Canadian Journal of Cardiology 35 (2019) 1106–1113

Clinical Research

Glomerular Filtration Rate-Specific Cutoffs Can Refine the Prognostic Value of Circulating Cardiac Biomarkers in Advanced Chronic Kidney Disease

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See editorial by Hundemer and Sood, pages 1082–1084 of this issue.

ABSTRACT

Background: Using standard cutoffs derived from healthy adults, high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are frequently elevated in patients with reduced glomerular filtration rate (GFR), with unclear implications. We sought to compare GFR-specific cutoffs of each biomarker with standard cutoffs for discrimination of cardiovascular risk in asymptomatic patients with chronic kidney disease.

Methods: We investigated a prospective cohort of 1956 participants with median GFR of 27 mL/min/1.73 m^2. Cox proportional hazards models were used to examine the association between each biomarker and first adjudicated cardiovascular event (unstable angina, myocardial infarction, heart failure, stroke, cardiovascular death). We used an outcome-based approach to identify optimal risk-based cutoffs for each biomarker within GFR strata (< 20, 20-29, 30-44 mL/min/1.73 m^2). We evaluated the added prognostic value of each biomarker to a multivariable base model, comparing GFR-specific with standard cutoffs.

Results: Hs-cTnT and NT-proBNP were elevated in 76% and 82% of participants, respectively. A total of 401 events were recorded during

RÉSUMÉ

Contexte : À l'aune des valeurs seuils standard établies chez les adultes en bonne santé, on constate que les taux de troponines cardiaques hypersensibles et de propeptide natriurétique de type B N-Terminal (NT-proBNP) sont fréquemment élevés chez les patients présentant un débit de filtration glomérulaire (DFG) réduit. Les implications de cette observation restent à élucider. Nous avons cherché à comparer les valeurs seuils de chaque biomarqueur selon le DFG aux valeurs seuils standards afin de déterminer le risque cardiovasculaire chez des patients asymptomatiques atteints d'insuffisance rénale chronique.

Méthodologie : Nous avons mené une étude de cohorte prospective regroupant 1956 sujets présentant un DFG médian de 27 ml/min/1,73 m^2. Des modèles à risques proportionnels de Cox ont servi à examiner l'association entre chaque biomarqueur et le premier événement cardiovasculaire confirmé (angine instable, infarctus du myocarde, insuffisance cardiaque, accident vasculaire cérébral, décès d'origine cardiovasculaire). Nous avons adopté une approche axée sur la survenue des événements afin de déterminer les valeurs seuils optimales fondées sur le risque au regard de chaque biomarqueur

Individuals with chronic kidney disease (CKD) represent a high-risk group for adverse cardiovascular outcomes.[1] The need for accurate prognostication has fueled interest in circulating biomarkers that can better inform risk stratification. In the general population, high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), markers of myocyte injury and myocardial stretch respectively, are strong predictors of cardiovascular outcomes.[2,3] There is comparatively less evidence to support their use in CKD. Most studies in CKD populations have been cross-sectional with small sample sizes.[4] Few prospective studies have investigated the association between cardiac biomarkers and cardiovascular outcomes,[5-7] and these studies have included low numbers of participants with advanced CKD. Patients with advanced CKD have traditional and nontraditional cardiovascular risk factors, the latter related to complications of their kidney dysfunction such as anemia, hyperphosphatemia, and inflammation. It is

Received for publication March 8, 2019. Accepted June 16, 2019.

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See page 1112 for disclosure information.

https://doi.org/10.1016/j.cjca.2019.06.014

6772 person-years at risk. Both biomarkers were independent predictors of cardiovascular events. Optimal cutoffs for each biomarker were higher than standard thresholds, being highest at GFR values < 20 mL/min/1.73 m^2. Addition of hs-cTnT to the base model using GFR-specific cutoffs significantly improved reclassification for events (52%) and nonevents (21%). Similar findings were observed for NT-proBNP. In contrast, use of standard cutoffs failed to reclassify patients who had no event as lower risk.

