Utility of Traditional Cardiac Biomarkers in Patients with CKD

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Dr. Hedayati is the Program Director for the Nephrology Fellowship Training Program at the University of Texas Southwestern, as well as the Chief of Nephrology at the VA North Texas Health Care System. In her role as the former, she mentors fellows in clinical research. Her main area of research interest is the epidemiology and outcomes of cardiovascular disease in patients with Chronic Kidney Disease (CKD) and End-Stage Renal Disease (ESRD). She is also currently conducting NIH and VA-funded randomized controlled trials in the treatment of depression in patients with CKD and ESRD. Dr. Hedayati serves on several national committees, including the American Society of Nephrology Hypertension Advisory Board and the Nephrology Training Program Directors' Executive Committee.

Purpose and Overview:

This presentation reviews associations between traditional cardiac biomarkers such as troponins, brain natriuretic peptide (BNP), N-terminal-pro-BNP (NT-pro-BNP), left ventricular (LV) mass index, and coronary artery calcium (CAC) scores and clinical outcomes in CKD patients in an attempt to highlight strengths and limitations of existing data for prognostication. In addition, data that supports the utility of their use for diagnostic purposes in the acute setting will be reviewed.

Educational Objectives:

- To understand that plasma levels of troponins and BNP/NT-pro-BNP are commonly elevated in asymptomatic patients with CKD and are associated with a poor cardiovascular (CV) prognosis.
- To understand that higher cut-offs, or a rise in level compared with previous values, have been proposed to aid in distinguishing acute myocardial infarction from chronic elevations of troponins in symptomatic CKD patients.
- To understand the diagnostic utility of BNP and NT-pro-BNP for acute congestive heart failure exacerbation in patients with CKD.
- To understand that CAC can be elevated in patients with CKD and can portend poor CV outcomes, but the role of CAC in routine screening and risk stratification has not been clearly established.
- To review the prognostic roles of elevated LV mass and LV dysfunction in this patient population.

Introduction

Cardiovascular Disease (CVD) is the leading cause of mortality in Chronic Kidney Disease (CKD) and End-Stage Renal Disease (ESRD) patients, accounting for up to 50% of all deaths (1). In addition, CKD patients with CVD have a lower survival than non-CKD patients with CVD, and there is a step-wise decrease in survival with more advanced CKD stages (1). Mortality in CKD stages 4-5 patients with congestive heart failure (CHF) or post-acute myocardial infarction (AMI) is similar to that in dialysis patients, and 2-year survival approaches 50% from CHF (**Figure 1**).

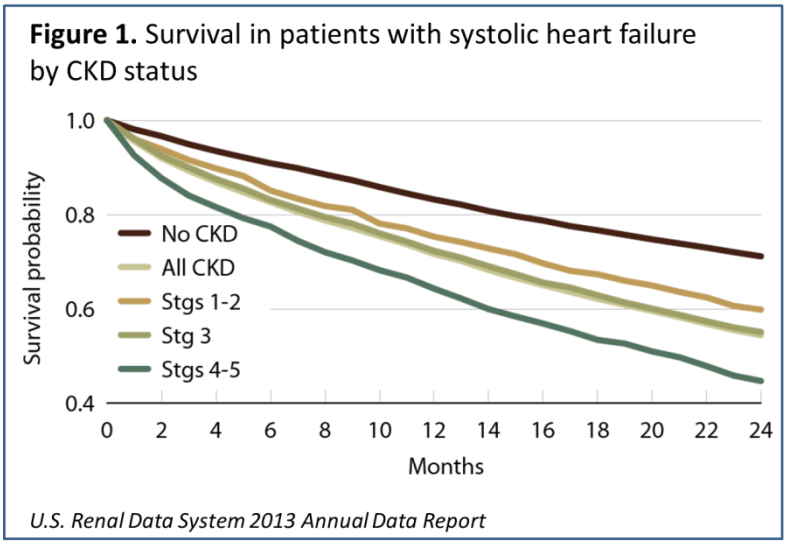

Figure 1. Survival in patients with systolic heart failure by CKD status

U.S. Renal Data System 2013 Annual Data Report

Cardiac biomarkers, such as cardiac troponin T (cTnT) and I (cTnI), brain natriuretic peptide (BNP), and N-Terminal-pro-BNP (NT-pro-BNP), are commonly used to aid in the diagnosis of AMI and CHF exacerbation. However, chronic elevations of cTnT are observed in 80-90% of asymptomatic patients with advanced CKD and ESRD (2). cTnT has evolved in to an important prognostic factor in dialysis-dependent ESRD patients, as elevated levels are associated independently with adverse CV outcomes (3). Fewer data are available describing an association between elevated troponins and CV disease in patients with non-dialysis dependent CKD. Other commonly-used circulating and imaging-based cardiac biomarkers are also associated with poor CV outcomes in asymptomatic ESRD patients, but such associations are less clearly established in CKD. The first aim of this protocol is to summarize studies that reported associations between traditional cardiac biomarkers, such as cTnT, BNP, NT-pro-BNP, measures of left ventricular (LV) mass, and coronary artery calcium (CAC) scores, and clinical outcomes in CKD patients not yet on maintenance dialysis in an attempt to highlight strengths and limitations of existing data for prognostication. The second aim is to review data that supports the utility of their use for diagnostic purposes in the acute setting. These specific biomarkers were chosen because they are non-invasive tests commonly used in clinical practice. For each biomarker, a general description is given, followed by discussion of levels in CKD, association with outcomes, and, finally, the clinical utility in CKD patients.

