N-Terminal Prohormone Brain Natriuretic Peptide as a Predictor of Cardiovascular Disease and Mortality in Blacks With Hypertensive Kidney Disease

The African American Study of Kidney Disease and Hypertension (AASK)

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Background—Higher levels of N-terminal prohormone brain-type natriuretic peptide (NT-proBNP) predict cardiovascular disease (CVD) in several disease states, but few data are available in patients with chronic kidney disease or in blacks.

Methods and Results—The African American Study of Kidney Disease and Hypertension trial enrolled hypertensive blacks with a glomerular filtration rate of 20 to 65 mL · min⁻¹ · 1.73 m² and no other identified cause of kidney disease. NT-proBNP was measured with a sandwich chemiluminescence immunoassay (coefficient of variation 2.9%) in 994 African American Study of Kidney Disease and Hypertension participants. NT-proBNP was categorized as undetectable, low, moderate, or high. Proteinuria was defined as 24-hour urinary protein-creatinine ratio >0.22. A total of 134 first CVD events (CVD death or hospitalization for coronary artery disease, heart failure, or stroke) occurred over a median of 4.3 years. Participants with high NT-proBNP were much more likely to have a CVD event than participants with undetectable NT-proBNP after adjustment (relative hazard 4.0 [95% confidence interval [CI] 2.1 to 7.6]). A doubling of NT-proBNP was associated with a relative hazard of 1.3 (95% CI 1.0 to 1.6) for coronary artery disease, 1.7 (95% CI 1.4 to 2.2) for heart failure, 1.1 (95% CI 0.9 to 1.4) for stroke, and 1.8 (95% CI 1.4 to 2.4) for CVD death. The association of NT-proBNP with CVD events was significantly stronger (Pinteraction = 0.05) in participants with than in those without proteinuria. Higher NT-proBNP was not associated with renal disease progression.

Conclusions—These results suggest that elevated NT-proBNP levels are associated with higher CVD risk among blacks with hypertensive kidney disease. This association may be stronger in individuals with significant proteinuria. (Circulation. 2008;117:1685-1692.)

Key Words: cardiovascular diseases ■ heart failure ■ hypertension, renal ■ kidney ■ natriuretic peptides

Individuals with chronic kidney disease (CKD) have an elevated risk of cardiovascular disease (CVD).¹-³ This increased risk is only partially explained by the prevalence of cardiovascular risk factors among these patients.⁴,⁵ Moderately decreased kidney function also is associated with increased left ventricular mass and prevalence of left ventricular hypertrophy,⁶ which strongly predict CVD, heart failure, and death among individuals with CKD.⁷

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The N-amino terminal fragment of the prohormone B-type natriuretic peptide (NT-proBNP) is released from myocytes in response to ventricular wall stretch and wall tension.⁸,⁹ As such, the circulating level of NT-proBNP serves as a sensitive marker of both left ventricular hypertrophy and volume expansion.¹⁰ Increased levels of NT-proBNP strongly predict...
mortality among patients with heart failure and acute coronary syndromes. More recently, higher NT-proBNP levels have been shown to predict cardiovascular events and mortality in the general population as well. Limited data also suggest that higher NT-proBNP levels predict progression of kidney disease. These study populations have been predominantly white, and it remains unclear whether the clinical significance of elevated NT-proBNP levels is similar in blacks.

NT-proBNP levels are elevated in individuals with reduced kidney function, although it remains unknown whether this is due solely to the increased left ventricular mass and prevalence of heart failure in this population or whether reduced clearance of NT-proBNP, volume overload, or other factors directly related to uremia may play a role. Studies in dialysis patients have found higher NT-proBNP levels to be highly predictive of cardiovascular events and mortality. Data on the predictive relevance of NT-proBNP levels among individuals with less severe forms of CKD are limited. Blacks have a much higher prevalence of left ventricular hypertrophy and larger mean left ventricular mass than whites, even after controlling for clinical and hemodynamic parameters. Nonetheless, data on the impact of elevated NT-proBNP among blacks with CKD are especially limited.

The purpose of the present study was to examine the relationship between NT-proBNP and subsequent cardiovascular events and renal disease progression in a population of blacks with hypertensive kidney disease.

