Journal of the American College of Cardiology Vol. 49, No. 22, 2007

Published by Elsevier Inc.
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.02.047

Glomerular Filtration Rate and N-Terminal Pro-Brain Natriuretic Peptide as Predictors of Cardiovascular Mortality in Vascular Patients

Ramin Shadman, MD, Matthew A. Allison, MD, MPH, Michael H. Criqui, MD, MPH

San Diego, California

Objectives The purpose of this work was to assess the prognostic role of glomerular filtration rate (GFR) and NT-terminal pro-B-type natriuretic peptide (NT-proBNP) for mortality end points in the vascular population.

Background The GFR and NT-proBNP have been shown to predict mortality end points in free-living and limited vascular populations, independent of traditional risk factors. However, their prognostic power in an unrestricted vascular population is poorly understood.

Methods A total of 412 subjects from a vascular cohort with a history of either peripheral arterial disease (PAD) and/or other cardiovascular disease (CVD) were included in this prospective cohort analysis and followed for an average of 6.7 years. Outcome variables were all-cause mortality, ischemic heart disease (IHD) mortality, and any cardiovascular mortality. The prognostic roles of GFR and NT-proBNP levels were determined using multivariate survival analysis.

Results Higher GFR (per 10 ml/min/1.73 m^2) was significantly protective for all-cause mortality (hazard ratio [HR] 0.81, $p < 0.001$), IHD mortality (HR 0.82, $p = 0.008$), and CVD mortality (HR 0.84, $p = 0.005$). Conversely, NT-proBNP was not a significant predictor of any mortality end point. The GFR showed the strongest association in subjects with a history of other CVD. Although NT-proBNP did not demonstrate a significant prognostic role in any of the subgroups, the data were suggestive for patients with PAD alone.

Conclusions Glomerular filtration rate was a robust predictor of all-cause, IHD, and cardiovascular mortality in the vascular population, particularly in those with a history of other CVD, while NT-proBNP showed a suggestive association limited to the group with PAD only. These findings suggest that these markers must be selectively applied in the vascular population for greatest clinical utility. (J Am Coll Cardiol 2007;49:2172–81) © 2007 by the American College of Cardiology Foundation

Peripheral arterial disease (PAD) affects approximately 8 million individuals in the U.S., and its presence has been shown to convey an increased risk of mortality and future cardiovascular events (1–4). However, in the clinical setting, relatively little is known about novel risk factors for cardiovascular mortality in vascular patients with a high prevalence of PAD. In particular, the measurement of renal function and B-type natriuretic peptide (BNP) have both received increasing interest in recent years because of the ease of their measurement in the clinical setting and their demonstrated prognostic power in free-living and some clinical populations (5–12).

B-type natriuretic peptide is a peptide hormone that is released from the cardiac ventricle as a result of myocyte stretch and is predominantly cleared by the kidneys. It has been postulated and widely believed that in response to increased intravascular volume, there is increased ventricular wall stretch and release of BNP into the circulation, where it has numerous systemic effects including vasodilatation, natriuresis, and inhibition of both the sympathetic nervous system and renin-angiotensin-aldosterone system (9). Importantly, numerous studies have demonstrated that BNP is a robust predictor of all-cause and cardiovascular (CVD) mortality in various free-living and patient populations (6,7,9,12–15). Similarly, the relationship between glomerular filtration rate (GFR), all-cause mortality, and cardiovascular mortality has been demonstrated in the general population and in patients with critical leg ischemia (10,11,16–18). Various mechanistic theories for the accelerated vascular disease in patients with renal impairment have been postulated, including endothelial dysfunction, reduced endothelial

From the University of California San Diego, San Diego, California. Peter A. McCullough, MD, served as Guest Editor for this paper.

Manuscript received October 10, 2006; revised manuscript received February 1, 2007, accepted February 6, 2007.

antioxidant capacity, dyslipidemia, and chronic inflammatory activity (19–21).

To date, there is relatively limited understanding of the utility of these 2 prognostic factors in patients with known vascular disease. Prior studies have been limited by absent or incomplete adjustment for renal function, which can dramatically affect BNP levels, the exclusion of subsets of the vascular patient population with relatively common conditions, such as those with congestive heart failure (CHF), short follow-up periods, or analyses failing to stratify patients according to the nature of their vascular disease history (7,22–24). Hence, we designed this study to better examine the role of GFR and BNP in predicting cardiovascular and all-cause mortality in patients with a history of known vascular disease.

Methods

Study population. The participants in this study included 412 patients who had visited the San Diego Veterans Administration Medical Center or the University of California, San Diego Medical Center vascular laboratories between 1990 and 1994 (25). Inclusion criteria included a history of either "PAD," defined by an ankle-brachial index (ABI) ≤0.90 or >1.4 in either leg or prior surgery/angioplasty for PAD in either leg, or "other CVD," defined by a history of myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass graft surgery, transient ischemic attack, or cerebrovascular accident. This ABI threshold has been shown to be 80% sensitive and 97% specific for angiographically diagnosed PAD. The ABI for each leg was determined using the measured ankle systolic pressure, determined by sphygmomanometric technique with detection at the toe by photoplethysmography, divided by the highest brachial blood pressure between the 2 arms. Patients were not included if they could not be located to complete the initial interview or refused participation. Of the 2,265 potential candidates for the study, 481 were deceased and 1,276 could not be located or declined invitation. Among the remaining subjects, 412 subjects fulfilled the inclusion criteria for the study.

