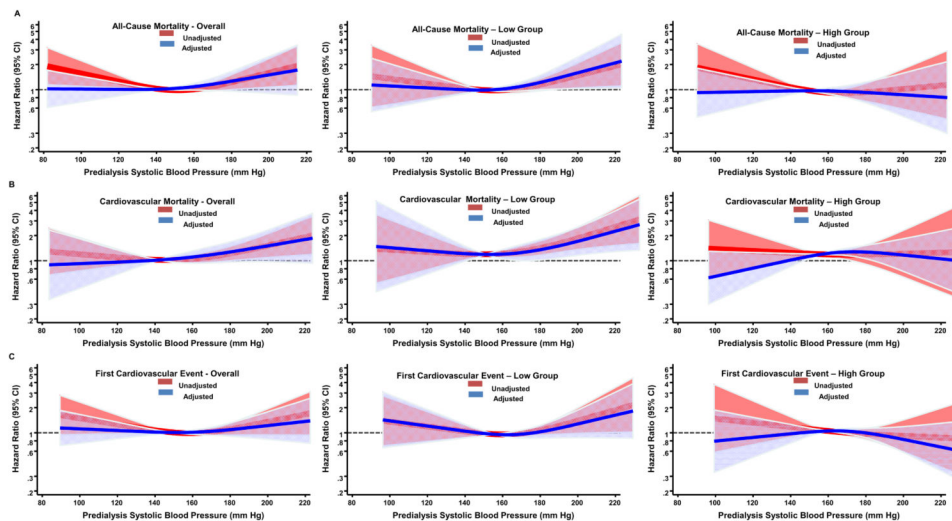
Figure 2.
Adjusted relative hazards of all-cause mortality associated with predialysis systolic blood pressure in 446 incident hemodialysis participants of the CHOICE Study. Those with cardiac troponin I (cTnI) 0.1 ng/mL or N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP) 9,252 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 10th, 50th and 90th 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.

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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^2)	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, x0.3229; SUN 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[1] (95% CI)
All-Cause Mortality		
Low cTnI and NT-proBNP	203	1.00 (reference)
High cTnI or NT-proBNP	120	1.75 (1.37–2.24)
CVD Mortality		
Low cTnI and NT-proBNP	76	1.00 (reference)
High cTnI or NT-proBNP	67	2.29 (1.55–3.38)
First CVD Event		
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.

[1]
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				0.01
Low cTnI and NT-proBNP	203	1.07 (1.01–1.14)	0.03	
High cTnI or NT-proBNP	120	0.99 (0.92–1.06)	0.7	
CVD Mortality				0.2
Low cTnI and NT-proBNP	76	1.10 (0.96–1.25)	0.2	
High cTnI or NT-proBNP	67	1.04 (0.98–1.11)	0.2	
First CVD Event				0.07
Low cTnI and NT-proBNP	167	1.04 (0.96–1.13)	0.4	
High cTnI 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 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.