Definition of Biomarker

Before reviewing the prognostic and diagnostic roles of traditional CV biomarkers in CKD patients, it is necessary to define what is meant by the term "*biomarker*." An NIH working group standardized the definition of a biomarker in 2001 as *a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention* (4). A biomarker may be measured on

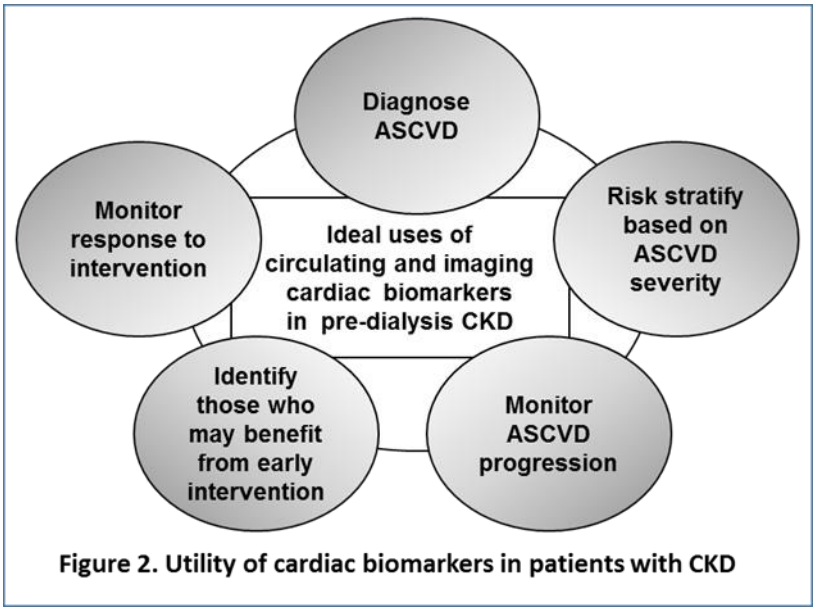

Figure 2. Utility of cardiac biomarkers in patients with CKD

a biosample (blood, urine, tissue), it may be a recording obtained from a patient (blood pressure, ECG, Holter), or an imaging test (4). **Figure 2** outlines the potential uses of an ideal circulating or imaging biomarker for atherosclerotic cardiovascular disease (ASCVD), which should be similar in patients with pre-dialysis CKD as in the general population. The specific CV biomarkers and imaging studies reviewed were chosen because they are traditional non-invasive cardiac tests commonly used in clinical practice.

Cardiac Troponin Levels in CKD

cTnI and cTnT are biomarkers of cardiac injury that can be measured with both standard assays as well as high sensitivity (hs) assays, which detect levels about 10-fold lower than the standard assay. However, the upper reference limits (URL) for cardiac troponins were originally derived in non-CKD individuals, and these biomarkers are elevated in up to 80% of asymptomatic CKD and ESRD patients (2). Troponin elevation in this context is not necessarily indicative of acute ischemia from coronary atherosclerosis, but may be due to decreased renal clearance and/or chronic myocardial injury, the mechanisms for which are multi-factorial and include myocardial strain from altered hemodynamics, inflammation, endothelial dysfunction, and subendocardial ischemia (3, 5) (**Figure 3**). The impact of renal clearance on circulating troponin concentrations is uncertain (3). Previous literature suggested cTnT levels, compared to cTnI, are more commonly elevated in asymptomatic ESRD patients (3). Plausible mechanisms for differential elevations include adsorption of cTnI on the dialyzer membrane imparting increased clearance, degradation of the labile cTnI molecule, advanced glycosylation of cTnT imparting decreased clearance, or uremic toxins causing conformational changes in the epitope region and altering the interaction with the assay antibodies (3) (**Figure 3**). Previous clinical data was heavily influenced by differing sensitivities of the cTnT and cTnI assays and is not relevant to contemporary clinical practice. Consensus guidelines, therefore, do not specify a preference for use of cTnI over cTnT in CKD patients (5). cTnT and cTnI provide largely identical information, and selection between them is typically influenced by laboratory equipment and vendor selection. Unlike the cTnT assay produced by a single manufacturer, cTnI assays are produced

by multiple manufacturers using different antibody pairs, and assays are not interchangeable across institutions or studies (6). This protocol, therefore, focuses on cTnT.