Conclusions: Among asymptomatic patients with advanced chronic kidney disease, optimal cutoffs for hs-cTnT and NT-proBNP differed according to GFR level and outperformed standard cutoffs for discrimination of cardiovascular risk.

selon la stratification du DFG (< 20, 20-29, 30-44 ml/min/1,73 m^2). Nous avons évalué la valeur pronostique ajoutée de chaque biomarqueur dans un modèle de base à variables multiples, comparant les valeurs seuils selon le DFG aux valeurs seuils standards.

Résultats : Les taux de troponines cardiaques hypersensibles et de NT-proBNP étaient élevés chez 76 % et 82 % des participants, respectivement. Au total, 401 événements ont été consignés au cours de 6772 années-personnes à risque. Les deux biomarqueurs ont constitué des prédicteurs indépendants des événements cardiovasculaires. Les valeurs seuils optimales de chaque biomarqueur étaient plus élevées que les valeurs seuils standards, culminant en présence d'un DFG < 20 ml/min/1,73 m^2. L'ajout de la troponine cardiaque hypersensible au modèle de base compte tenu des valeurs seuils selon le DFG a amélioré sensiblement la reclassification des cas où il y avait présence d'événements (52 %) ou absence d'événements (21 %). Des résultats similaires ont été observés pour la NT-proBNP. En revanche, l'utilisation des valeurs seuils standards n'a pas entraîné la reclassification des patients n'ayant pas eu d'événement dans une catégorie de risque inférieure.

Conclusions : Chez les patients asymptomatiques atteints d'insuffisance rénale chronique avancée, les valeurs seuils optimales de troponines cardiaques hypersensibles et de NT-proBNP différaient selon le DFG et se sont avérées plus concluantes que les valeurs seuils standards pour déterminer le risque cardiovasculaire.

unknown if hs-cTnT and NT-proBNP are independently associated with cardiovascular outcomes in this population, or whether they provide prognostic value over and above traditional and nontraditional risk factors.

The interpretation of hs-cTnT and NT-proBNP is challenging in patients with reduced glomerular filtration rate (GFR). Among asymptomatic individuals with CKD, values of hs-cTnT and NT-proBNP frequently exceed standard cutoffs in the general population.[8] Whether this reflects reduced renal clearance or increased production, due to subclinical heart disease, is not clear. Irrespective of the mechanism, the inverse correlation of cardiac biomarkers with GFR makes it difficult to disentangle their contribution to cardiovascular risk beyond their association with deteriorating kidney function. Using a biomarker threshold derived from the general population identifies many CKD patients as having a "positive" test, but might not discriminate well between those who will or will not experience a cardiovascular event.

We sought to investigate the relationship between cardiac biomarkers and cardiovascular events in asymptomatic patients with advanced CKD. We hypothesized that GFR-specific cutoffs for hs-cTnT and NT-proBNP would improve prognostication of cardiovascular events, compared with a standard cutoff fixed across the GFR range.

Methods

Design

This was a retrospective cohort analysis from the **Can**adian study of **P**rediction of **R**isk and **E**volution to **D**ialysis, **D**eath and **I**nterim **C**ardiovascular Events Over **T**ime (CanPREDDICT), a multicentre cohort of adult predialysis patients with estimated GFR of 15-45 mL/min/1.73 m^2. Excluded patients had a life expectancy < 12 months, active vasculitis, or organ transplantation. Participants were followed at 6-month intervals for the first 3 years and annually thereafter.[9] The present analysis included 1956 participants who had hs-cTnT and NT-proBNP measured at baseline and complete data for outcomes (Supplemental Fig. S1). Participants provided informed written consent and ethical approval was granted by the institutional review boards of all 25 participating centres. Experimental procedures adhered to the Declaration of Helsinki. CanPREDDICT is registered at www.clinicaltrials.gov (NCT00826319).