After informed consent, subject information concerning demographic data, risk factors, and previous and current vascular disease was determined by standardized subject interview, medical record review, primary care physician questionnaire, physical examination, and blood sample collection. Participants provided written consent for participation in the studies and the use of their data for future research. Institutional review board approval was obtained from the University of California, San Diego.

Laboratory methods. At the baseline evaluation, blood samples were collected from subjects into tubes containing ethylenediaminetetraacetic acid. Blood chemistries were performed at the time of collection using standardized laboratory tests with the remainder of the blood being stored at −70°C. The concentration of high-density lipoprotein (HDL) cholesterol was determined using a direct enzymatic colorimetric assay (26). The frozen samples were thawed in 2004 and analyzed for plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels using a chemiluminescence sandwich immunoassay technology in array format (Pierce SearchLight, Rockford, Illinois). Intra-assay and interassay precision was 6.6% and 15%, respectively. The linear range of detection of this assay was 22 to 12,500 pg/ml. Plasma creatinine levels were determined using a kinetic Jaffe method (Hitachi 917, Roche Pharmaceuticals, Basel, Switzerland). Plasma GFR was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) formula, which uses serum creatinine, age, and race. The MDRD formula has been shown to be a more accurate indicator of true renal function, rather than using a proxy such as serum creatinine alone, and should particularly be used in populations with significant renal insufficiency (27–29).

Abbreviations and Acronyms

ABI = ankle-brachial index
ACE = angiotensin-converting enzyme
BNP = B-type natriuretic peptide
CHF = congestive heart failure
CVD = cardiovascular disease
GFR = glomerular filtration rate
HDL = high-density lipoprotein
HR = hazard ratio
ICD-9 = International Classification of Diseases, Ninth Revision
IHD = ischemic heart disease
MDRD = Modification of Diet in Renal Disease
NT-proBNP = N-terminal pro-B-type natriuretic peptide
PAD = peripheral arterial disease

Mortality ascertainment. The subjects were followed for an average of 6.7 years until they either died or the end of the study period on December 31, 2001. A certified nosologist examined death certificates of all the subjects who died and coded their underlying and contributing cause of death by International Classification of Diseases-Ninth Revision (ICD-9) code. Mortality from ischemic heart disease (IHD) was defined using the ICD-9 code range of 410-414, and mortality from any CVD was defined as ICD-9 code range of 410-414 or 420-438.

Statistical methods. For purposes of analysis, in addition to the analysis of the whole population, 3 subgroups were defined: those with a history of other CVD and without PAD, those with a history of PAD and without other CVD, and those with a history of both PAD and other CVD. The subgroup of subjects with both PAD and other CVD histories was the reference group for comparisons. We compared baseline descriptive characteristics across subgroups using *t* test for normally distributed continuous variables and a chi-square test for categorical variables. Additionally, mean NT-proBNP and GFR levels between the subgroups were compared using 1-way analysis of variance (ANOVA) tests. Significance was determined as p value <0.05.

The association between predictor variables and mortality end points was evaluated using Cox regression analyses. The NT-proBNP levels were log-transformed to improve normality of distribution in the model. Covariates that were included in the model were based on Framingham criteria for cardiovascular risk assessment outlined in the NCEP-ATPIII (National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults) panel report: age, gender, total cholesterol, HDL cholesterol, whether the subject was a current smoker, the systolic blood pressure, and whether they were currently taking antihypertensive medication (30). We also controlled for diabetes and the use of medications for dyslipidemia.

The NT-proBNP measurement was missing for 1 subject (0.2%), and calculated GFR measurement could not be performed due to missing information in 9 subjects (2.1%). To further characterize whether a threshold level existed for these prognostic variables, regression analyses were performed using stratified NT-proBNP and GFR levels. To increase comparability with prior studies, we examined whether the prognostic relationship varied by follow-up time: 3 years, 5 years, or the full study duration (average 6.7 years). All analyses were performed using SPSS statistical software 14.0 (SPSS Inc., Chicago, Illinois).

Results

The characteristics of the entire study population in addition to the characteristics of the three previously defined subgroups of patients are shown in Table 1. The population was predominantly non-Hispanic white men. A significant proportion of subjects were active smokers (31%), had diabetes mellitus (32%), had elevated systolic blood pressures (mean 144 mm Hg), or had borderline elevated total cholesterol (mean 209 mg/dl). Sixty-one percent had a history of other CVD, 86% had a history of PAD, and 47% had a history of both conditions. The subgroup of patients with other CVD alone had significantly less active smokers, lower systolic blood pressure, and a lower mean total cholesterol than patients who had a history of both other CVD and PAD. Twelve percent were taking an angiotensin-converting enzyme (ACE) inhibitor, 19% were taking a diuretic, and 48% were taking aspirin. Similarly, patients with PAD alone had significantly less use of antihypertensive medications and higher HDL levels than the reference group. Similar proportions of patients were using the aforementioned medications. There was a significant difference in the mean GFR levels (± SD) between the 3 subgroups of the population: other CVD and PAD population (54 ± 15 pg/ml), other CVD only population (58 ± 15 pg/ml), PAD only population (59 ± 15 pg/ml)