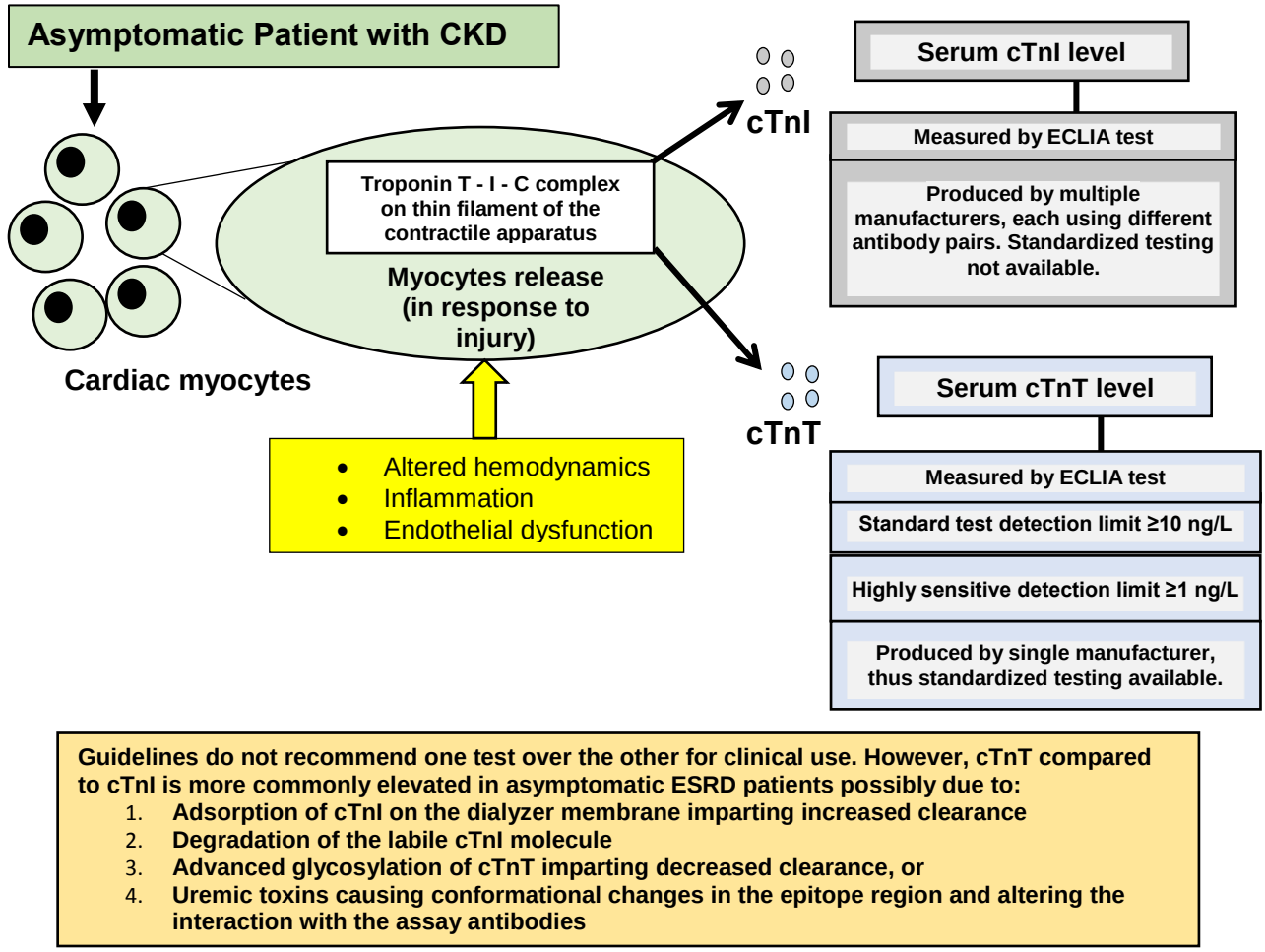

Figure 3. Cardiac Troponins in CKD

Diagnostic Utility of Cardiac Troponins for Acute Coronary Syndrome in CKD

Higher cut-offs than used in non-CKD patients for the diagnosis of AMI were suggested in CKD and ESRD individuals. A cTnT cut-off of 350 ng/L (>10-fold higher than the recommended cutoff for general use) was found to have the best sensitivity (95%) and specificity (97%) for AMI in 284 ESRD patients presenting with chest pain (7). In 89 asymptomatic CKD stages 3-5 patients, the 95th percentile for hsTnT was 139 ng/L, >10-fold higher than that derived in the general population (8), with levels increasing across higher CKD stages. Another study reported that the specificity of a cut-off of >14.0 ng/L, as recommended for diagnosis of AMI in the general population, was much lower in those with an estimated glomerular filtration rate (eGFR) of ≤60 (54%) vs. >60 mL/min/1.73 m^2 (87%) (9). A higher cut-off of >43.2 ng/L had a much higher specificity (88%) in those with eGFR ≤60.

Cardiac Troponin Levels in CKD vs. Non-CKD Patients: The Dallas Heart Study

We investigated whether cTnT and hsTnT levels were different based on the presence of CKD, and whether there was a graded increase in levels across higher CKD stages in 3,279 asymptomatic participants of the Dallas Heart Study (DHS), a multi-ethnic, population-based cohort over-sampled for women and African Americans (unpublished data). CKD was defined as eGFR <60 mL/min/1.73 m^2 or a urinary albumin-to-creatinine ratio ≥17 mg/g in men or ≥25 in women. cTnT levels were higher in CKD vs. non-CKD participants, with mean ±SD of 7 ±10 vs. 5 ±1 ng/L, respectively, *p* <0.0001. Similarly, hsTnT levels were higher in those with CKD vs. no CKD (10 ±10 vs. 3 ±5 ng/L, *p* <0.0001). Also, percentages of participants with detectable cTnT or hsTnT were significantly higher if CKD was present (*p* <0.0001 for both), and there were graded increases in percentages with detectable troponins as CKD severity increased across stages (*p* for trend <0.0001 for both biomarkers) (**Table 1**).

Table 1. Percent with detectable troponins by CKD presence

Group	cTnT ≥10 ng/L		hsTnT ≥3 ng/L		*P* value
	%	Total N	%	Total N	
No CKD	0.43	2,992	24.2	2,992	<0.0001
All CKD	8.0	287	58.3	288	
CKD 1	3.5	143	47.6	143	<0.0001
CKD 2	5.3	75	61.8	76	
CKD 3	15.3	59	74.6	59	
CKD 4/5	50.0	10	90.0	10	

The updated consensus definition of AMI requires a rise and/or fall in serial levels, with at least one value above the 99th percentile of the URL, in addition to appropriate ECG changes, imaging consistent with myocardial damage, or new regional wall abnormalities (5), but does not specify different thresholds for defining AMI in CKD. It seems reasonable, however, to consider higher threshold values in CKD and/or rely more heavily on assessment on serial changes to confirm AMI diagnosis. Similarly, we found that the 99th percentile threshold values for both cTnT and hsTnT were higher in those with CKD vs. no CKD among DHS participants (**Table 2**). In addition to higher cut-offs, a rise in troponins compared with previous chronically-elevated values, or rise and/or fall using serial measurements, has been proposed to aid in distinguishing AMI from chronic elevations of cTnT in advanced CKD/ESRD patients (5).

Table 2. 99th percentiles for cardiac troponins based on CKD vs. no CKD and CKD stages

Group	hsTnT (ng/L)		cTnT (ng/L)	
	N	99th Percentile (95% CI)	N	99th Percentile (95% CI)
Entire cohort	3298	37.0 [23.9, 43.0]	3279	13 [5, 19]
Non-CKD	3010	18.9 [15.6, 23.9]	2992	5 [5, 5]
All CKD	288	81.5 [54.1, 116.8]	287	61 [31, 96]
CKD stage 1	143	81.5 [46.4, 116.8]	143	34 [30, 88]
CKD stage 2	76	54.1 [28.1, 54.1]	75	24 [16, 24]
CKD stage 3	59	109.2 [41.8, 109.2]	59	96 [30, 96]
CKD stage 4/5	10	62.5 [ ]	10	61 [ ]

There are no recommendations to support a specific threshold of change in CKD patients, although recent data in 19 ESRD patients supports the use of ≥20% change for hsTnT (10) a value that exceeds analytical variation alone (6).