Methods

The African American Study of Kidney Disease and Hypertension

The African American Study of Kidney Disease and Hypertension (AASK) was a multicenter randomized clinical trial designed to test the effectiveness of 3 antihypertensive drug regimens and 2 levels of (AASK) was a multicenter randomized clinical trial designed to test the effectiveness of 3 antihypertensive drug regimens and 2 levels of blood pressure control on the progression of hypertensive kidney disease. The trial enrolled 1094 self-identified blacks, aged 18 to 70 years, with hypertension and glomerular filtration rate (GFR) between 20 and 65 mL · min⁻¹ · 1.73 m⁻² and no other identified causes of renal insufficiency. The patients were enrolled from 21 clinical centers in the United States. Exclusion criteria included diastolic blood pressure <95 mm Hg, diabetes mellitus, serious systemic disease, and ejection fraction <35% or symptomatic heart failure. On the basis of a 3×2 factorial design, participants were randomized equally to a usual mean arterial pressure goal of 102 to 107 mm Hg or to a lower mean arterial pressure goal of ≥92 mm Hg and, by means of a 2:2:1 allocation ratio, to treatment with 1 of 3 antihypertensive drugs (a β-blocker, metoprolol; an angiotensin-converting enzyme inhibitor, ramipril; or a dihydropyridine calcium channel blocker,amlodipine). If the blood pressure goal could not be achieved by the randomized drug, additional open-labeled antihypertensive drugs were added sequentially (diuretics, β-blockers, and direct vasodilators). Participant enrollment began in February 1995 and ended in September 1998, and planned follow-up to the end of the study in September 2001 was 3 to 6.4 years; mean follow-up time was 4.3 years. On the recommendation of the data and safety monitoring board, the amlodipine arm was halted in September 2000, at which point patients randomized to amlodipine were switched to ramipril.

Measurement of Demographic, Biochemical, and Clinical Data

Information collected before randomization included a physical examination and data on lifestyle, education, family income, and history of CVD identified by self-report, chart review, and ECG reading. Twelve-lead ECGs were collected by clinical center personnel using customary techniques and were read by the local center investigator. Seated blood pressure was taken by trained, certified staff using Hawksley random-zero sphygmomanometers. GFR was measured twice before randomization by the renal clearance of subcutaneously injected 125I-labeled iothalamate. The mean of these 2 measurements was used for analysis. A 24-hour urine collection was performed on the day before the first prerandomization GFR measurement to ensure excretion of sodium, potassium, creatinine, and protein. Proteinuria was evaluated on the basis of the ratio of urinary protein to urinary creatinine. Proteinuria was defined as urinary protein–urinary creatinine ratio ≥0.22 (which corresponded to 24-hour urinary protein excretion of ≥0.3 mg/d). Because of the highly skewed distribution, urinary protein-creatinine was log-transformed for continuous analyses. The difference between total cholesterol and high-density lipoprotein (HDL) cholesterol was used as an estimate of low-density lipoprotein cholesterol level because low-density lipoprotein could not be evaluated in 251 patients at their baseline evaluation. NT-proBNP was measured on samples collected at baseline with an electrochemiluminescence sandwich immunoassay (Roche Diagnostics, Indianapolis, Ind; coefficient of variation 6.0%) at the Cleveland Clinic Foundation.

Cardiovascular Events

Cardiovascular outcomes were specified in the AASK protocol as a secondary end point of high priority. All potential cardiovascular hospitalizations were reviewed by the AASK Cardiovascular Outcome Committee using discharge summary and laboratory reports from these hospitalizations. Routine follow-up for nonfatal events was terminated after a participant reached end-stage renal disease (ESRD; n=153). CVD deaths after ESRD were reviewed and adjudicated. Two members of the Cardiovascular Outcome Committee reviewed each potential cardiovascular hospitalization, and if they were in agreement that a cardiovascular outcome had occurred, the case was classified as such. Otherwise, the full Outcome Committee reviewed the case and adjudicated the decision.

