Published in final edited form as:

Mayo Clin Proc. 2019 November ; 94(11): 2189–2198. doi:10.1016/j.mayocp.2019.03.033.

Estimated Glomerular Filtration Rate, Activation of Cardiac Biomarkers and Long-Term Cardiovascular Outcomes: A Population-Based Cohort

Shravya Vinnakota, MBBS¹, Christopher G Scott, MSc², Richard J Rodeheffer, MD³, Horng H Chen, MB, BCh³

¹Department of Internal Medicine

²Division of Biomedical Statistics and Informatics

³Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA

Abstract

Objective—To classify subjects in a general population per their renal function and characterize the cardiac biomarker levels, LV function and cardiovascular outcomes over a 10.2 year follow up (IQR: 5.1–11.4).

Patients and Methods—This was a retrospective review of a population-based random sample of residents aged 45 years. Data was collected between January 1, 1997 and December 31, 2000). 1981 individuals were classified based on eGFR into group I (>90 mL/min/1.73m²), group II (60–89 mL/min/1.73m²) and group III (<60 ; CKD mL/min/1.73m²). Age/gender-adjusted baseline characteristics, tertiles of NT-proBNP and hs-TnT and their interactions with eGFR were examined. Outcomes measured included incident MI, CHF, stroke and all-cause mortality.

Results—819 were classified as Group I, 1036 as Group II and 126(6.4%) as Group III or CKD. Subjects in Group III were older and had a higher incidence of hypertension, diabetes and MI at baseline. Over a 10.2-year follow-up, CKD was associated with an increased risk of MI [HR: 1.95(1.2–3.14); $P=.006$] and composite cardiovascular outcomes including MI, CHF, stroke and all-cause mortality [HR: 1.38(1.05–1.83); $P=.02$]. Subjects with NT-proBNP or hs-TnT in the third tertile were at greater risk of cardiovascular events without significant interactions between eGFR and levels of NT-proBNP and hs-TnT.

Conclusions—Subjects with CKD had significantly elevated cardiac biomarkers and were at an increased risk of MI and adverse cardiovascular events. This warrants future studies to investigate if these cardiac biomarkers could identify high-risk CKD patients for aggressive management of cardiovascular risk factors.

Corresponding Author: Dr. Horng H. Chen, MB, BCh, Mayo Clinic, 200 1st St SW, Rochester, MN USA 55902, Chen.horng@mayo.edu, Phone: (507)284-2511.

Disclosures: None of the authors have industry sponsors or conflicts of interest in relation to this study.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

INTRODUCTION

Chronic kidney disease is widely prevalent and associated with a poor prognosis, which can be largely attributed to cardiovascular mortality and morbidity¹. Cardiovascular disease (CVD) has long been identified as the major cause of premature death in CKD, even with mildly impaired renal function^{2–5}. This can be explained in part by shared common risk factors including hypertension, diabetes, hyperlipidemia, smoking and obesity. However, there is growing evidence that impaired kidney function and raised albuminuria are risk factors independent of traditional factors like hypertension and diabetes.² In addition, there are pathological mechanisms that are unique to CKD which promote vascular disease, thus contributing to the increased burden of CVD.²

NT-proBNP and hs-TnT have important diagnostic and prognostic value in patients with CVD. However, these biomarkers are often significantly elevated in CKD, even without clinically evident cardiovascular disease⁶. Their renal clearance confounds their significance in estimating cardiovascular risk in CKD⁷. Several studies have demonstrated elevated NT-proBNP levels in CKD, but there is insufficient data to establish a strict upper limit of normal for corresponding eGFR. Similarly, the challenge with interpretation of hs-TnT in CKD lies in the stable elevation of levels with decreasing renal function. The extent of elevation of these cardiac markers at low renal function is highly variable and not well-studied⁸.

Studies have shown that aggressive risk modification can substantially reduce the burden of CVD⁹. However, there is a paucity of studies stratifying cardiovascular risk in patients with CKD. The objectives of the current study were to classify subjects per their renal function, characterize the trends of cardiac biomarker activation, left ventricular function and report cardiovascular outcomes over a 10-year follow-up.

METHODS

The Institutional Review Boards of Mayo Clinic and Olmsted Medical Center approved this study before data collection.

Study Design

This was a retrospective analysis of the Olmsted County Heart Function Study cohort.

Study Population

Random samples of Olmsted County residents aged 45 years or older were identified by applying a sampling fraction of 7% within each sex- and age-specific (5 years) stratum. 2042 residents participated at first visit, which made up the cohort of this study. Subjects were excluded if creatinine measurement was not available. These patients underwent clinical evaluation, medical record abstraction, detailed drug history, biochemical evaluation and echocardiography during visit 1 (January 1, 1997 to December 31, 2000).

Follow up

Participants were followed clinically for a median of 10.2 years (IQR: 5.1 – 11.4).