Table 1 Baseline Characteristics Stratified by Total Population and Subgroups

Characteristic*	Total Population (n = 412)	Both PAD and Other CVD History (n = 193)	Only Other CVD History (n = 58)	Only PAD History (n = 161)
Age (yrs), mean ± SD	69 ± 9	70 ± 9	69 ± 9	69 ± 9
Men	369 (90%)	177 (92%)	51 (88%)	141 (88%)
Non-Hispanic white	358 (86.9%)	173 (89.6%)	51 (87.9%)	134 (83.2%)
Current cigarette smoker	126 (31%)	60 (31%)	8 (14%)†	58 (36%)
Systolic blood pressure (mm Hg), mean ± SD‡	144 ± 22	147 ± 23	135 ± 19†	144 ± 21
Currently taking medication for hypertension	263 (64%)	147 (76%)	36 (62%)	80 (50%)†
ACE inhibitor use	72 (18%)	39 (20%)	7 (12%)	26 (16%)
Diuretic use	110 (27%)	64 (33%)	11 (19%)†	35 (22%)†
Aspirin use	223 (54%)	125 (65%)	28 (48%)†	70 (44%)†
Total cholesterol (mg/dl), mean ± SD	209 ± 42	210 ± 42	202 ± 41§	211 ± 42
HDL cholesterol (mg/dl), mean ± SD	46 ± 13	44 ± 12	46 ± 12	48 ± 15†
Currently taking medication for cholesterol	87 (21%)	44 (23%)	11 (19%)	32 (20%)
Diabetes mellitus	131 (32%)	64 (33%)	19 (33%)	48 (30%)
History of other cardiovascular disease	251 (61%)			
History of peripheral arterial disease	354 (86%)			
Glomerular filtration rate (ml/min/1.73 m^2), mean ± SD§	56 ± 15	54 ± 15	58 ± 15	59 ± 15†
NT-proBNP (pg/ml), mean ± SD	510 ± 810	490 ± 589	411 ± 262	570 ± 1,110
Mortality‖				
Time to mortality or study completion (days), mean ± SD	2,442 ± 1,197	2,236 ± 1,199	2,579 ± 1,180	2,638 ± 1,168†
All-cause mortality	254 (62%)	133 (69%)	32 (55%)	89 (55%)†
Ischemic cardiac death	128 (31%)	80 (42%)	16 (28%)	32 (20%)†
Cardiovascular death	207 (50%)	123 (64%)	22 (38%)†	62 (39%)†

*History of peripheral arterial disease (PAD) (ankle-brachial index ≤0.9 or >1.4 or previous PAD surgery); history of other cardiovascular disease (CVD) (history of myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass graft surgery, transient ischemic attack, or cerebrovascular accident); †$p < 0.05$ when compared patients with both PAD and other CVD histories; a *t* test was used for normally distributed continuous variables and a chi-square test for categorical variables; ‡measured in the highest arm; §calculated using the Modification of Diet in Renal Disease formula; ‖ischemic cardiac death (ICD-9 code 410-414); any cardiovascular death (ICD-9 code 410-414 or 420-438).

ACE = angiotensin-converting enzyme inhibitor; HDL = high-density lipoprotein; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

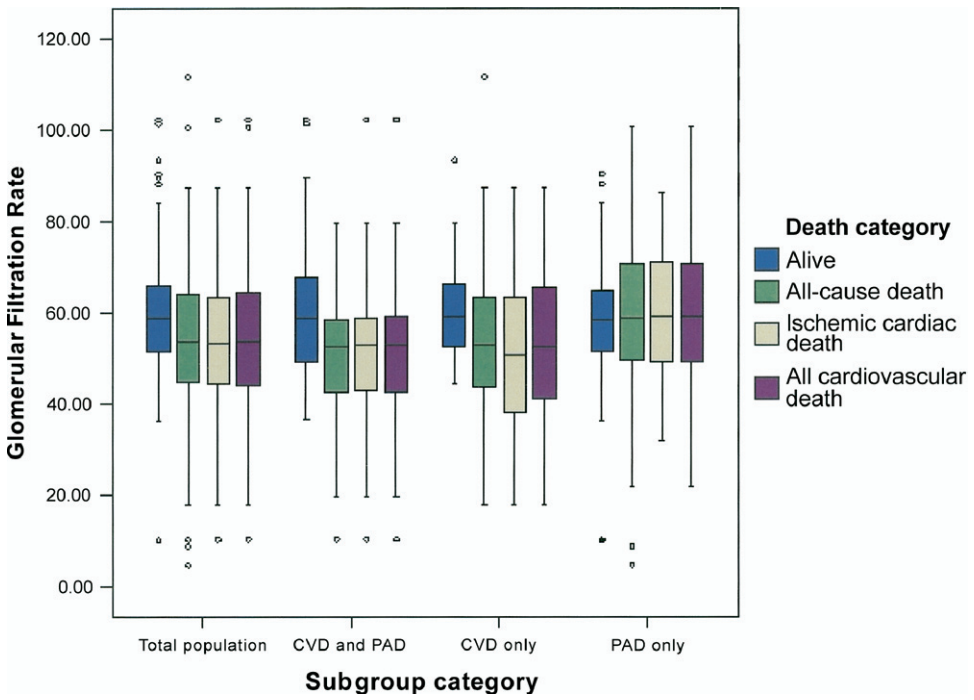

Figure 1 Glomerular Filtration Rate According to Population Subgroup and Cause of Death

Boxes show the 25th and 75th percentile with the mean shown. **Whiskers** represent 1.5 times the interquartile range. Glomerular filtration rate calculated based on the Modification of Diet in Renal Disease formula (ml/min/1.73 m^2). Ischemic cardiac death (International Classification of Diseases [ICD]-9 code 410-414); cardiovascular death (ICD-9 code 410-414 or 420-438). CVD = history of nonperipheral arterial disease cardiovascular disease; PAD = history of lower extremity peripheral arterial disease.