Cardiovascular outcomes of interest were coronary artery disease, heart failure, and stroke. Definite coronary artery disease was defined by clinical report of myocardial infarction with either enzymatic confirmation (elevation of creatine phosphokinase ≥2 times the upper limit of normal and a subsequent decrease in elevated creatine phosphokinase serum concentration of at least 50%, elevation of the MB fraction, or elevation of cardiac troponin I) or, in the absence of cardiac-specific enzymes, ECG evidence (the appearance of new pathological Q waves in 2 or more contiguous leads, or the appearance of an R wave with an R–S ratio in lead V₅ >1.0 in the absence of another explanation for these or a loss of progression of R waves in leads V₁ through V₅) or cardiac revascularization procedure such as CABG or percutaneous intervention (eg, angioplasty or percutaneous stent). Heart failure was defined by a clinical diagnosis during a hospitalization that necessitated therapy with an inotropic agent, vasodilator, angiotensin-converting enzyme inhibitor, increased dose of diuretic, ultrafiltration, or dialysis. Definite stroke was defined by clinical report of a permanent neurological deficit of ≥24 hours’ duration attributed to a stroke and confirmed by radiographic imaging. Probable stroke was defined as symptoms that lasted ≥24 hours without confirmation by radiographic imaging. The primary analyses were based on the composite outcome of any CVD event, defined by the occurrence of CVD death or the first CVD-related hospitalization after randomization. Deaths due to CVD were analyzed separately, as was each specific type of CVD event. Participants could be included in >1 type-specific analysis.

Renal Events

Renal disease progression was defined in AASK as the composite outcome of ESRD or a decline in GFR of ≥50% of baseline or ≥25 mL · min⁻¹ · 1.73 m⁻².
**Table 1. Baseline Characteristics of 983 AASK Participants by NT-proBNP Category**

| NT-proBNP Category | Overall (n=994) | Undetectable (n=204) | Low (n=362) | Moderate (n=214) | High (n=214) | P_min
|-------------------|----------------|---------------------|-------------|-----------------|--------------|---
| NT-proBNP, median (IQR), pg/mL | 154.5 (63, 447) | ... | 110 (77, 161) | 309 (232, 415) | 1124.5 (683, 2189) | ... |
| Age, y | 54.6 (10.6) | 53.4 (10.6) | 58.2 (8.7) | 51.9 (10.9) | 52.5 (11.4) | <0.001 |
| Female, % | 38.8 | 32.8 | 44.5 | 36.9 | 36.9 | 0.99 |
| GFR, mL · min⁻¹ · 1.73 m⁻² | 46.5 (13.6) | 54.3 (11.2) | 47.6 (12.6) | 44.3 (14.2) | 39.1 (12.3) | <0.001 |
| Urinary protein-creatinine ratio, median (IQR) | 0.08 (0.03, 0.36) | 0.03 (0.02, 0.09) | 0.06 (0.03, 0.23) | 0.12 (0.04, 0.54) | 0.24 (0.08, 0.69) | <0.001 |
| Proteinuria, % | 33.1 | 16.7 | 26.5 | 39.3 | 53.7 | <0.001 |
| Urinary sodium-potassium ratio | 2.3 (1.2) | 2.2 (1.1) | 2.2 (1.2) | 2.4 (1.2) | 2.4 (1.2) | 0.06 |
| Systolic blood pressure, mm Hg | 150.3 (24.0) | 141.3 (19.9) | 147.7 (23.0) | 150.8 (23.0) | 163.1 (25.1) | <0.001 |
| Diastolic blood pressure, mm Hg | 95.4 (14.4) | 93.6 (12.1) | 93.3 (13.2) | 95.3 (14.0) | 100.8 (17.4) | <0.001 |
| Non-HDL cholesterol, mg/dL | 163.4 (44.9) | 176.0 (41.8) | 163.1 (40.9) | 158.2 (48.1) | 156.3 (49.2) | <0.001 |
| Abnormal ECG, % | 80.4 | 71.6 | 74.9 | 84.1 | 94.4 | <0.001 |
| Body mass index, kg/m² | 30.6 (6.6) | 31.5 (6.3) | 30.4 (6.3) | 30.5 (6.9) | 30.3 (7.0) | 0.10 |

IQR indicates interquartile range. Values expressed as mean (SD) unless otherwise specified. *Proteinuria defined as urinary protein-creatinine ratio >0.22.