Subgroup Classification

Estimated glomerular filtration rate (eGFR) was calculated using the four-variable equation in the Modification of Diet in Renal Disease (MDRD) study¹⁰. CKD was defined in accordance with the modified National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines¹¹, albuminuria was not included in our classification of subjects. Subjects with normal renal function constituted Group I (eGFR ≥ 90 mL/min/1.73m²). Group II included patients with mild renal insufficiency (eGFR 60–89 mL/min/1.73m²). Group III included the rest of the subjects with CKD (eGFR < 60 mL/min/1.73m²).

Outcomes

Over a median follow-up of 10.2 years, outcomes measured were myocardial infarction (MI), cerebrovascular accident, CHF, hospitalized major adverse cardiovascular events (MACE) and all-cause mortality. Outcomes were electronically collected from medical records using appropriate *International Classification of Diseases, Ninth Revision* codes. Hypertension was defined by the *Joint National Committee VI* criteria. The diagnosis of DM was based on documentation by a physician in medical records. *Framingham criteria* were used to diagnose incident heart failure. Cardiac structural parameters such as systolic dysfunction (ejection fraction < 50%), diastolic dysfunction, and LV mass index were measured by echocardiography. Cardiovascular biomarkers NT-proBNP and hs-TnT were also measured by previously described methods¹².

Echocardiography

The section on echocardiography was previously described in an article by the corresponding author¹³. Two-dimensional, M-mode, and tissue Doppler echocardiography was performed for all patients¹⁴, interpreted by a single echocardiologist. M-mode echocardiography, quantitative 2-dimensional (biplane Simpson) method and semi-quantitative 2-dimensional visual estimate method were used to quantitate ejection fraction¹⁵. As there was a high correlation between these 3 methods, visual estimate ejection fraction was used in the final interpretation⁴. To quantitate the LV mass, standard formulas based on M-mode measurement of diastolic dimension and wall thickness were used. Pulsed-wave Doppler examination of mitral flow (before and during Valsalva) and pulmonary venous inflow, as well as by Doppler tissue imaging of the mitral annulus was used to measure diastolic dysfunction⁵. A 4-point ordinal scale was created to grade diastolic dysfunction: (1) normal; (2) *mild diastolic dysfunction*, defined as abnormal relaxation without increased LV end-diastolic filling pressure (peak early (*E*) to peak late [atrial] (*A*) diastolic filling velocity ratio < 0.75); (3) *moderate* or “*pseudonormal*” *diastolic dysfunction*, defined as abnormal relaxation with increased LV end-diastolic filling pressure (*E/A* ratio of 0.75–1.5, deceleration time > 140 ms, and 2 other Doppler indices of elevated LV end-diastolic filling pressure); and (4) *severe diastolic dysfunction*, defined as advanced reduction in compliance with restrictive filling (*E/A* ratio > 1.5, deceleration time < 140 ms, and Doppler indices of elevated LV end-diastolic filling pressure).

Statistical Analysis

Categorical variables were summarized as percentages and continuous variables as means $\pm$ standard deviation or as median and quartiles, depending on the distribution. Comparison between groups was based on linear regression models for continuous variables and logistic regression for categorical variables, in order to account for age and gender differences. In these models, to test for trends, CKD was modelled as an ordinal term across groups (1, 2, 3). For all analyses, continuous variables were examined for normality and transformed as necessary. The Kaplan-Meier method was used to estimate probabilities of events, and subjects without events were censored at their last known clinical follow-up. Associations of clinical and echocardiographic variables with each endpoint were assessed with Cox proportional hazards regression, in order to control for age and gender differences. Analysis of the optimal cutpoint for the biomarkers for prediction of the pooled outcome was done using the approach of Contal and O'Quigley. Interactions of CKD group with NT-proBNP and Hs-TnT were assessed by including interaction terms in the proportional hazards regression. To maximize power, continuous biomarkers, after log transformation due to skewed distribution, were tested in the interaction. Analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC) and two-sided p-values $\leq .05$ were considered statistically significant.

RESULTS

Baseline characteristics

Of the 1981 patients, 126 were found to have CKD (GFR <60 mL/min/1.73m², Group III), estimating a prevalence of 6.4%. 1036 (52.2%) of the patients had mild renal insufficiency (60–89 mL/min/1.73m², Group II) and 819 (41.3%) had normal renal function, GFR >90 mL/min/1.73m² (Group I).