($p = 0.01$). The NT-proBNP levels showed no significant difference between subgroups.

Figure 1 shows the distributions of GFR levels between the subgroups as well as information on mortality for these groups. In the overall population, the mean GFR (± SD) was 56 ± 15 ml/min/1.73 m^2. The population who died from any cause had significantly worse renal function than those who did not die (54 ml/min/1.73 m^2 vs. 60 ml/min/1.73 m^2, respectively, $p < 0.001$). Similarly, those who remained alive had significantly higher GFR than those who died of IHD (53 ml/min/1.73 m^2, $p < 0.001$) and those who died of any cardiovascular event (53 ml/min/1.73 m^2, $p < 0.001$). A similar significant relationship was seen in the subgroups with other CVD alone or with other CVD and PAD.

The NT-proBNP levels were also stratified between subgroups and according to cause of death (Fig. 2). In the overall population, the mean NT-proBNP level (± SD) was 510 ± 810 pg/ml. There was no significant difference in the mean NT-proBNP levels between those who were alive (479 pg/ml) and those who died of any cause (530 pg/ml), died of IHD (466 pg/ml), or died of any cardiovascular event (479 pg/ml). In the subgroup analysis, there was no significant difference in ln(NT-proBNP) levels between the subgroups of the population. Additionally, there was a nonsignificant difference when ln(NT-proBNP) was stratified by GFR category: <45 (5.69), 45 to 59 (5.97), and ≥60 ml/min/1.73 m^2 (5.93) ($p = 0.053$ by ANOVA). There was a weakly positive and suggestive correlation between calculated GFR and NT-proBNP using Spearman's rank order correlation (r 0.084, R^2 0.0071, $p = 0.094$) as shown in Figure 3. As shown in this scatterplot stratified by subgroup and mortality, at GFR levels below the mean, there was a higher overall mortality within the other CVD/PAD and other CVD only subgroups. However, within the PAD only subgroup, mortality was more evenly distributed around the mean GFR. Additionally, higher mortality above the mean ln(NT-proBNP) level was limited to the PAD only subgroup.

Table 2 shows the hazard ratio (HR) for all-cause mortality, death from IHD, and death from any cardiovascular event for NT-proBNP (per log unit) and GFR (per 10 ml/min/1.73 m^2) in the whole vascular population as well as its subgroups. In this vascular cohort, GFR was significantly predictive of all-cause mortality (HR 0.81, $p < 0.001$), ischemic cardiac death (HR 0.82, $p = 0.008$), and any cardiovascular death (HR 0.84, $p = 0.005$). In patients with other CVD, GFR was predictive for all-cause mortality (HR 0.67, $p = 0.049$), IHD death (HR 0.38, $p = 0.011$), and all cardiovascular death (HR 0.61, $p = 0.063$). Additionally, in patients with a history of both other CVD and PAD, GFR was significantly predictive of all-cause mortal-