**Statistical Analyses**

Study participants were categorized by NT-proBNP levels as undetectable (below the minimally detectable limit of 50 pg/mL; n=204), low (≥50 pg/mL but below the upper reference limits, which were 88 and 153 pg/mL in men and women <50 years old, respectively, or 227 and 334 pg/mL in men and women ≥50 years old, respectively; n=362), moderate (above the upper reference limits but below the sex-specific medians of such values, which were 472 and 565 pg/mL in men and women, respectively; n=214), or high (≥472 and ≥562 pg/mL in men and women, respectively; n=214). Other analyses considered NT-proBNP as a continuous variable and modeled associations with a doubling of NT-proBNP. For these analyses, levels below the minimally detectable limit of 50 pg/mL were set to 25 pg/mL. Participant characteristics were compared across NT-proBNP categories by χ² tests or linear regression models, with tests for linear trends as appropriate. Event-free survival time was calculated from randomization to the occurrence of the first CVD event or a censoring event (eg, withdrawal, non-CVD death, or end of the study). Incidence rates were compared by Kaplan–Meier curves and log-rank tests. Associations between NT-proBNP levels and composite CVD outcome were tested by multivariable Cox proportional hazards models. Tests for trends assumed linearity across NT-proBNP categories. All multivariable models were adjusted for age, sex, baseline GFR, log urinary protein-creatinine, systolic and diastolic blood pressure, urinary sodium-potassium, non-HDL cholesterol, abnormal ECG, body mass index, and randomization group assignment.

Analyses were repeated for each type of CVD event and for CVD death separately, as well as after stratification by sex, age (≤55 or >55 years), GFR (<45 or ≥45 mL · min⁻¹ · 1.73 m⁻²), presence of proteinuria (urinary protein-creatinine ratio ≤0.22 or >0.22), and randomized treatment assignment (antihypertensive medication and blood pressure goal). Interactions between these stratification variables and doubling of NT-proBNP were also tested in multivariable models. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

A total of 1006 (92%) of the 1094 AASK participants had NT-proBNP levels available, of whom 12 had missing information on other covariates. Of the remaining 994 participants, 204 had an NT-proBNP level below the minimally detectable limit (<50 pg/mL). Greater NT-proBNP levels were significantly associated with younger age, lower GFR, greater urinary protein excretion, greater systolic and diastolic blood pressure, lower non-HDL cholesterol, greater prevalence of abnormal ECG findings, and lower body mass index (Table 1). The correlation between GFR and NT-proBNP was −0.21 (P<0.001). The correlation between GFR and log(NT-proBNP) was −0.39 (P<0.001).

**Association of NT-proBNP With Any CVD Event**

A total of 134 CVD events occurred over a median follow-up of 4.3 years. Individuals with high and moderate NT-proBNP levels were much more likely to have a cardiovascular event than those with undetectable NT-proBNP (Figure 1). The incidence rate of CVD events was 3.34 per 100 person-years (Table 2). The incidence rate of CVD events among the 214 participants with high NT-proBNP levels was 6.53 per 100 person-years, which was >3 times higher than for those with...
undetectable NT-proBNP. This association remained after adjustment for age, sex, baseline GFR, log urinary protein–creatinine, systolic and diastolic blood pressure, urinary sodium–potassium ratio, non-HDL cholesterol, abnormal ECG, body mass index, and randomization group assignment. After adjustment, participants with moderate NT-proBNP levels had a relative hazard (RH) of 1.80 (95% CI 0.93 to 3.48), and those with high NT-proBNP levels had an RH of 4.04 (95% CI 2.14, 7.64). A doubling of NT-proBNP was associated with an RH of 1.44 (95% CI 1.26 to 1.64) for any CVD event \((P<0.001)\).

Association of NT-proBNP Level With Specific CVD Events

Estimates of the association of NT-proBNP category with specific CVD events were based on far fewer events (Table 2); nonetheless, trends were evident for several outcomes. The associations of NT-proBNP category with heart failure \((n=45\) events) were extremely strong (RH=7.56 [95% CI 2.04 to 27.94] for the highest NT-proBNP category). Those participants in the highest NT-proBNP category had an RH for coronary artery disease \((n=36\) events) of 2.97 (95% CI 0.94 to 9.38) and an RH for stroke \((n=50\) events) of 1.66 (95% CI 0.61 to 4.53). NT-proBNP category also was strongly associated with fatal CVD events \((n=29;\) RH=18.79 [95% CI 2.25 to 157.04] for the highest NT-proBNP category). A doubling of NT-proBNP was associated with an RH of 1.26 (95% CI 0.97 to 1.63) for coronary artery disease, 1.74 (95% CI 1.39 to 2.19) for heart failure, 1.14 (95% CI 0.92 to 1.43) for stroke, and 1.81 (95% CI 1.37 to 2.39) for CVD death.