Prognostic Utility of Cardiac Troponins in CKD

Several studies reported correlations between cTnT or hsTnT with surrogate outcomes such as eGFR, LV mass index, presence of LVH, and LV systolic dysfunction in asymptomatic non-dialysis dependent CKD patients. However, lesser prospective data are available regarding the association of cTnT with hard CV outcomes in such patients. In a British study, cTnT was detectable (≥10 ng/L) in 43% of asymptomatic CKD stages 3-5 patients (11). Detectable cTnT was associated with increased all-cause mortality at 19 months (11) (**Table 3**). Similar results for the association of cTnT with increased CV events were reported in Spanish patients with CrCl <60 mL/min (12). Given low event rates, however, these studies were limited by lack of multivariable analysis and adjustment for confounders (11, 12, 13). More recently, however, reports from larger cohorts were able to show an independent association between hsTnT and CV events among CKD patients in adjusted analyses (14, 15) (**Table 3**).

Table 3. Studies reporting associations of cTnT and hsTnT with outcomes in CKD

Study	N	Study Design	Sample	Outcomes
Abbas[11]	222	Longitudinal	Asymptomatic British outpatients with CKD stage 3-5	Detectable vs. undetectable cTnT conferred all-cause mortality, uOR 3.47 (95% CI: 1.27. 10.39) (N =23)
Goicoechea[12]	176	Longitudinal	Asymptomatic Spanish outpatients, 128 with CrCl <60 mL/min	Detectable vs. undetectable cTnT increased hazard of CV event, uHR 12.3 (95% CI: 4.91, 31.02) (N =21)
Chrysochou[13]	82	Longitudinal	Asymptomatic British outpatients with atherosclerotic renovascular disease	cTnT independently associated with all-cause mortality, uHR 3.9, (95% CI: 1.8, 8.5)
Scheven[14]	8,121 PREVEND	Longitudinal	Asymptomatic Dutch outpatients; 18% CKD (ACR >30 mg/g or eGFR <60)	hsTnT independently associated with CV events (adjusted for eGFR, albuminuria, CV risk factors), aHR 1.18 (95% CI not given, p =0.03)
Hasegawa[15]	442	Longitudinal	Asymptomatic Japanese outpatients with eGFR <60	hsTnT ≥33 vs. ≤9 pg/mL conferred CV events, aHR 6.18 (95% CI: 1.38, 27.7) (N =63)

SUMMARY: Clinical Utility of Cardiac Troponins in CKD

In summary, the impact of renal clearance on circulating troponin concentrations is uncertain, and levels are commonly high in asymptomatic patients with advanced CKD. Although previous literature suggested that cTnT as compared with cTnI levels are more commonly elevated in asymptomatic ESRD patients, consensus guidelines do not specify a preference for use of cTnI over cTnT in CKD. Since troponin URLs were originally derived in non-CKD samples, knowledge gaps exist in establishing consensus regarding appropriate diagnostic cut-off values in CKD patients, as well as the required magnitude of the threshold of change in serial values. Until more data is available, higher threshold cut-offs and/or serial changes in troponins showing further elevations, as compared with previous chronically elevated levels, should be considered

for the diagnosis of AMI in patients with advanced CKD and ESRD. For prognostic purposes, it appears that detectable compared with undetectable troponins portend higher risk for future death and CV events. Future research needs to ascertain whether further workup or intervention is warranted when a detectable troponin is found in asymptomatic CKD patients.

BNP and NT-pro-BNP in CKD

NT-pro-BNP and BNP are commonly tested in symptomatic patients suspected of acute CHF exacerbation, and were found to be elevated in 56% of asymptomatic CKD patients (16). Pre-pro-BNP is synthesized within the cardiac myocytes in response to ventricular wall stress and stretch. After removal of a signaling peptide within the cytosol, pro-BNP is further cleaved into the inactive form (NT-pro-BNP) and the active hormone (BNP) either at the time of release from the myocyte or in the circulation (**Figure 4**). NT-pro-BNP is more stable with a longer half-life and may be a better biomarker for chronic volume expansion or stress than BNP (17). Reduced renal function decreases the fractional plasma clearance of both BNP and NT-pro-BNP, and studies reported correlations between graded elevations in these peptides and declining eGFR or advancing CKD stages (16, 17). The clearance of NT-pro-BNP is predominantly renal, while BNP is also degraded systemically (17) (**Figure 4**). This may explain the observed correlation of reduced eGFR to a greater extent with NT-pro-BNP than with BNP (17), and the increased ratio of NT-pro-BNP/BNP with advancing CKD stages (18), a finding not borne out by all studies. One study reported an equal dependence on renal clearances for both peptides, although most subjects had a GFR ≥30 ml/min/1.73 m^2 (19), suggesting that clearance may be similar for both until renal function deteriorates to advanced stages.