Baseline characteristics of the subjects are described in Table 1. Compared to those with normal renal function, subjects with CKD were more likely to be older (75 ± 9 vs. 58 ± 9) and male (65% vs 49%). When adjusted for age and gender, they were more likely to have a history of hypertension, diabetes and MI at baseline. They were also more likely to be on anti-hypertensive or anti-lipemic medications. No significant trend was noted in the prevalence of CAD across the groups. Both CHF (6%) and stroke (8%) were more frequent in the CKD group, but were not statistically significant. Median values of NT-proBNP were 49.1, 78.7 and 249.8 pg/ml in groups I, II and III respectively ($P < .001$). Median CRP levels were higher in the CKD group at 7.9 mg/L when compared to 3.1 and 3.6 mg/L in groups I and II, although not statistically significant. Levels of hs-TnT were higher in group III at 6.3 ng/L in comparison to 2.4 and 3.3 ng/L in groups I and II ($P < .001$). A higher percentage of the subjects in the CKD group had EF $<40\%$ (6%) and moderate-severe diastolic dysfunction (21%), although not statistically significant. Subjects in group III had a higher prevalence of LV hypertrophy, increased left atrial volume index and E/e' prime values, but these differences were not statistically significant.

Outcomes by CKD stage

The primary outcome of our study was a composite end-point including CHF, MI, stroke and all-cause mortality. The results are noted in table 2. After adjustment for age and gender, we found that CKD was associated with a significantly increased composite risk of death, CHF, MI and stroke by 38% [1.38 (1.05, 1.83), $P=.02$] compared to normal. When the data was further stratified to analyze for individual events, CKD was associated with a 95% increased risk of MI [1.95(1.21 to 3.14), $P=.006$]. Subjects with CKD were also noted to have an increased incidence of stroke [1.44(0.98 to 2.11), $P=.06$] and CHF [1.36(0.88 to 2.11), $P=.16$], but this was not statistically different from Group I. There was not a significant difference in the risk of overall mortality for group III when compared to Group I [HR=1.15 (0.80 to 1.654), $p=.45$]. No significant difference in outcomes, both individual and combined, were noted between groups I and II.

Interactions between Biomarkers and eGFR in predicating clinical outcomes

When tertiles of NT-proBNP and hs-TnT were analyzed for their interaction with eGFR with regards to the clinical end-points of CHF, MI, stroke and all-cause mortality, we did not find a significant interaction. The tertiles of NT pro-BNP were 4.5–37.3, 37.4–113.6, and 113.7–7899 pg/ml. The tertiles of hs-TnT were 0.1–2.1, 2.2–4.2, and 4.3–523.5 ng/L. The distribution of subjects within each group across tertiles of biomarkers are given in table 3. There is a notable increase in the proportion of subjects in the third tertile of both biomarkers in group III. We further analyzed the optimal cutpoint for the biomarkers for prediction of the pooled outcome and these cutpoints were similar to the third tertile for both biomarkers. For NT-proBNP the cutpoint for the overall sample was 97.1 pg/ml. For hs-TnT the optimal cutpoint for the overall sample was 3.8 ng/L.

In table 4, it is noted that the risk is highest in the top tertiles across levels of eGFR, with the effect being fairly similar (hazard ratios ranging from 1.9–2.6).

The results of interaction tests in table 4 suggest that the association of biomarkers and composite outcome is not significantly different by group. This suggests that the association of biomarkers and outcome should be significant within the $eGFR < 60$ subgroup as with the other groups. To maximize power for this relatively small subgroup analysis, we have tested the outcome association within the $eGFR < 60$ subgroup utilizing a trend across tertiles. The age and gender adjusted HR for the composite endpoint for a one tertile increase in NT-ProBNP was 1.71 (1.09, 2.68), $p=.02$. Similarly, the age and gender adjusted HR for a one tertile increase in hs-TnT was 1.63 (1.08, 2.46), $p=.02$.

DISCUSSION

The current study estimates the prevalence of CKD stage III (defined as $eGFR < 60$ mL/min/1.73 m²) at 6.4% among subjects above 45 years of age. Subjects with CKD were associated with an increased risk of a composite cardiovascular endpoint of CHF, MI, stroke and all-cause mortality. With analysis of individual events, CKD was associated with a 95% increased risk of MI, which persisted even after adjustment for age and gender. Across levels of eGFR, subjects with NT-proBNP and hs-TnT in the highest tertile were at a greater risk of

adverse cardiovascular outcomes including CHF, MI, stroke and all-cause mortality. No interaction was noted between eGFR and either of the biomarkers.

Prevalence of CKD

The prevalence of CKD in the US appears to have a stable trend in the last few decades. The National Health and Nutrition Examination Survey (NHANES) database has been analyzed to provide updates in the trends of CKD^{16, 17}. Murphy et al demonstrated encouraging results of stabilizing trends in the prevalence of stages CKD 3 and 4 (eGFR<60 and >15mL/min/1.73 m²)¹⁸. There was an overall lack of increase across all age and gender strata, even when stratified by diabetes status. The overall prevalence was estimated at 4.8% in 1988–1994, increased to 6.9% in 2003–2004, and remained at 6.9% in 2011–2012. Hsu et al revealed similar findings across the US as well as other developed countries including England, Norway and South Korea¹⁹. Our results were consistent with this trend. We estimated the prevalence of CKD (defined as eGFR<60 mL/min/ 1.73 m² by MDRD-4 study equation) to be 6.4% among subjects aged 45 years or older. While this age group differs from the subject population in the studies referenced above, the study confirms an overall stability in the prevalence of CKD.