Association of NT-proBNP Level With Renal Disease Progression

A total of 160 participants reached ESRD. An additional 87 participants reached the GFR-based end point (ie, decrease of ≥50% from baseline or decrease ≥25 mL·min\(^{-1}·1.73\text{m}^2\)). The incidence rate for these events combined was 6.22 per 100 person-years (Table 2). The incidence rate was 8.31 per 100 person-years among those with high NT-proBNP levels compared with 3.50 among those with undetectable levels \((P<0.001)\). This association, however, was no longer present after adjustment for either baseline GFR or proteinuria. After full adjustment, a doubling of NT-proBNP was associated with an RH of 0.97 (95% CI 0.86 to 1.10) for renal disease progression \((P=0.58)\). Similar results were found for analyses of the time to ESRD only (RH=0.97 [95% CI 0.86 to 1.10]).

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<th>Table 2. Incidence of Cardiovascular Events and Renal Disease Progression by NT-proBNP Category</th>
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<td><strong>NT-proBNP Category</strong></td>
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*Adjusted for age, sex, baseline GFR, log urinary protein-creatinine, systolic and diastolic blood pressure, urinary sodium-potassium, non-HDL cholesterol, abnormal ECG, body mass index, and randomization group assignment.
Stratified Analyses

Associations of NT-proBNP with any CVD events were generally similar in analyses stratified by sex, age, and baseline GFR (Table 3). The association of NT-proBNP category was stronger among participants with proteinuria than among those with less protein excretion ($P_{interaction}$ for trend across categories = 0.003; Figure 2). Among those with proteinuria, moderate and high NT-proBNP categories were associated with RHs of 9.87 (95% CI 1.23 to 79.32) and 15.85 (95% CI 2.02 to 124.16), respectively. Corresponding RHs for those without proteinuria were 1.04 (95% CI 0.46 to 2.34) and 2.62 (95% CI 1.22 to 5.62). A doubling of NT-proBNP was associated with an RH of any cardiovascular event of 1.81 (95% CI 1.45 to 2.27) among those with proteinuria and an RH of 1.26 (95% CI 1.07 to 1.50) among those without proteinuria ($P_{interaction}$ = 0.05). Compared with individuals with undetectable NT-proBNP and without proteinuria, those in the highest NT-proBNP category with proteinuria had an adjusted RH of 4.85 (95% CI 2.36 to 9.99) for any CVD event (Figure 2). No evidence was present of significant interactions with any of the randomization groups. A doubling of NT-proBNP was associated with a significantly higher risk for all CVD events for each of the study drugs (all $P<0.02$) and for both blood pressure goals (both $P<0.001$). No significant interactions existed across any of the subgroups for the association of NT-proBNP with renal disease progression.

Discussion

We found a strong association between higher NT-proBNP level and incidence of cardiovascular events in a cohort of blacks with hypertensive kidney disease. The association was especially strong for incident heart failure and CVD death and was stronger among participants with proteinuria (urinary protein-creatinine ratio $>0.22$). We found no association between NT-proBNP level and risk of renal disease progression after adjustment for other risk factors. To the best of our knowledge, this is the largest study of the association of NT-proBNP levels with cardiovascular risk among patients with CKD and among blacks. The AASK study included extensive data collection, thorough participant follow-up over $>4$ years, and systematic review of all CVD events. Blood pressure was strictly controlled, and antihypertensive medications remained relatively constant during follow-up.