Outcome

The outcome was a composite of: (1) unstable angina or myocardial infarction as documented on comprehensive clinic notes, serial electrocardiograms, and/or cardiac biomarkers; (2) congestive heart failure, defined as dyspnea plus 2 of the following: bibasilar rales, raised jugular venous pressure, or pulmonary edema on chest X-ray; (3) stroke, defined as acute infarction on brain imaging; and (4) cardiovascular death. Outcomes were adjudicated using source documentation by a panel of physicians including a nephrologist, cardiologist, and neurologist. We chose a composite outcome because we were investigating the prognostic value of hs-cTnT and NT-proBNP, and both biomarkers have been shown to be independent predictors of multiple cardiovascular end points.[5,10-12]

Exposure

Hs-cTnT and NT-proBNP were measured in an accredited laboratory using an electrochemiluminometric immunoassay (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) using a Roche Cobas e601 analyzer (Roche Diagnostics International Ltd). For hs-cTnT the standard cutoff was 14 ng/L, the 99th centile from the distribution in healthy adults. For NT-proBNP we defined the standard cutoff as 125 pg/mL, as recommended by international guidelines.[13]

Covariates

Demographic variables included age and sex. Clinical variables included diabetes and preexisting cardiac disease. Medications including β-blockers, renin-angiotensin-aldosterone system blockers, diuretics, aspirin, and statins were ascertained at the initial visit. Pulse pressure was calculated as the difference between systolic and diastolic pressures. Creatinine, urinary albumin to creatinine ratio, hemoglobin, and phosphate were measured in local accredited laboratories using standardized assays. GFR was estimated from creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation.[14] High-sensitivity C-reactive protein was measured using a Siemens BNII Nephelometric Immunoassay (Siemens, Oakville, ON).

Statistical analysis

Analyses were performed using Stata version 14.1 (StataCorp, College Station, TX) and SAS version 9.4 (SAS Institute, Cary, NC). Continuous variables are presented as mean (SD) or median (interquartile range [IQR]) as appropriate. Categorical variables are described as count (percentage). We investigated the relationship between each biomarker and cardiovascular events using Kaplan-Meier curves and multivariable Cox proportional hazards models. No universally accepted cardiovascular risk prediction model has been specifically validated in CKD.[15] Candidate covariates were chosen on the basis of previous literature.[16] The association between each covariate and cardiovascular events was first explored in a univariable analysis. Consistent with previous studies in CKD populations, neither body mass index nor hyperlipidemia were associated with cardiovascular events. The final base model included the traditional risk factors age, sex, pulse pressure, preexisting cardiac disease (a history of ischemic heart disease, heart failure, or both), and diabetes. We also included the following CKD-specific risk factors: GFR, urinary albumin to creatinine ratio, hemoglobin, high-sensitivity C reactive protein, and phosphate.[17-20]

We used an outcome-oriented approach to explore risk-based cutoffs for hs-cTnT and NT-proBNP within GFR strata. This method uses repeated log rank tests to identify an optimal cut point along the distribution of a continuous covariate that maximally differentiates high- vs low-risk populations for a specific outcome.[21,22] Potential cutoffs for hs-cTnT and NT-proBNP were sought by performing the procedure within categories of GFR: < 20, 20-29, 30-44 mL/min/1.73 m^2. We chose these categories to be consistent with clinical staging of GFR, while acknowledging the heterogeneity among patients with GFR values of 15-30 mL/min/1.73 m^2. From these results we generated "GFR-specific" cutoffs: each individual was assigned a "positive" or "negative" result for hs-cTnT or NT-proBNP on the basis of whether their biomarker value was greater than or less than the cutoff identified as high risk for their GFR category.

To explore the independent association between hs-cTnT and NT-proBNP and cardiovascular events, we added each biomarker to a base model (incorporating the variables described previously) as a categorical variable (quartiles) and a continuous variable (log-transformed). We repeated the analysis after considering noncardiovascular death as a competing risk and renal replacement therapy as a time-varying covariate. To evaluate the added value of hs-cTnT or NT-proBNP for prediction of cardiovascular events at 3 years, they were added to the base model as categorical variables on the basis of standard or GFR-specific cutoffs, because thresholds are more easily implemented in clinical practice than continuous variables or quartiles. For each type of cutoff we calculated C-statistics, category-free net reclassification indices (NRIs) and integrated discrimination improvement for the addition of hs-cTnT or NT-proBNP to the multivariable base model.[23-25] We used bootstrapping with replacement to generate 95% confidence intervals for these estimates. The continuous NRI evaluates the ability of a model to increase predicted risk in those who experience the outcome of interest, or decrease predicted risk among those who do not experience the outcome.