Association with cardiac biomarkers

The renal clearance of NT-proBNP and hs-TnT confounds their significance in estimating cardiovascular risk amongst patients with CKD. Studies have established well-defined mechanisms for BNP elimination including binding by natriuretic peptide receptor C and neutral endopeptidase mediated degradation²⁰. In contrast, very little is known about the mechanism of clearance of NT-proBNP. It attains detectable levels in urine and is often elevated in patients requiring hemodialysis, provoking the theory that its clearance is more dependent on glomerular filtration rather than extra-renal degradation²¹. However, it is important to note that although plasma levels of NT-proBNP are progressively higher in patients with CKD, it does not increase in a consistent manner across all CKD stages, suggesting that factors besides renal clearance are involved²². Many investigators suggest a higher cut-off when interpreting NT-proBNP levels as CKD stage advances, but the data is limited. Results from the ProBNP investigation of dyspnea in the Emergency Department (PRIDE) study²³ postulated a higher NT-proBNP cut off of >1200 pg/ml to improve sensitivity and specificity for diagnosis of acute heart failure in subjects with eGFR<60mL/min/1.73m²..

Unlike NT-proBNP, both free and bound TnT are relatively large molecules and their elevated levels in CKD are less likely to be a result of impaired renal clearance. This is more likely linked to cardiac etiologies like silent micro-infarctions²⁴, LV hypertrophy and subclinical heart failure. Elevated hs-TnT levels have been associated with an increased risk of MACE and all-cause mortality in CKD^{25, 26}.

Our study confirms several of the above mentioned findings, but more importantly, we demonstrate that across levels of eGFR, subjects with NT-proBNP or hs-TnT in the third tertile were at greater risk of cardiovascular events compared to subjects in the lower tertiles. We analyzed the optimal cutpoint for the biomarkers for prediction of the pooled outcome

and these cutpoints were similar to the third tertile for both biomarkers, 97.1 pg/ml for NT-proBNP and 3.8 ng/L for hs-TnT. Our findings validate the importance of monitoring these levels in patients with CKD and propose an additional tool to identify those at highest risk for adverse cardiovascular events. In comparison to prior studies, this data suggests lower thresholds of both biomarkers for prediction of poor outcomes. While these biomarkers are often used in cases of acute manifestations of CHF or coronary syndromes in the general population^{27–29}, there has been considerable reluctance to clinically utilize these in patients with CKD, given concerns that they may be falsely elevated due to impaired renal clearance^{28, 30, 31}. However, we examined tertiles of NT-proBNP and hs-TnT and their interactions with eGFR with regards to the clinical end-points of CHF, MI, stroke and all-cause mortality; we did not find significant interactions between eGFR and levels of NT-proBNP and hs-TnT. Hence, it would be incorrect to attribute the higher levels of these biomarkers to impaired renal clearance entirely. Classifying patients with CKD and elevated biomarkers to a high risk group that receives rigorous cardiovascular monitoring and preventive strategies may aid in decreasing the burden of CVD. Additional studies are required to ascertain higher cut off levels for these biomarkers in CKD.

CKD and cardiovascular outcomes

Cardiovascular events are the leading cause of mortality in patients with CKD. In early stages of CKD (IIIA and B), the incidence of cardiovascular mortality is even higher than the incidence of kidney failure.^{2, 32} In the early stages, there is a predominance of atherosclerotic events such as MI and stroke, whereas in end-stage renal disease (ESRD), accelerated arteriosclerosis leads to increased vascular resistance, LVH and systolic or diastolic dysfunction³³. A large meta-analysis by noted that cardiovascular mortality was twice as high in patients with stage 3 CKD (eGFR 30–59mL/min/1.73m²) and three times higher at stage 4 (15–29mL/min/1.73m²) when compared to those with normal renal function. Glomerular filtration rates <60mL/min/1.73m² were also associated with increased risk of CHF, stroke, peripheral artery disease, coronary heart disease and atrial fibrillation². Matsushita et al demonstrated that lower eGFR and higher albuminuria were independent predictors of all-cause mortality in the general population. The adjusted hazard ratios for all-cause mortality at eGFR 60, 45, and 15 (versus 95) were 1.18 (1.05–1.32), 1.57 (1.39–1.78), and 3.14 (2.39–4.13) respectively³⁴. Similar results were observed by Go et al- there was an independent graded association between lower levels of eGFR and risk of death, composite cardiovascular outcomes and hospitalization over a follow up of 2.8 years. This was evident at eGFR <60mL/min/1.73m² and substantially increased at levels <45³². Bansal et al found that CKD was associated with a two-fold increased risk of heart failure and coronary disease³⁰. There is also a striking increase in the prevalence of left ventricular hypertrophy in CKD, seen in around 50% of patients with eGFR<30mL/min/1.73m².²

In comparison to the above-mentioned studies^{30, 32}, our study had one of the longest follow-up periods. We expand on these outcomes and demonstrate that over a 10 year follow-up, patients with CKD had a significantly increased risk (36%) of composite adverse cardiovascular events including CHF, MI, stroke and all-cause mortality. Subjects with CKD had a 95% increased risk of developing MI, compared to subjects with normal renal function. In addition, they were found to have an elevated risk for stroke. A trend was also

noted between decreasing eGFR and incidence of heart failure. These associations remained significant even after adjusting for age and gender. Furthermore, the current study demonstrates that subjects with mild renal dysfunction (eGFR between 61–89 mL/min/1.73 m²) had similar long-term clinical outcomes as those with normal renal function.