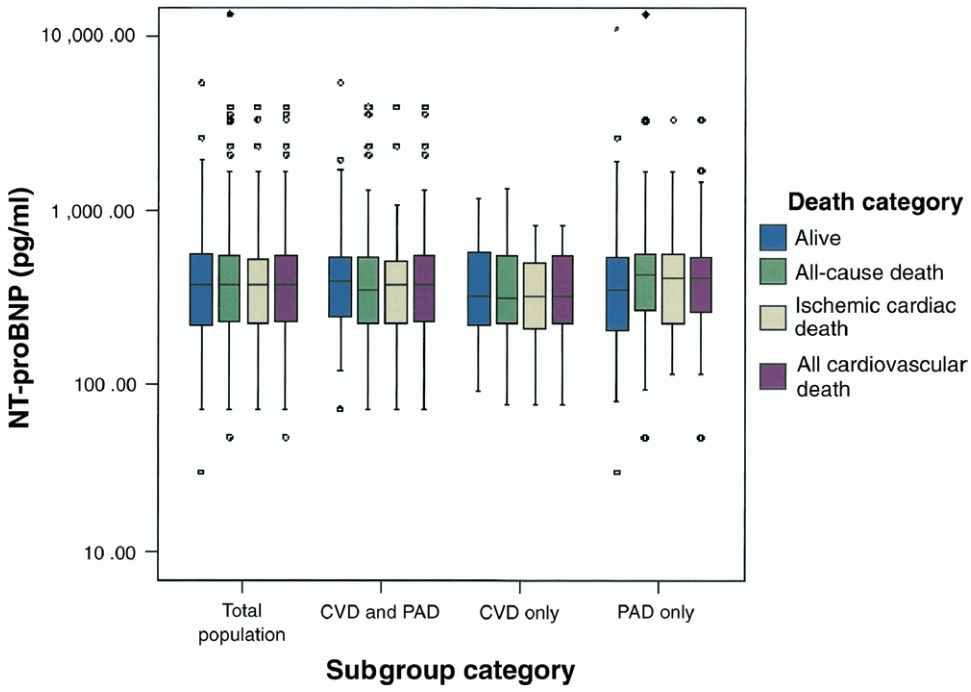

Figure 2 NT-proBNP Levels According to Population Subgroup and Cause of Death

Boxes show the 25th and 75th percentile with the mean shown. **Whiskers** represent 1.5 times the interquartile range. Ischemic cardiac death (ICD-9 code 410-414); cardiovascular death (ICD-9 code 410-414 or 420-438). NT-proBNP = N-terminal pro-B-type natriuretic peptide; other abbreviations as in Figure 1.

ity (HR 0.79, p = 0.003), IHD death (HR 0.82, p = 0.042), and all cardiovascular death (HR 0.84, p = 0.025). As demonstrated in Figure 4, using pairwise log-rank comparisons of Kaplan-Meier survival curves, a significant difference in cumulative survival was demonstrated between each GFR category for all-cause mortality. A significant difference in survival was seen between the lowest GFR category and the 2 higher GFR categories for ischemic cardiac mortality and any cardiovascular mortality.

Furthermore, after controlling for risk factors and renal function, NT-proBNP as a continuous variable was not a significant predictor of all-cause mortality, ischemic cardiac death, or any cardiovascular death in this vascular population. In subgroup analyses, NT-proBNP levels showed an association in patients with a history of PAD only: all-cause mortality (HR 1.30, p = 0.054), ischemic cardiac death (HR 1.47, p = 0.103), or any cardiovascular death (HR 1.21, p = 0.277) (Table 2). In patients who had other CVD, either alone or with PAD, NT-proBNP was not significantly protective of any of the outcome variables. No significant threshold was found between tertiles of NT-proBNP and all-cause mortality, ischemic cardiac mortality, or any cardiovascular mortality. Kaplan-Meier survival analysis did not show a significant difference between tertiles of NT-proBNP in cumulative all-cause mortality, ischemic cardiac death, or any cardiovascular death.

On repeat analysis using 3- and 5-year cutoff periods, there were no notable changes in the prognostic relationship between either GFR or NT-proBNP and the 3 outcome variables. The relationships found in the full-length subgroup analyses were similar as well.

Discussion

The utility of GFR and BNP in predicting all-cause and cardiovascular mortality has been examined in a variety of populations, including limited vascular cohorts. However, prior studies have exhibited various shortcomings, such as excluding patients with CHF, having limited follow-up duration, and not fully stratifying by prior cardiovascular history, which has limited their applicability to a clinical vascular population. To our knowledge, this study is the first to demonstrate, in an unrestricted vascular population stratified by the presence of PAD or other CVD, the association of GFR and NT-proBNP levels with long-term all-cause mortality, ischemic cardiac mortality, and mortality from any cardiovascular cause.

Primary outcome analysis. The relationship between GFR and all-cause mortality, specifically in populations with severe vascular disease, has been established. O'Hare et al. (11) established in a large cohort of veterans with critical leg ischemia that GFR (estimated by the MDRD formula) was significantly predictive of 1-year all-cause

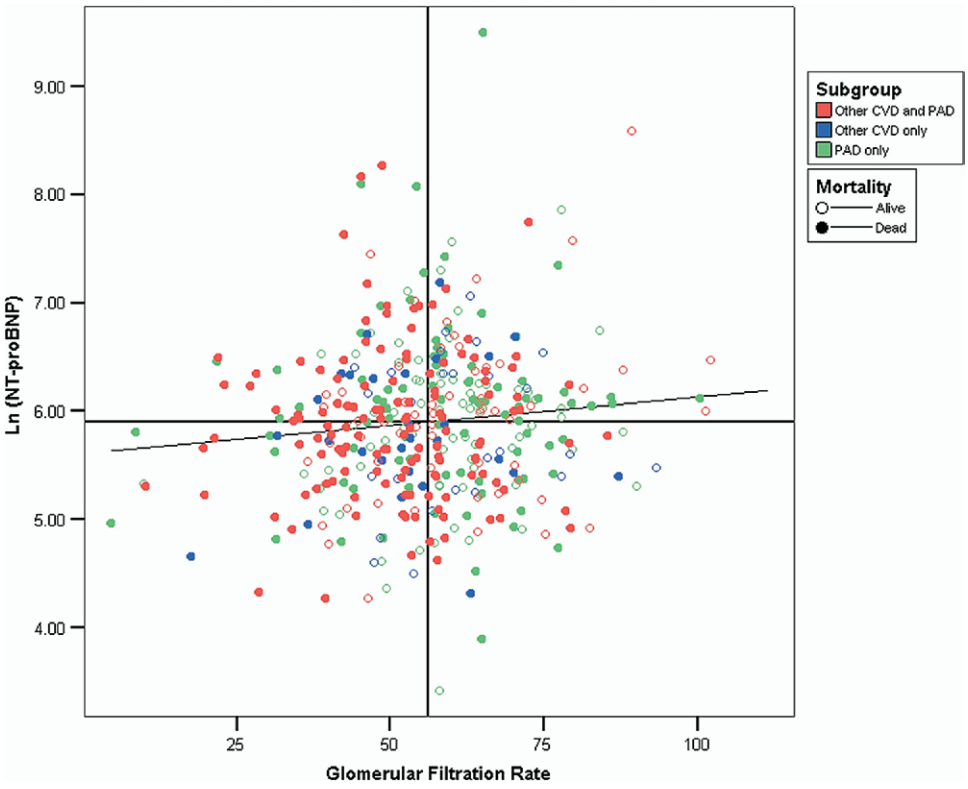

Figure 3 Correlation Between NT-proBNP and Glomerular Filtration Rate According to Subgroup and Mortality