Results

Participant characteristics

Table 1 show the characteristics of the cohort, overall and according to quartile of hs-cTnT. As expected in an actively managed CKD cohort, most were receiving antihypertensive medications and statins. With increasing quartiles of hs-cTnT, participants tended to be older and have a higher prevalence of diabetes. They also tended to have higher values of pulse pressure, high-sensitivity C-reactive protein, and phosphate, and lower levels of hemoglobin. A similar pattern was observed across quartiles of NT-proBNP (Supplemental Table S1).

Association between cardiac biomarkers and cardiovascular events

Median follow-up was 4.0 (IQR, 2.1-5.0) years, encompassing 6772 person-years at risk, during which time 401 cardiovascular events were recorded. A total of 147 participants experienced a cardiovascular event and kidney failure, most of whom (91; 62%) experienced their cardiovascular event before initiating renal replacement therapy. The relationship between each biomarker and cardiovascular events is illustrated in Supplemental Figure S2 and described in Supplemental Table S2. Quartiles of hs-cTnT showed a stepwise increased risk of cardiovascular events, which was robust to multivariable adjustment. Results were unchanged after further adjustment for cardiovascular medications (data not shown). Results were similar in a model treating non-cardiovascular death as a competing event (Supplemental Table S3) and renal replacement therapy as a time-varying covariate (Supplemental Table S4). Quartiles of NT-proBNP also showed a stepwise increased risk of cardiovascular events (Supplemental Fig. S2). In the multivariable model, only NT-proBNP values above the median remained associated with cardiovascular events (Supplemental Table S2). A similar pattern was observed in models in which death was treated as a competing risk (Supplemental

Table 1. Patient characteristics overall and according to quartile of high-sensitivity cardiac troponin T

Characteristic	Overall	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Mean age (SD), years	68.1 (12.7)	60.4 (14.4)	68.9 (11.3)	71.7 (10.3)	71.6 (11.0)
Female sex	722 (36.9)	278 (56.9)	181 (37.0)	158 (32.3)	105 (21.5)
Diabetes	958 (49.0)	126 (25.8)	215 (44.0)	274 (56.0)	343 (70.1)
CVD					
None	1078 (55.1)	377 (77.1)	278 (56.9)	231 (47.2)	192 (39.3)
IHD	355 (18.2)	45 (9.2)	90 (18.4)	114 (23.3)	106 (21.7)
CHF	214 (10.9)	39 (8.0)	61 (12.5)	51 (10.4)	63 (12.9)
IHD and CHF	309 (15.8)	28 (5.7)	60 (12.3)	93 (19.0)	128 (26.2)
Mean SBP (SD), mm Hg	134.2 (19.9)	129.9 (17.5)	133.8 (17.8)	136.4 (20.4)	136.4 (22.6)
Mean DBP (SD), mm Hg	70.9 (11.8)	73.9 (11.4)	71.5 (11.0)	69.9 (11.9)	68.3 (12.0)
Mean PP (SD), mm Hg	63.3 (18.7)	56.0 (16.4)	62.4 (17.9)	66.5 (17.9)	68.1 (20.1)
Median Hs-cTnT (IQR), ng/L	24.8 (14.4-40.6)	9.8 (7.1-12.0)	18.8 (16.6-21.8)	31.1 (27.7-35.3)	58.8 (48.1-80.6)
Median GFR (IQR), mL/min	27 (20-33)	30 (24-37)	27 (21-34)	25 (20-32)	22 (18-29)
Median ACR (IQR), mg/mmol	18.1 (3.3-92.6)	8.2 (1.7-56)	13.4 (2.7-65.5)	20.7 (4.5-116.9)	36.9 (6.8-175.4)
Mean Hb (SD), g/L	123.2 (15.4)	127.1 (15.0)	125.4 (15.6)	121.1 (14.8)	119.2 (15.2)
Median hs-CRP (IQR), nmol/L	2.9 (1.1-6.7)	2.0 (0.9-5.1)	2.5 (1.1-5.8)	3.3 (1.3-7.2)	3.9 (1.5-8.4)
Mean PO_4 (SD), mmol/L	1.22 (0.25)	1.18 (0.27)	1.18 (0.22)	1.25 (0.24)	1.26 (0.26)
Aspirin	1055 (53.9)	188 (38.5)	260 (53.2)	293 (59.9)	314 (64.2)
β-Blocker	906 (46.3)	171 (35.0)	232 (47.4)	252 (51.5)	251 (51.3)
Statin	1351 (69.1)	282 (57.7)	338 (69.1)	371 (75.9)	360 (73.6)
RAASi	1403 (71.7)	366 (74.9)	374 (76.5)	339 (69.3)	324 (66.3)
Diuretic	1320 (67.6)	237 (48.6)	324 (66.3)	366 (74.9)	393 (80.5)