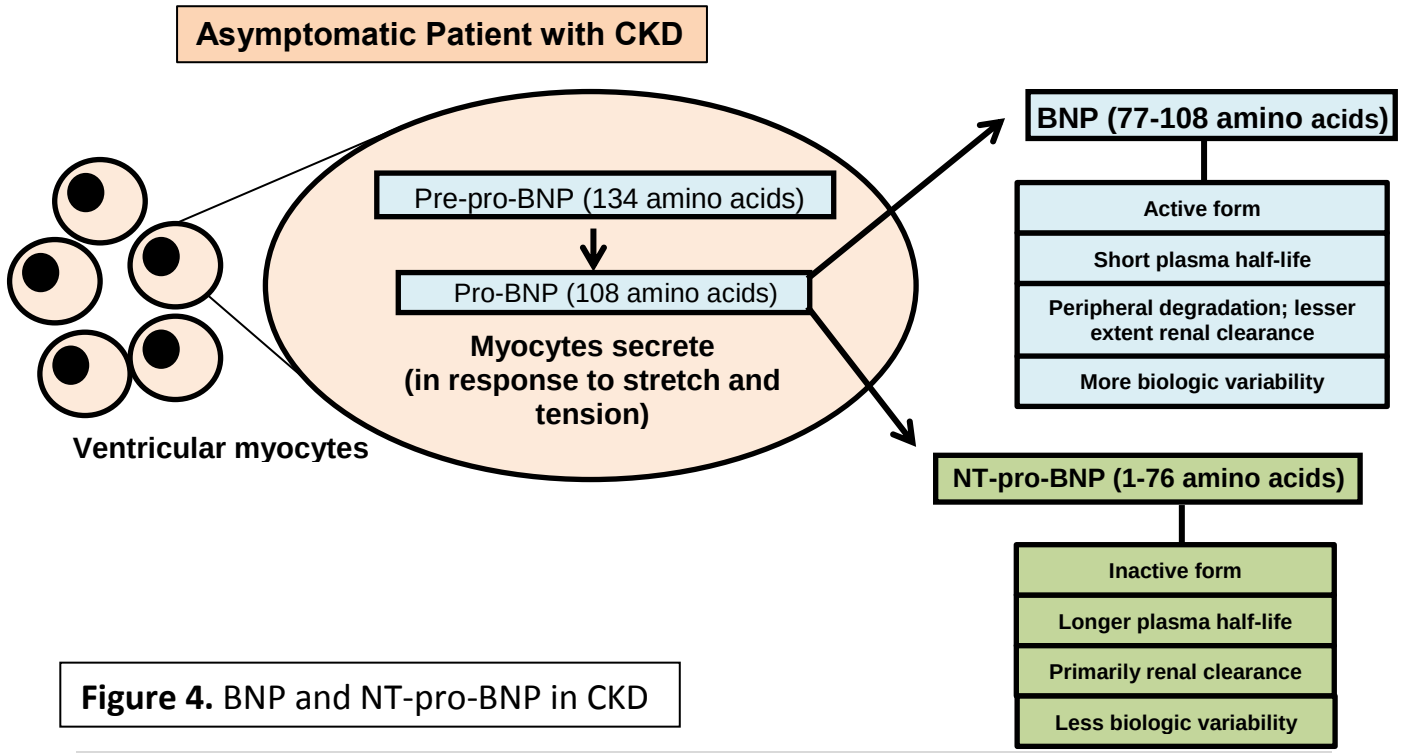

Figure 4. BNP and NT-pro-BNP in CKD

In the analysis of the DHS cohort, we revealed that levels of both BNP and NT-pro-BNP were higher in CKD vs. non-CKD participants (**Table 4**). Percent of participants with detectable levels of both biomarkers increased with increasing CKD stages (**Table 5**).

Table 4. Biomarker levels by presence of CKD: The Dallas Heart Study

Biomarker	No CKD (N = 2992)	CKD (N = 287)	*P* value
	Mean ± SD	Mean ± SD	
BNP (pg/mL)	10.9 ± 32.5	55.5 ± 314.8	<0.0001
Median [IQR]	2.9 [0.05, 12.5]	5.4 [0.05, 25.3]	
NT-pro-BNP (pg/mL)	53.4 ± 117.5	319.7 ± 1225.7	<0.0001
Median [IQR]	28.0 [13.0, 56.5]	54.9 [18.6, 152.9]	

Table 5. Percent with detectable BNP and NT-pro-BNP by CKD stage

CKD Stage	BNP ≥0.1 pg/mL		NT-Pro-BNP ≥5 pg/mL	
	%	N	%	N
1	63.3	139	85.3	143
2	73.3	75	94.7	75
3	77.6	58	98.3	59
4 and 5	90.0	10	100.0	10
Total N		282		287
***P* value**	0.01		0.001	

Diagnostic Utility of BNP and NT-pro-BNP for Acute CHF Exacerbation in CKD

A study of patients presenting with dyspnea revealed that NT-pro-BNP may be a useful diagnostic test for acute CHF in both non-CKD and CKD patients, although the diagnostic cut-off was higher in those with eGFR <60 (>1,200 pg/mL) than ≥60 mL/min/1.73 m^2 (>450 pg/mL if age <50 years; >900 if ≥50) (20). More prospective, well-controlled studies are needed to confirm these findings.

Prognostic Utility of BNP and NT-pro-BNP in CKD

Elevated levels of both BNP and NT-pro-BNP correlated with abnormal echocardiographic findings in CKD patients, such as increased LV mass index (LVMI) and presence of LVH, as well as both diastolic and systolic LV dysfunction. BNP and NT-pro-BNP are also associated with hard outcomes in CKD (**Table 6**). In a Japanese study, both BNP and NT-pro-BNP were associated with death and the composite of death and CV events (21). Based on the areas under the curve (AUC), the authors concluded that NT-proBNP may be a superior marker to BNP for composite events in patients with CKD stages 4-5 (vs. 1-3), although a formal statistical test was not used to determine if the curves were significantly different (21). Among the AASK cohort, those with elevated NT-pro-BNP had 4 times higher hazard of CV events than those with undetectable levels (22) (**Table 6**). The association was significantly stronger in those with than without proteinuria (interaction p =0.05) (22). In Chinese patients with known CAD, NT-pro-BNP was associated with all-cause death if eGFR <60 mL/min/1.73 m^2 (23). In addition, the NT-pro-BNP cut-off associated with mortality was higher in CKD (2,584 pg/mL) vs. non-CKD (370 pg/mL) patients (23). Several other studies reported similar associations between NT-pro-BNP, CV events and all-cause death (**Table 6**).