The linear regression equation for the entire population is ln(NT-proBNP) = 5.61 + 0.01 (glomerular filtration rate) and shown in the **graph** ($r = 0.104$, $R^2 = 0.011$, $p = 0.038$ by Pearson correlation). Linear regression equations for subgroups did not differ significantly. The **vertical line** represents the mean glomerular filtration rate and the **horizontal line** represents the mean ln(NT-proBNP) level. Abbreviations as in Figures 1 and 2.

mortality after controlling for confounders. Patients with a GFR <30 had nearly triple the risk of mortality than those with GFR ≥60. Furthermore, despite the coexistence of diabetes and hypertension in populations with renal dysfunction, the independent prognostic power of GFR has been demonstrated previously in the PAD population (10). Our study confirmed the relationship of lower GFR and increased all-cause mortality in a population with a wide range of vascular disease severity. Additionally, we demonstrated that patients with progressive renal dysfunction are at a significantly increased risk of cardiovascular death and specifically ischemic cardiac death. The mechanism of this relationship is poorly understood, although the associated extracellular volume overload, increased oxidative stress,

Table 2 Hazard Ratios for Mortality According to Baseline NT-proBNP* and Glomerular Filtration Rate†

	Entire Population		Other CVD Only		PAD Only		Both Other CVD and PAD	
	HR	p Value	HR	p Value	HR	p Value	HR	p Value
Glomerular filtration rate (per 10 ml/min/1.73 m^2)								
All-cause mortality	0.81	<0.001	0.67	0.049	0.89	0.165	0.79	0.003
Ischemic cardiac death	0.82	0.008	0.38	0.011	0.93	0.636	0.82	0.042
Any cardiovascular death	0.84	0.005	0.61	0.063	0.94	0.579	0.84	0.025
NT-proBNP level (per log unit)								
All-cause mortality	1.11	0.264	1.48	0.279	1.30	0.054	0.94	0.652
Ischemic cardiac death	1.02	0.900	0.82	0.701	1.47	0.103	0.89	0.504
Any cardiovascular death	1.04	0.720	0.99	0.978	1.21	0.277	0.98	0.887

*NT-proBNP standardized by natural log transformation; †the model included age, gender, current smoking, diabetes, systolic blood pressure, whether taking antihypertensive medication, total cholesterol, high-density cholesterol, whether taking medication for cholesterol, NT-proBNP level, and glomerular filtration rate; the model on the entire population also included variables to control for a history of other CVD or PAD. Ischemic cardiac death (ICD-9 code 410-414); any cardiovascular death (ICD-9 code 410-414 or 420-438).

HR = hazard ratio; other abbreviations as in Table 1.