Limitations

The Olmsted County Heart Function study cohort provided valuable information on a community-based cohort over a longitudinal period of time. However, the lack of diversity of the population (largely Caucasian) could limit the generalizability of our results. Similar results were observed in a multi-centric study that identified African-American patients with CKD and hypertensive kidney disease- higher NT-proBNP levels were strongly associated with cardiovascular events and mortality³⁵. Further studies in different ethnic groups are warranted before these results may be generalizable to diverse populations. The absence of data on duration and severity of co-existing conditions or data on cardiac medications can influence patient outcomes. Standard Doppler was used for echocardiographic data collection and newer modalities like myocardial strain imaging were unavailable at the time. Cardiac biomarkers were only measured once at the start of the study and their trends over time were not assessed. In addition, only a small portion of the cohort had eGFR<60 mL/min/1.73 m². This appeared to be largely age related, which may not reflect the impact of substantial intrinsic disease. This could explain the lack of statistical significance in the difference in CRP between the groups as well as the absence of difference in some of the components of the pooled cardiovascular mortality outcome.

Conclusions

The majority of patients with CKD having an increased risk for cardiovascular events have an eGFR<60mL/min/1.73m². No significant difference in outcomes was noted between the groups with eGFR of 60–89 and >90mL/min/1.73m². NT-proBNP and hs-TnT are useful prognostic indicators of cardiovascular morbidity and mortality in CKD. As we better define the cardiovascular burden in this population, there is an emphasis on identifying such factors that may predict cardiovascular outcomes and identify targets for aggressive preventive therapies.

Acknowledgements

1. An abstract of this article was published in Journal of American College of Cardiology.

(Vinnakota S, Scott C, Rodeheffer R, Chen HH. Neurohumoral Activation and Long-Term Cardiovascular Outcomes In Chronic Kidney Disease: A Population-Based Cohort. Journal of the American College of Cardiology. 2017, Mar; 69(11): 930) [dummy_incomplete para]

2. The section on echocardiography was previously described in an article by the corresponding author.

(Patel PA, Scott CG, Rodeheffer RJ, Chen HH. The Natural History of Patients With Isolated Metabolic Syndrome. Mayo Clin Proc. 2016;91(5):623-33)

Financial Support: The design and conduct of the study; collection, management, analysis, and interpretation of the data were supported by these grants from National Institutes of Health [P01 HL76611, R01HL84155 and R01HL136440 to H.H.C] and [HL RO1-55502 to R.J.R].

Abbreviations

CKD	Chronic Kidney Disease
CVD	Cardiovascular Disease
MI	Myocardial Infarction
eGFR	Estimated Glomerular Filtration Rate
MACE	Major Adverse Cardiovascular Events
HTN	Hypertension
DM	Diabetes
CAD	Coronary Artery Disease
CHF	Congestive Heart Failure
NT-proBNP	N-terminal pro b-type natriuretic peptide
NT-ANP	N-terminal atrial natriuretic peptide
CRP	C-reactive protein
hs-TNT	high sensitivity troponin T

REFERENCES

1. Kendrick J, Chonchol M. Cardiovascular disease in CKD in 2013: Reducing cardiovascular risk--light at the end of the tunnel. *Nature reviews. Nephrology* 2014;10:71–72. [PubMed: 24322975]
2. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *The Lancet*. 2013;382:339–352.
3. Liu M, Li XC, Lu L, et al. Cardiovascular disease and its relationship with chronic kidney disease. *European review for medical and pharmacological sciences*. 2014;18:2918–2926. [PubMed: 25339487]
4. Garcia-Gil M, Parramon D, Comas-Cufi M, et al. Role of renal function in cardiovascular risk assessment: A retrospective cohort study in a population with low incidence of coronary heart disease. *Prev Med*. 2016;89:200–206. [PubMed: 27287663]
5. Eisen A, Hoshen M, Balicer RD, et al. Estimated Glomerular Filtration Rate Within the Normal or Mildly Impaired Range and Incident Cardiovascular Disease. *The American journal of medicine*. 2015;128:1015–1022.e1012. [PubMed: 25863153]
6. Matsushita K, Sang Y, Ballew SH, et al. Cardiac and kidney markers for cardiovascular prediction in individuals with chronic kidney disease: the Atherosclerosis Risk in Communities study. *Arteriosclerosis, thrombosis, and vascular biology*. 2014;34:1770–1777.
7. Vickery S, Price CP, John RI, et al. B-type natriuretic peptide (BNP) and amino-terminal proBNP in patients with CKD: relationship to renal function and left ventricular hypertrophy. *Am J Kidney Dis*. 2005;46:610–620. [PubMed: 16183415]
8. Bjurman C, Petzold M, Venge P, Farbemo J, Fu ML, Hammarsten O. High-sensitive cardiac troponin, NT-proBNP, hFABP and copeptin levels in relation to glomerular filtration rates and a medical record of cardiovascular disease. *Clinical biochemistry*. 2015;48:302–307. [PubMed: 25637776]