Data are presented as n (%) except where otherwise noted. Data are missing for blood pressure (n = 1), urinary ACR (n = 2), hs-CRP (n = 27), and diuretic use (n = 2).

ACR, albumin to creatinine ratio; CHF, congestive heart failure; CVD, cardiovascular disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; Hb, hemoglobin; hs-CRP, high sensitivity C reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; IHD, ischemic heart disease; IQR, interquartile range; PO_4, phosphate; PP, pulse pressure; RAASi, renin angiotensin aldosterone system inhibitor; SBP, systolic blood pressure.

Table S3) and renal replacement therapy as a time-varying covariate (Supplemental Table S4).

Defining optimal cutoffs for hs-cTnT and NT-proBNP

Median values of hs-cTnT and NT-proBNP were 24.8 (IQR, 14.4-40.6) ng/L and 444 (IQR, 176-1214) pg/mL respectively, and progressively increased with decreasing GFR (Fig. 1). Using standard cutoffs, most participants had elevated levels of hs-cTnT (n = 1483; 76%) and NT-proBNP (n = 1622; 83%). We used an outcome-based approach to identify optimal risk-based cutoffs for each biomarker within GFR categories. For hs-cTnT, these cutoffs were all higher than the standard cutoff (14 ng/L) and increased in a graded fashion with decreasing GFR: 1.6, 1.9, and 2.5 times the standard cutoff for GFR categories, 30-44, 20-29, and < 20 mL/min/1.73 m^2, respectively (Table 2). For NT-proBNP, optimal cutoffs were also higher than the standard cutoff (125 pg/mL), although a graded increase was less evident. Nonetheless, the cutoff for participants with GFR < 20 mL/min/1.73 m^2 was 765 pg/mL, approximately 6 times the standard cutoff.

Using the GFR-specific cutoffs, both biomarkers were strongly associated with cardiovascular events (Supplemental Fig. S3). After multivariable adjustment, individuals with a positive hs-cTnT using the GFR-specific cutoffs had a 2.7-fold increased risk of a cardiovascular event (hazard ratio, 2.66; 95% confidence interval [CI], 2.08-3.42), compared with individuals whose hs-cTnT was below the threshold for their GFR category (Table 3). This risk estimate was similar to that using the standard cutoff to define a positive or negative test, however, the distribution of patients was quite different depending on the choice of cutoff. GFR-specific cutoffs captured a much larger proportion of patients (n = 1072; 55%) as having a negative hs-cTnT compared with the standard cutoff (n = 473; 24%). After multivariable adjustment, those with a positive NT-proBNP using GFR-specific cutoffs had a threefold increased risk of a cardiovascular event (hazard ratio, 3.17; 95% CI, 2.45-4.11), higher than the estimate associated with the standard cutoff (hazard ratio, 1.94; 95% CI, 1.20-3.14). Using GFR-specific cutoffs, the relationship between each cardiac biomarker and cardiovascular events was consistent across subgroups of age (above or below the median age of 70 years), sex, diabetes, and preexisting cardiac disease (Supplemental Table S5).