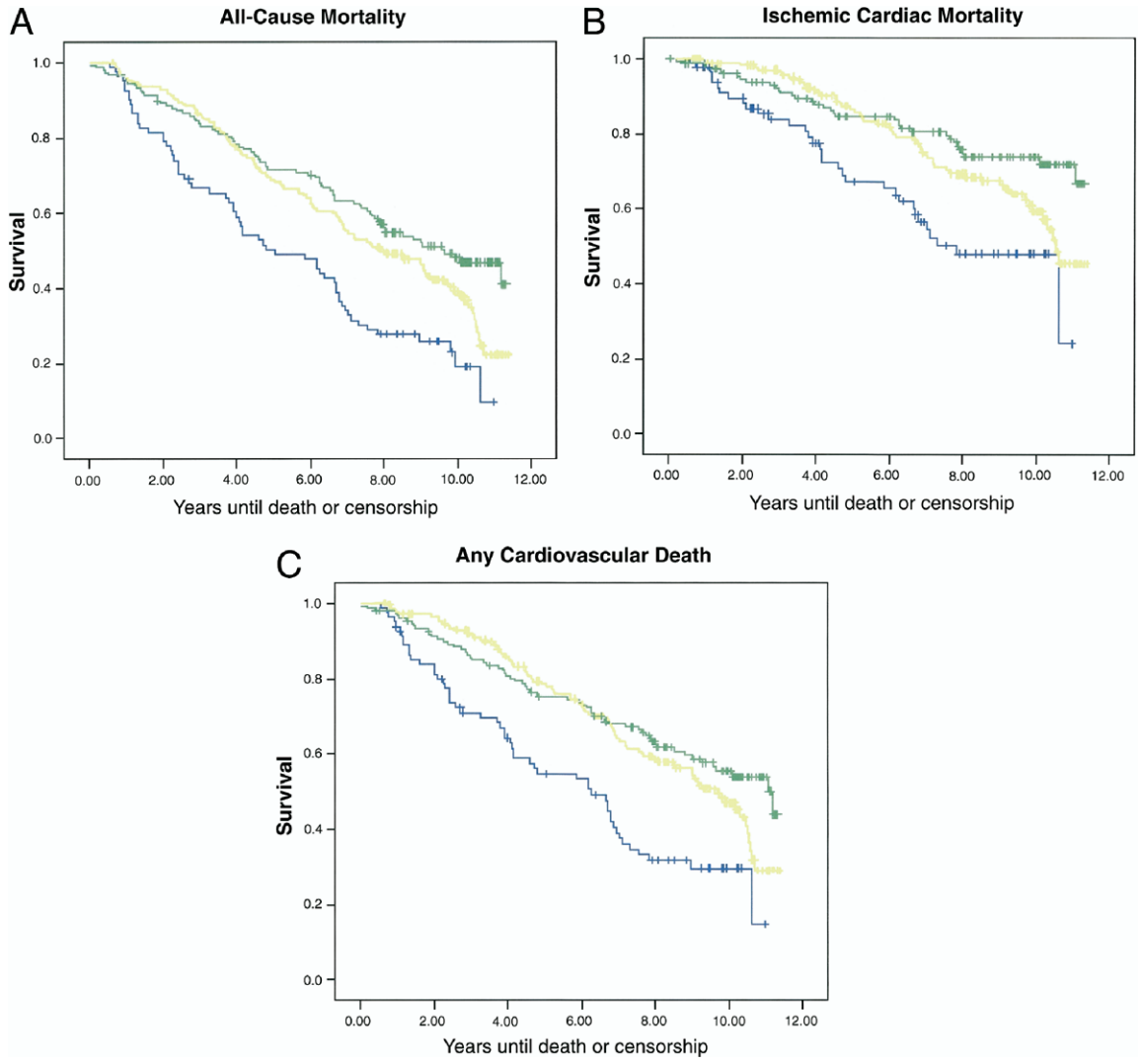

Figure 4 **Overall Survival Among All Patients According to Mortality Cause and Glomerular Filtration Rate**

Green = glomerular filtration rate >60 ml/min/1.73 m^2; **yellow** = glomerular filtration rate 45 to 59 ml/min/1.73 m^2; **blue** = glomerular filtration rate <45 ml/min/1.73 m^2. Comparisons made by pairwise log-rank tests.

electrolyte imbalances, and anemia in patients with chronic renal dysfunction have all been proposed (17,31). Alternatively, the differential use of ACE inhibitors, aspirin, thrombolytics, percutaneous intervention, or platelet inhibitors in these patients has been proposed (32). Interestingly, in our study population, there was no significant difference in aspirin use by GFR tertile. Although there was a significant difference in ACE inhibitor use by GFR tertile, after controlling for its use, GFR remained strongly predictive of all-cause and any cardiovascular mortality.

The utility of BNP and NT-proBNP in predicting outcomes in various populations has also received considerable attention in recent years. In a landmark paper, Wang et al. (5) described how BNP was predictive of death independent of traditional risk factors in a community population, but was not predictive of future coronary heart disease events. These findings were later supported in an older adult community population (8). Both of these studies excluded patients with evidence of CHF or renal insufficiency. Studies soon looked to examine whether a similar prognostic power exists in patients with a history of CVD. Kragelund et al. (9) examined whether NT-proBNP possessed long-term prognostic power in a population of patients with minimal renal impairment, referred for elective angiography for signs or symptoms or coronary artery disease. They found that, independent of traditional risk factors or calculated creatinine clearance, NT-proBNP levels were significantly predictive of all-cause mortality. Similar findings have been seen in predicting myocardial infarction based on

NT-proBNP populations with cerebrovascular disease and without CHF (6). In the recently published HOPE (Health Outcomes Prevention Evaluation) study, using a vascular population without heart failure, overt nephropathy, or recent myocardial infarction/cerebrovascular accident, and controlling for traditional risk factors in addition to creatinine level, researchers found that NT-proBNP was predictive of the combined outcome of myocardial infarction, cerebrovascular accident, or cardiovascular death over a mean 4.5-year follow-up duration.

Of particular note, our findings suggest that the prognostic power of NT-proBNP seen in other populations may be significantly attenuated in a less selective vascular population, with a high prevalence of PAD, CVD, renal, and cardiac dysfunction. Several important differences distinguish our study from previous ones. First, the relationship between NT-proBNP and CHF is well established, and the prevalence of CHF is estimated between 40% to 60% in some vascular populations (9,33). Hence, the elimination of patients with CHF from other study populations makes the results difficult to truly extend to the full vascular spectrum. Secondly, as discussed earlier, in patients with a significant degree of renal insufficiency (mean ± SD GFR 56 ± 15 ml/min/1.73 m^2 in our population) and obesity (mean ± SD body mass index 27 ± 8 kg/m^2 in our population), the better estimation of true renal function is the use of the MDRD formula (27,34). Many prior studies have either used calculated creatinine clearance rate using the Cockcroft-Gault equation, or simply used serum creatinine levels. Given the interdependence of NT-proBNP levels and renal function and demonstrated independent prognostic power of GFR on mortality, suboptimal adjustment for renal function may falsely enhance the predictive power of NT-proBNP (24). Finally, the mean levels of NT-proBNP in this population were significantly higher than prior studies (512 pg/ml vs. 144 pg/ml in the HOPE study) likely reflecting worse cardiovascular dysfunction in our population. We feel that these differences may account for the absence of consistent prognostic power for NT-proBNP in this population.