Table 6. Studies reporting associations of BNP and NT-pro-BNP with outcomes in CKD				
Study	**N**	**Study Design**	**Sample**	**Outcomes**
Astor[22]	994 AASK	Longitudinal	African Americans with eGFR 20-65 mL/min/1.73 m^2 and HTN	Elevated vs. undetectable NT-pro-BNP associated with CV events, aHR 4.0, (95% CI: 2.1, 7.6)
Horii[21]	1,083	Longitudinal	Japanese with CKD 1-5, CV disease on cardiac cath; ACS and acute CHF were excluded	BNP and NT-pro-BNP associated with death and CV composite; Composite event AUC NT-pro-BNP = 0.72 and BNP = 0.67; cut-offs for composite: CKD 1-3: BNP 91, NT-pro-BNP 260 pg/mL; CKD 4-5: BNP 157, NT-pro-BNP 5,112
deFilippi[16]	207	Cross-sectional	VA outpatients with pre-dialysis CKD 1-5	NT-pro-BNP >490 pg/mL independently associated with prior CAD events, N =67, AUC =0.69
Fu[23]	999	Longitudinal	Chinese CAD patients >60 years; 358 with CKD (eGFR <60)	NT-pro-BNP associated with all-cause death if eGFR <60, aHR 1.54 (95% CI: 1.32, 1.80)
Bruch[24]	341	Longitudinal	German outpatients with stable CHF, 183 with CKD	Elevated NT-pro-BNP independently associated with CV events (including death) in stable CHF patients with and without CKD; cut-off for both = 1,474 pg/mL
Tarnow[25]	386	Longitudinal	Danish outpatient type 1 diabetics, 198 with diabetic nephropathy	Elevated NT-pro-BNP independently associated with death in patients with diabetic nephropathy (aRR =2.49, 95% CI: 1.22-5.08)
Anwaruddin[20]	599	Cross-sectional	Dyspneic patients suspected of CHF presenting to urban ED; 207 with CKD (eGFR <60)	Elevated NT-pro-BNP and eGFR inversely correlated; NT-pro-BNP independently associated with 60-day mortality in both CKD and non-CKD

Associations of BNP and NT-pro-BNP with Death in CKD: the Dallas Heart Study

We investigated whether the association between BNP and NT-pro-BNP with death was modified by CKD in the DHS cohort and which natriuretic peptide was a better biomarker for death in CKD. Logistic regression determined the association between BNP and NT-pro-BNP with all-cause death at 7 years, adjusted for age, gender, race, diabetes mellitus, and hypertension. The interaction of CKD with biomarkers was tested using a significance level p <0.1. Receiver operating characteristic (ROC) curves were constructed using data above the detectable level for biomarkers to derive optimal cut-offs for mortality based on Youden's Index. The area under the ROC curve (AUC) for each biomarker was compared for CKD vs. non-CKD groups. The adjusted odds ratio (aOR) for death per $\log_e$ unit increase for BNP was intensified and significant for CKD at 1.22, 95% CI (1.08, 1.37), p =0.001, but not significant for non-CKD, aOR 1.06 95% CI (0.98, 1.15), p =0.15, with the interaction p value being significant at 0.05. aORs of NT-pro-BNP per $\log_e$ unit increase for death were 1.40 (1.21, 1.63) if no CKD and 1.66 (1.36, 2.04) if CKD, p <0.0001 for

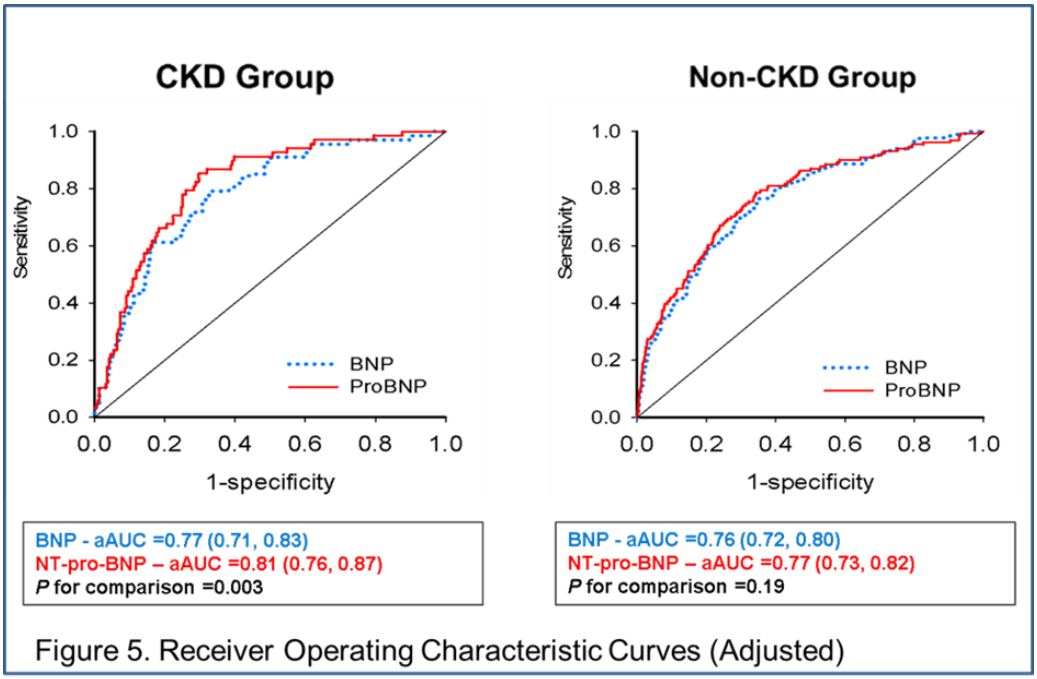

Figure 5. Receiver Operating Characteristic Curves (Adjusted)

both; interaction p =0.12. The optimal NT-pro-BNP cutoff for death was higher in CKD vs. no CKD (123 vs. 56 pg/mL). NT-pro-BNP was a superior marker for death than BNP in CKD (p value for AUC comparison =0.003) (**Figure 5**). The AUCs for BNP and NT-pro-BNP were not different if no CKD (p value for AUC comparison =0.19). CKD modified the association of BNP with death. NT-pro-BNP was a superior marker than BNP for all-cause death in asymptomatic CKD patients without baseline CV disease. Higher NT-pro-BNP cut-offs were associated with death in CKD vs. in non-CKD individuals, although future larger studies should confirm these results.