9. Snyder JJ, Collins AJ. Association of preventive health care with atherosclerotic heart disease and mortality in CKD. *Journal of the American Society of Nephrology: JASN*. 2009;20:1614–1622. [PubMed: 19423688]
10. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Annals of internal medicine*. 1999;130:461–470. [PubMed: 10075613]
11. Inker LA, Astor BC, Fox CH, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis*. 2014;63:713–735. [PubMed: 24647050]
12. Redfield MM, Jacobsen SJ, Burnett JC Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *Jama*. 2003;289:194–202. [PubMed: 12517230]
13. Patel PA, Scott CG, Rodeheffer RJ, Chen HH. The Natural History of Patients With Isolated Metabolic Syndrome. *Mayo Clinic proceedings*. 2016;91:623–633. [PubMed: 27063063]
14. Kane GC, Karon BL, Mahoney DW, et al. Progression of left ventricular diastolic dysfunction and risk of heart failure. *Jama*. 2011;306:856–863. [PubMed: 21862747]
15. Salmasi AM, Frost P, Dancy M. Impaired left ventricular diastolic function during isometric exercise in asymptomatic patients with hyperlipidaemia. *International journal of cardiology*. 2004;95:275–280. [PubMed: 15193832]
16. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *Jama*. 2007;298:2038–2047. [PubMed: 17986697]
17. Foley RN. Temporal trends in the burden of chronic kidney disease in the United States. *Current opinion in nephrology and hypertension*. 2010;19:273–277. [PubMed: 20164765]
18. Murphy D, McCulloch CE, Lin F, et al. Trends in Prevalence of Chronic Kidney Disease in the United States. *Annals of internal medicine*. 2016;165:473–481. [PubMed: 27479614]
19. Hsu RK, Powe NR. Recent trends in the prevalence of chronic kidney disease: not the same old song. *Current opinion in nephrology and hypertension*. 2017;26:187–196. [PubMed: 28319485]
20. Cataliotti A, Malatino LS, Jougasaki M, et al. Circulating natriuretic peptide concentrations in patients with end-stage renal disease: role of brain natriuretic peptide as a biomarker for ventricular remodeling. *Mayo Clinic proceedings*. 2001;76:1111–1119. [PubMed: 11702899]
21. Palmer SC, Richards AM. Does renal clearance differ between the B-type natriuretic peptides (BNP versus NT-proBNP)? *Journal of the American College of Cardiology*. 2009;53:891–892. [PubMed: 19264248]
22. Srisawasdi P, Vanavan S, Charoenpanichkit C, Kroll MH. The effect of renal dysfunction on BNP, NT-proBNP, and their ratio. *American journal of clinical pathology*. 2010;133:14–23. [PubMed: 20023254]
23. Anwaruddin S, Lloyd-Jones DM, Baggish A, et al. Renal function, congestive heart failure, and amino-terminal pro-brain natriuretic peptide measurement: results from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study. *Journal of the American College of Cardiology*. 2006;47:91–97. [PubMed: 16386670]
24. Ooi DS, Isotalo PA, Veinot JP. Correlation of antemortem serum creatine kinase, creatine kinase-MB, troponin I, and troponin T with cardiac pathology. *Clinical chemistry*. 2000;46:338–344. [PubMed: 10702520]
25. Michos ED, Wilson LM, Yeh HC, et al. Prognostic value of cardiac troponin in patients with chronic kidney disease without suspected acute coronary syndrome: a systematic review and meta-analysis. *Annals of internal medicine*. 2014;161:491–501. [PubMed: 25111499]
26. Gregg LP, Adams-Huet B, Li X, et al. Effect Modification of Chronic Kidney Disease on the Association of Circulating and Imaging Cardiac Biomarkers With Outcomes. *Journal of the American Heart Association*. 2017;6.
27. Lainchbury JG, Campbell E, Frampton CM, Yandle TG, Nicholls MG, Richards AM. Brain natriuretic peptide and n-terminal brain natriuretic peptide in the diagnosis of heart failure in patients with acute shortness of breath. *Journal of the American College of Cardiology*. 2003;42:728–735. [PubMed: 12932611]