The present study is limited by the relatively small number of CVD events of any 1 type; nonetheless, the analyses of 45 incident heart failure events and 29 CVD deaths showed very strong associations of higher NT-proBNP levels with increasing risk. The association with coronary artery disease (n=36 events) was weaker. Another limitation arises from the definition of coronary artery disease, which was based on total creatine phosphokinase in some cases rather than the current guidelines that require MB fraction and cardiac troponins to define myocardial infarction. We also are limited by the lack of information on nonfatal CVD events that occurred after study participants reached ESRD. We expect, however, that this potential misclassification would bias our results toward the null, because we do not expect a different association between NT-proBNP and CVD among individuals who reach ESRD before experiencing a CVD event. Another limitation is the lack of study participants with causes of CKD other than hypertension, such as diabetes mellitus. Others have found, however, that NT-proBNP also strongly predicts all-cause and CVD-related mortality in individuals with type 2 diabetes mellitus.26

Several previous studies have found that higher levels of NT-proBNP predict cardiovascular events in patients with heart failure, in older individuals, and in patients on dialy-
Data on individuals with moderate kidney disease, however, are scarce and come primarily from cross-sectional studies. Vickery et al. showed that echocardiographically defined left ventricular hypertrophy were independently associated with NT-proBNP levels among individuals with stage 3 to 5 CKD. In that study, estimated GFR was independently associated with NT-proBNP. This finding was confirmed in a study of individuals across a wide range of kidney function levels. Prospective data from individuals with CKD are especially limited. In a study of 171 individuals with CKD, primarily stage 3 or 4, individuals with NT-proBNP above the median of 1250 pg/mL were more likely to reach the end point of cardiac hospitalization or mortality. In a study of 83 CKD patients without heart failure, the 10 who had a CVD event or died during follow-up had higher NT-proBNP levels than their counterparts. Takami et al. found that higher plasma BNP predicted incident heart failure among 103 non–diabetes-dependent patients with severe CKD (mean creatinine clearance 15 mL/min). Our findings add to these previous studies in that the present study comprised a much larger sample size, a larger number of events, and longer follow-up and provided needed data on the impact of NT-proBNP in blacks with less severe CKD.

Higher NT-proBNP predicted mortality independent of albuminuria status in previous studies. The present findings, however, suggest that the association of elevated NT-proBNP levels with cardiovascular risk is stronger among individuals with than among those without significant proteinuria. A doubling of NT-proBNP was associated with 81% higher risk among those with proteinuria. It is unsurprising that individuals with proteinuria were at greatest risk, but the reasons for the apparent interaction of proteinuria with NT-proBNP are unclear. Intravenous infusion of BNP has been shown to increase urinary albumin excretion in previously normalalbuminuric individuals, which suggests that higher proteinuria among those with elevated NT-proBNP may be a marker of past NT-proBNP levels, susceptibility to the effects of elevated NT-proBNP, or a secondary indicator that decreases any misclassification of NT-proBNP category. We are limited by sample size in our ability to explore whether proteinuria modifies the association of NT-proBNP with cardiovascular risk is stronger among blacks with hypertension and kidney disease. The interaction of elevated NT-proBNP with proteinuria warrants further investigation.

Conclusions

Higher NT-proBNP levels were strongly associated with greater risk of cardiovascular events and cardiovascular mortality in a population of blacks with hypertensive kidney disease. The interaction of elevated NT-proBNP with proteinuria warrants further investigation.

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Disclosures

None.

References


Individuals with chronic kidney disease are at an elevated risk of adverse cardiovascular outcomes. This study found that among hypertensive blacks with a glomerular filtration rate of 20 to 65 mL · min⁻¹ · 1.73 m⁻² and no other identified cause of kidney disease, higher levels of N-terminal prohormone brain-type natriuretic peptide strongly predicted the occurrence of coronary artery disease, heart failure, and cardiovascular death. These results extend previous findings demonstrating that N-terminal prohormone brain-type natriuretic peptide was a cardiovascular risk marker for blacks and for individuals with chronic kidney disease in whom it had been suggested that N-terminal prohormone brain-type natriuretic peptide may not be predictive of future events because of confounding by reduced renal clearance. Higher N-terminal prohormone brain-type natriuretic peptide levels did not predict progression of renal disease.
N-Terminal Prohormone Brain Natriuretic Peptide as a Predictor of Cardiovascular Disease and Mortality in Blacks With Hypertensive Kidney Disease: The African American Study of Kidney Disease and Hypertension (AASK)


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