SUMMARY: Clinical Utility of BNP and NT-pro-BNP in CKD

To summarize, NT-pro-BNP and BNP can be used for prognostication in CKD patients as elevated levels are associated with both adverse surrogate and hard outcomes in this population. However, the vast majority of studies included asymptomatic samples, and clinicians are still left with the imperative question of how to best interpret elevated BNP and NT-pro-BNP levels for acute CHF diagnosis in symptomatic patients. Reduced renal function decreases the fractional plasma clearance of both BNP and NT-pro-BNP, but studies reported correlation of reduced eGFR to a greater extent with NT-pro-BNP than with BNP for more advanced CKD stages (eGFR <30 mL/min/1.73 m^2). One study reported that NT-pro-BNP may be a useful diagnostic test for CHF exacerbation in CKD, but that the diagnostic cut-off was higher in those with eGFR <60 vs. ≥60 mL/min/1.73 m^2 (20). More prospective, well-controlled studies are needed to confirm these findings.

CAC in Patients with CKD

CAC as measured by computed tomography is a noninvasive measurement of the burden of coronary atherosclerosis. CKD patients have higher CAC scores compared to age-matched non-CKD controls, and CKD patients without baseline calcification exhibit higher incidence rates of developing future de novo CAC (26). Cross-sectional analyses have reported a graded relationship between lower eGFR and increasing CAC (26). These associations were attenuated after adjustment for traditional CV risk factors, such as diabetes, but remained statistically significant for those with eGFR <30 mL/min/1.73 m^2 (26). It is not entirely clear whether a decline in eGFR plays a mechanistic role for developing de novo CAC and CAC progression. Interestingly, several analyses reported higher baseline CAC and CAC progression to be associated with eGFR decline and worsening proteinuria. A plausible explanation may be that the progression of CAC and CKD are collinear due to the presence of similar risk factors for both disease processes.

Both traditional and non-traditional CV risk factors are associated with the presence and severity of CAC in non-dialysis dependent CKD patients. Traditional factors explored included advanced age, white race, male gender, higher BMI, and diabetes mellitus, in particular (27). A retrospective study of CKD stages 2-5 subjects with well-controlled blood pressure (BP) reported

higher prevalence of CAC in diabetics vs. non-diabetics (77 vs. 33%), and another study found more rapid progression of CAC among CKD patients with vs. without diabetes (27). We previously reported in a multi-ethnic, population-based asymptomatic cohort that 3 non-traditional risk factors - calcium-phosphorus-product, homocysteine, and osteoprotegerin - were independently associated with high CAC scores, and diminished the magnitude of the association between the presence of CKD and elevated CAC, suggesting they may play mechanistic roles in the development of CAC (28).

Prognostic Utility of CAC in CKD Patients

There are less data reporting unfavorable clinical implications of CAC in pre-dialysis CKD vs. in ESRD samples. The few observational studies reporting associations of CAC with adverse outcomes are limited by low event rates, limited follow-up or ethnic homogeneity (27, 29, 30, 31) (**Table 7**). A study of a predominantly Latino diabetic cohort with proteinuria reported that those with highest compared to lowest quartile of baseline CAC had a higher hazard of all-cause mortality at 39 months (29). During a 25-month follow-up, there was 4 times higher risk of CV death or MI among CKD stages 2-5 outpatients with baseline CAC scores >100 compared to ≤100 AU (30). Finally, in renal transplant recipients, CAC score assessed at the inception of the cohort was associated with the composite of CV death, MI, stroke, transient ischemic attack, and revascularization at 2.3 years (31) (**Table 7**). However, models were over-adjusted for the few events in the last two studies (30, 31).

Table 7. Studies reporting association of CAC with outcomes in CKD

Study	N	Study Design	Sample	Outcomes
Russo[27]	341, 60 diabetic	Longitudinal	Single-center Italian inpatients and outpatients with CKD stages 2-5 and well-controlled HTN	CAC prevalence higher in diabetics *vs.* non-diabetics; diabetics with CKD had higher annualized percent increase in CAC and CV events
Russo[30]	181	Longitudinal	Italian CKD stages 2-5 outpatients without symptomatic CVD	Compared to subjects with baseline CAC score ≤100, those with >100 AU had a higher hazard of CV death or MI, aHR 4.11 (95%CI: 1.77, 9.57) (events =29)
Chiu[29]	225, all diabetic	Longitudinal	Proteinuric subjects with mean UPCR 2.7 and eGFR 52; 70% Latino	Those with highest (compared with lowest) quartile baseline CAC had a higher hazard of all-cause death, aHR 2.61 (95%CI: 1.23, 5.54), (events =54)
Nguyen[31]	281, 42 diabetic	Longitudinal	Single-center Belgian (98% white) kidney transplant recipients	Baseline CAC score was associated with CV composite, aHR 1.40 (95% CI: 1.12, 1.75), (events =31, 8 CV deaths)

SUMMARY: Clinical Utility of CAC in CKD

CAC is being used as a screening test to assess risk of future CV events in non-CKD patients with intermediate CV risk, as it may add to the prognostic utility of the Framingham Risk Score (32). Asymptomatic non-CKD individuals without CAC have a very low risk of CV events, whereas those with scores >400 AU have elevated risk similar to those with diabetes or

peripheral vascular disease (32). Studies in non-CKD patients reported a strong correlation between CAC and total atherosclerotic plaque burden at the individual level (r = 0.90) (32). Although current guidelines *do not* recommend the routine use of CAC for risk stratification, they do recommend its use to inform treatment decision-making in non-CKD patients, if, after quantitative risk assessment using traditional CV risk factors, a risk-based treatment decision is uncertain (33). However, it is too early to recommend the standard use of CAC for risk stratification in CKD patients, as it remains unclear whether such calcific lesions in a coronary artery segment increase or decrease biomechanical stability of atherosclerotic plaques in CKD (34). Similarly, it is not known whether increased CAC or its progression truly play a mechanistic role in the development of future CV events or are merely surrogates for other CV risk factors in CKD patients. Finally, there are not enough data to show that CAC is a modifiable risk factor in CKD. For example, it is currently not known whether the reduction of calcium or phosphate using various binders persistently influences regression of CAC in CKD, and if CAC regression translates to improved outcomes.