28. Colbert G, Jain N, de Lemos JA, Hedayati SS. Utility of traditional circulating and imagingbased cardiac biomarkers in patients with predialysis CKD. *Clinical journal of the American Society of Nephrology : CJASN*. 2015;10:515–529. [PubMed: 25403922]
29. Cleland JG, Taylor J, Freemantle N, Goode KM, Rigby AS, Tendera M. Relationship between plasma concentrations of N-terminal pro brain natriuretic peptide and the characteristics and outcome of patients with a clinical diagnosis of diastolic heart failure: a report from the PEP-CHF study. *European journal of heart failure*. 2012;14:487–494. [PubMed: 22505395]
30. Bansal N, Hyre Anderson A, Yang W, et al. High-sensitivity troponin T and N-terminal pro-B-type natriuretic peptide (NT-proBNP) and risk of incident heart failure in patients with CKD: the Chronic Renal Insufficiency Cohort (CRIC) Study. *Journal of the American Society of Nephrology : JASN*. 2015;26:946–956. [PubMed: 25278510]
31. Mishra RK, Li Y, Ricardo AC, et al. Association of N-terminal pro-B-type natriuretic peptide with left ventricular structure and function in chronic kidney disease (from the Chronic Renal Insufficiency Cohort [CRIC]). *Am J Cardiol*. 2013;111:432–438. [PubMed: 23178053]
32. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *The New England journal of medicine*. 2004;351:1296–1305. [PubMed: 15385656]
33. Sarafidis PA, Bakris GL. Cardiovascular disease in CKD in 2014: new insights into cardiovascular risk factors and outcomes. *Nature reviews. Nephrology*. 2015;11:70–72.
34. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet (London, England)*. 2010;375:2073–2081.
35. Astor BC, Yi S, Hiremath L, et al. 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). *Circulation*. 2008;117:1685–1692. [PubMed: 18362234]

Table 1:

Baseline characteristics

Baseline characteristics for overall cohort.

Variable	eGFR ^a ≥90 (n=819)	eGFR=60–89 (n=1036)	eGFR<60 (n=126)	p-value ^b
Age at exam	57.9 (8.5)	65.2 (10.2)	74.8 (9.3)	<.001
Gender, n (%)	399 (49%)	551 (53%)	82 (65%)	.01
BMI ^a	28.6 (5.5)	28.3 (5.1)	28.5 (4.8)	.31
Verified Hypertension, n (%)	161 (20%)	324 (31%)	70 (56%)	<.001
Diabetes, n (%)	46 (6%)	80 (8%)	20 (16%)	.05
MI ^a at baseline, n (%)	20 (2%)	57 (6%)	19 (15%)	.006
CHF ^a at baseline, n (%)	7 (1%)	29 (3%)	8 (6%)	.15
Stroke at baseline, n (%)	11 (1%)	13 (1%)	10 (8%)	.09
Anti-hypertensive drug, n (%)	204 (25%)	407 (39%)	89 (71%)	<.001
Cardiovascular drug, n (%)	205 (25%)	424 (41%)	91 (72%)	<.001
Anti-lipemic therapy, n (%)	94 (13%)	197 (21%)	37 (30%)	.002
NT-proBNP ^a , median (Q1, Q3), pg/ml	49.1 (19.6, 102.4)	78.7 (33.2, 159.0)	249.8 (129.2, 782.6)	<.001
CRP ^a , median (Q1, Q3) mg/L	3.1 (0.9, 14.0)	3.6 (1.2, 14.0)	7.9 (2.1, 14.0)	.07
Hs-TnT ^a , median (Q1, Q3), ng/L	2.4 (1.4, 4.2)	3.3 (2.0, 5.7)	6.3 (3.9, 10.3)	<.001
Ejection Fraction ^c	62.9 (6.6)	63.1 (7.1)	60.8 (10.3)	.01
EF ^a category, n (%)				.14
• ≥50%, n (%)	792 (97%)	990 (96%)	111 (88%)	
• 40–49%, n (%)	18 (2%)	33 (3%)	8 (6%)	
• <40%, n (%)	9 (1%)	13 (1%)	7 (6%)	
Left Atrial Volume Index (mL/m ²)*	24.2 (12.1)	25.4 (8.9)	28.9 (11.2)	.08
E/e prime*	8.3 (3.0)	8.8 (3.1)	9.7 (3.4)	.07
Average LV ^a Mass (g)*	183.0 (52.1)	183.2 (48.5)	203.0 (64.1)	.61
Diastolic Dysfunction, n (%)				.09
Normal	610 (82%)	595 (64%)	41 (39%)	
Mild	82 (11%)	228 (25%)	42 (40%)	
Moderate/Severe	50 (7%)	101 (11%)	22 (21%)	

^a BMI: Body Mass Index, CHF: Congestive Heart Failure, CRP: C-reactive protein, EF: Ejection Fraction, eGFR: Estimated Glomerular Filtration Rate, hs-TnT: High sensitivity troponin T, LV: Left Ventricle, MI: Myocardial Infarction, NT-proBNP: N-terminal pro b-type natriuretic peptide.