In this population, we did not observe the expected negative correlation between GFR and NT-proBNP as has been described in other populations (14,15,35). Although there was only a weak correlation between the 2 variables, this relationship did not change with correction for age, gender, diuretic use, or other potential confounders. This relationship may be a result of the large proportion of patients with PAD in this study (86%) compared with others (typically <20%) as well as the higher levels of NT-proBNP observed in patients with PAD (vs. age- and gender-matched control subjects) (36,37). However, given the relatively little known about GFR and NT-proBNP in PAD populations, future examination of this topic in this group is certainly warranted.

Subgroup analysis. The subgroup analysis of renal function and mortality was of particular interest. Prior studies have demonstrated that, in high-risk populations with CVD, such as those with heart failure, postacute coronary syndrome, and postcoronary bypass surgery, GFR is predictive of mortality (32). Furthermore, a limited number of studies have examined whether this concept can be applied to the entire vascular population. Mlekusch et al. (10) demonstrated in a vascular cohort that, independent of traditional cardiovascular risk factors, subjects with the lowest GFR quartile (<44.8) had nearly a 7 times greater hazard of mortality than those with the highest GFR (>82.7). However, this and other similar studies did not repeat the analysis after exclusion of the 45% with known CVD and 23% with a history of myocardial infarction. To our knowledge, our study is the first to answer this question.

Our findings do confirm that in the whole vascular population, as well as the subgroup with known other CVD (either other CVD alone or both other CVD and PAD), lower GFR conferred a significant or strongly suggestive increased hazard of all-cause, cardiovascular, and ischemic mortality. However, when this subgroup was excluded from the analysis, the predictive power of GFR on mortality failed to persist in subjects with PAD alone. These findings are in line with prior studies of community populations with a relatively low prevalence or with exclusion of patients with known CVD (38,39). Our findings support the concept that, in patients with only PAD, renal insufficiency may be simply a marker of underlying cardiovascular risk factors rather than an independent risk factor for cardiovascular or all-cause mortality. However, further research needs to be performed to better examine this question.

In the subgroup analysis, NT-proBNP showed the strongest prognostic ability in the population with only PAD, with an increased risk approaching significance of all-cause mortality and ischemic cardiac death. This finding is in concordance with other studies of other general and clinical populations suggesting an increased risk of all-cause mortality and ischemic cardiac mortality with higher levels of NT-proBNP. Furthermore, this finding is supportive of the theory that, in patients with underlying CVD, likely directly involving the heart, there is a greater likelihood of other factors, such as the presence of CHF or the concomitant use of diuretics/angiotensin receptor blockers, which can independently alter BNP and attenuate its prognostic power (40). Additionally, the differential prognostic role according to subgroup suggests the possibility that the prognostic power of NT-proBNP demonstrated in other studies may in fact be a proxy for the strong role of renal dysfunction, particularly given the inadequate or absent adjustment for renal function in multivariate analyses. Similarly, it is possible that given the strong hazard risk conferred by worsening renal function in populations with CVD, the independent effect of NT-proBNP may be attenuated in this subgroup.

Study strengths and limitations. The strengths of this study include its prospective design, the use of ICD-9 codes for mortality classification, longer duration of follow-up, use

of the MDRD method of GFR estimation, and independent examination of subgroups according to CVD history. However, some limitations include that the study population was predominantly comprised of non-Hispanic white male veterans and was relatively small compared with larger multicenter cohorts. Hence, it is unclear whether these findings can be extended to other populations, such as African Americans. Additionally, as described in the preceding text, though the MDRD formula for GFR calculation is more accurate in the setting of renal insufficiency than serum creatinine or that calculated by the Cockcroft-Gault formula, the study is limited by the singular measurement of GFR and BNP rather than a multiple measurements over time.

Finally, an estimation of cardiac function would have provided a useful backdrop, particularly for BNP interpretation, in patients with suspected CHF and potentially varying volume status. However, there is extensive research in this field demonstrating the prognostic power of BNP independent of left ventricular function. Brain natriuretic peptide has been shown to be predictive of mortality in community populations without heart failure or after controlling for evidence of heart failure at the time of enrollment (5,41). Additionally, multiple studies, including those recently published by Rothenbacher et al. (42) examining patients with known coronary artery disease, have demonstrated that BNP is predictive of cardiovascular mortality independent of left ventricular function (9). Thus, we would not expect left ventricular function data to have significantly affected our results.

Conclusions

In a vascular population at high risk of overall mortality, GFR was a more robust predictor of all-cause, overall cardiovascular mortality, and ischemic cardiac mortality than NT-proBNP levels. In particular, our findings suggest GFR has its strongest role in the subset of the vascular population with a known history of prior coronary artery or cerebrovascular disease. The prognostic utility of NT-proBNP in the vascular population requires further examination, although its role may be greatest in the subset of the population with isolated PAD. A better understanding of the utility and role of these 2 prognostic markers will help physicians better risk-stratify their patients and target therapies accordingly.

Reprint requests and correspondence: Dr. Michael H. Criqui, Department of Family and Preventive Medicine, University of California San Diego, 9500 Gilman Drive, 352 SCRB, La Jolla, California 92093. E-mail: mcriqui@ucsd.edu.

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