LV mass or LV dysfunction in CKD

LV hypertrophy (LVH) and abnormal LV function, based on echocardiographic parameters, are highly prevalent among CKD patients who initiate dialysis. Based on a Canadian cohort, 74% have LVH, 36% LV dilation, and 15% LV systolic dysfunction (LVSD) (35). Higher baseline LVMI is associated with severity of CKD as well as progression, but it is not clear whether this is independent of high BP.

CKD stage severity parallels increases in LVMI and decreases in LV ejection fraction (EF). CKD stages 3-5 patients with LVH compared to without had lower eGFR and greater proteinuria, and there was a weak inverse correlation between LVMI and eGFR (36). However, in multivariable models that included systolic BP and BMI, eGFR was not independently associated with LVH (36). Another cross-sectional study did report a correlation between urinary protein-to-creatinine ratio (UPCR) and LVMI, independent of systolic BP, although a similar correlation was not observed with eGFR (37). These studies were limited by lack of non-CKD controls. Interestingly, there was higher LV mass, greater degree of LV diastolic dysfunction (LVDD), but no difference noted in LVEF among CKD patients compared to age- and gender-matched controls using univariate analyses (38). However, pulse pressure (PP) was significantly higher in CKD cases than in controls, which could account for the observed differences (38). Finally, three prospective longitudinal studies reported changes in LV geometry to independently correlate with eGFR decline and progression to ESRD (39-41).

Prognostic Value of LV mass and LV dysfunction in CKD

LVMI was independently associated with increased all-cause and CV mortality in patients initiating dialysis in a prospective study, even after adjusting for age, CAD, DM, and systolic BP (35). These findings were extended to CKD stages 3-5 outpatients where higher LVMI and

LVEF <55% vs. ≥55% at baseline were associated with CV events including death, MI, sustained ventricular arrhythmia, hospitalization for unstable angina, congestive heart failure, transient ischemic attack, or stroke at 26 months (42) (**Table 8**).

Table 8. Studies reporting associations of LV mass and function with outcomes in CKD

Study	N	Study Design	Sample	Outcomes
Chen[39]	415	Longitudinal, 53% diabetic	Taiwanese CKD 3-5 outpatients	cLVH measured by echo was associated with progression to ESRD, aHR 2.03 (95% CI: 1.00, 4.10)
Chen[40]	540	Longitudinal, 50% diabetic	Taiwanese CKD 3-5 outpatients	Those with higher uric acid and LVMI had higher hazard of progression to dialysis and higher odds of rapid decline in eGFR, aHR 1.83 (95% CI: 1.01, 3.33) and aOR 2.23 (95% CI: 1.06, 4.70)
Park[41]	3,866 MESA	Longitudinal, 11% diabetic	eGFR >60 at baseline	During a median follow-up of 4.8 years, each SD higher LV concentricity was associated with a 9% and 8% decline in $eGFR_{cr}$ and $eGFR_{cys}$
Silberg[35]	91	Longitudinal	Single center Canadian subjects with incident ESRD	Those with highest vs. lowest quintile of LVMI at baseline experienced higher hazards of all-cause mortality and CV mortality, aHR 2.9 (95% CI: 1.3, 6.9) and 2.7 (95% CI: 0.9, 8.2)
Chen[42]	505	Longitudinal, 56% diabetic	Taiwanese CKD 3-5 outpatients	Every g/m^2 increase in LVMI and LVEF <55% vs. ≥55% were associated with increased CV events, aHR 1.006 (95% CI: 1.002, 1.010) and 2.01 (95% CI: 1.01, 3.74)

SUMMARY: Clinical utility of LV mass or LV dysfunction in CKD

LVH and LV dysfunction are prevalent among patients with stages 3-5 CKD and among those with ESRD initiating dialysis. Although data suggest that LVH and increased LVMI are associated with CKD progression and CV events, elevated BP and PP, highly prevalent in this patient population, may be major confounders in these analyses. In addition, lack of well-controlled prospective studies limit the utility of echocardiographic parameters in predicting outcomes in clinical practice. Future studies need to analyze how changes in LV mass and function over time may be used to prognosticate hard clinical outcomes.

CONCLUSIONS

Observational studies reporting associations between cTnT and NT-pro-BNP and decline in eGFR in non-dialysis CKD patients may be confounded by decreased renal clearance of these biomarkers in the setting of advanced CKD. The same traditional and non-traditional factors that are associated with CAC are likely also correlated with CKD progression. Although the evidence presented suggests that biomarkers such as cardiac troponins, BNP and NT-pro-BNP may be used to prognosticate future CV events and mortality in asymptomatic CKD patients, future studies need to confirm reliable cut-offs for the utility of these biomarkers as diagnostic tests in patients presenting with symptoms concerning for ACS or acute CHF. In addition, it remains unclear whether cardiac biomarkers such as cTnT, NT-pro-BNP, BNP, and CAC, in asymptomatic CKD patients are modifiable and amenable to interventions to reduce future CV

risk. Given current knowledge gaps, more data needs to become available before all of these markers can be reliably utilized in this patient population. Further studies are needed to inform whether better risk stratification scores, that include novel in addition to traditional biomarkers, should be developed for quantification of CV risk in CKD individuals.

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