^b Age/gender adjusted trend p-value.

^c Values refer to mean + standard deviation or as median and quartiles.

Table 2:**Outcomes by CKD stage**

Outcomes classified by CKD stage. All hazard ratios were adjusted for age and gender.

Variable	eGFR ^a ≥90 (n=819)	eGFR=60–89 (n=1036)	eGFR<60 (n=126)
Death/CHF/MI/Stroke			
HR ^a (95% CI) [p-value]	1.0 (reference)	1.02 (0.85, 1.21) [p=.86]	1.38 (1.05, 1.83) [p=.02]
MI^a			
HR (95% CI) [p-value]	1.0 (reference)	0.85 (0.62, 1.18) [p=.34]	1.95 (1.21, 3.14) [p=.006]
Stroke			
HR (95% CI) [p-value]	1.0 (reference)	1.22 (0.95, 1.57) [p=.12]	1.44 (0.98, 2.11) [p=.06]
CHF^a			
HR (95% CI) [p-value]	1.0 (reference)	0.87 (0.64, 1.18) [p=.38]	1.36 (0.88, 2.11) [p=.16]
Death			
HR (95% CI) [p-value]	1.0 (reference)	0.75 (0.58, 0.97) [p=.03]	1.15 (0.80, 1.64) [p=.45]

^a CHF: Congestive Heart Failure, eGFR: Estimated Glomerular Filtration Rate, HR: Hazard Ratio, MI: Myocardial Infarction.

Table 3:
Interactions of biomarkers with outcomes in CKD

Tertiles of NT-proBNP and hs-TnT with distribution of subjects based on renal function.

Group	NT-ProBNP ^a 4.5 – 37.3 pg/ml	NT-ProBNP 37.4 – 113.6 pg/ml	NT-ProBNP 113.7 – 7899 pg/ml
I	43%	35%	22%
II	28%	35%	37%
III	7%	15%	78%
Group	hs-TnT ^a 0.1 – 2.2 ng/L	hs-TnT 2.2 – 4.2 ng/L	hs-TnT 4.3 – 523.5 ng/L
I	44%	31%	25%
II	30%	34%	36%
III	11%	22%	67%

^ahs-TnT: High sensitivity troponin T, NT-proBNP: N-terminal pro b-type natriuretic peptide.

Table 4:

Interactions of NT-proBNP and Hs-TnT with a composite outcome of MI/CHF/Stroke/Death across the levels of GFR.

Outcome=Death/MI/Stroke/CHF					
Parameter	Pr > ChiSq	HR ^a	95% CI ^a		Int. p-value ^b
Age	<.0001	1.07	1.06	1.08	.24
Female	<.0001	0.56	0.48	0.66	
GFR 90, NT-proBNP Tertile1		1.0	(ref)		
GFR 90, NT-proBNP Tertile2	.82	1.04	0.72	1.50	
GFR 90, NT-proBNP Tertile3	<.0001	2.32	1.63	3.30	
GFR 60–89, NT-proBNP Tertile1	.64	0.92	0.64	1.30	
GFR 60–89, NT-proBNP Tertile2	.13	1.28	0.93	1.77	
GFR 60–89, NT-proBNP Tertile3	<.0001	1.95	1.40	2.69	
GFR<60, NT-proBNP Tertile1	.34	1.57	0.63	3.91	
GFR<60, NT-proBNP Tertile2	.46	1.32	0.64	2.70	
GFR<60, NT-proBNP Tertile3	<.0001	2.54	1.69	3.81	
Parameter	Pr > ChiSq	HR	95% CI		Int. p-value ^b
Age	<.0001	1.07	1.06	1.08	.21
Female	.0006	0.75	0.64	0.89	
GFR 90, Hs-TNT Tertile1		1.0	(ref)		
GFR 90, Hs-TNT Tertile2	.31	1.23	0.83	1.82	
GFR 90, Hs-TNT Tertile3	<.0001	2.23	1.54	3.25	
GFR 60–89, Hs-TNT Tertile1	.94	0.99	0.67	1.46	
GFR 60–89, Hs-TNT Tertile2	.15	1.30	0.91	1.86	
GFR 60–89, Hs-TNT Tertile3	.0001	1.99	1.40	2.84	
GFR<60, Hs-TNT Tertile1	.29	1.66	0.66	4.18	
GFR<60, Hs-TNT Tertile2	.16	1.56	0.85	2.86	
GFR<60, Hs-TNT Tertile3	<.0001	2.64	1.72	4.06	

^aCI: Confidence Interval, HR: Hazard Ratio, hs-TNT: High sensitivity troponin T, MI: Myocardial Infarction, NT-proBNP: N-terminal pro b-type natriuretic peptide.

^bInteraction p-value.