Added prognostic value of hs-cTnT and NT-proBNP

Table 4 shows the superiority of GFR-specific cutoffs over standard cutoffs for prediction of cardiovascular events. Our base model, incorporating traditional and CKD-related risk factors, had a C-statistic of 0.763 (95% CI, 0.746-0.788). Adding hs-cTnT and NT-proBNP to the base model, dichotomized using their standard cutoffs, resulted in either a modest improvement (hs-cTnT) or no improvement (NT-proBNP) in C-statistics and net reclassification. Adding hs-cTnT using the standard cutoff of 14 ng/L appropriately reclassified 38.9% of patients who experienced a cardiovascular event as higher risk (event NRI), but failed to reclassify patients who did not experience an event as lower risk (nonevent NRI). The addition of NT-proBNP to the base model using the standard cutoff of 125 pg/mL also failed to reclassify patients who did not experience an event as lower risk. In contrast, adding GFR-specific cutoffs of hs-cTnT or NT-proBNP not only improved the C-statistic of the base model, but also resulted in substantial reclassification for events and nonevents. In the case of hs-cTnT, the GFR-specific cutoff reclassified 52% of patients who experienced

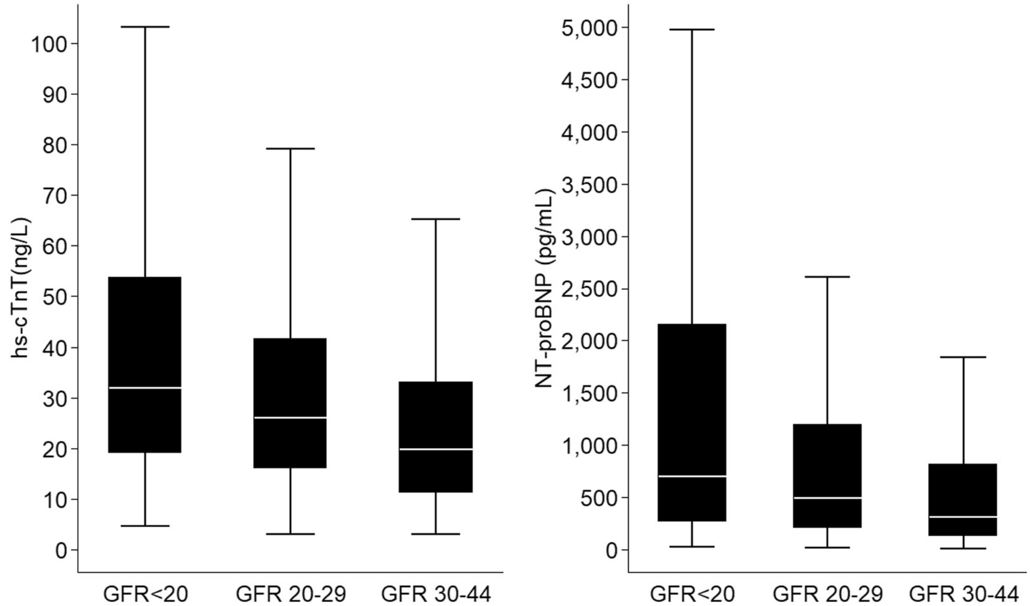

Figure 1. Median and interquartile range of high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro-B type natriuretic peptide (NT-proBNP) across categories of glomerular filtration rate (GFR).

an event as higher risk (event NRI), and 21% of patients who did not experience an event as lower risk (nonevent NRI). For NT-proBNP the corresponding figures were 56.3% and 25.3%, respectively. GFR-specific cutoffs of NT-proBNP were also superior compared with the suggested age-independent standard cutoff[26] of 300 pg/mL (Supplemental Table S6).

Discussion

The key findings from this study were fourfold: (1) hs-cTnT showed a strong and graded association with cardiovascular events in patients with advanced CKD after adjusting for traditional and nontraditional risk factors. Higher values of NT-proBNP were also independently associated with cardiovascular events; (2) we identified optimal risk-based cutoffs for hs-cTnT and NT-proBNP that differed according to GFR category; (3) GFR-specific cutoffs for hs-cTnT and NT-proBNP were strongly associated with cardiovascular events in multivariable-adjusted models; and (4) GFR-specific cutoffs showed superior prognostic value compared with standard cutoffs. Taken together, these findings support the concept of GFR-specific cutoffs for hs-cTnT and NT-proBNP for cardiovascular risk stratification in asymptomatic patients with advanced CKD.

Table 2. Optimal cut points for hs-cTnT and NT-proBNP within strata of GFR

GFR category	Optimal hs-cTnT cut point	Optimal NT-proBNP cut point
30-44 mL/min	22.7 ng/L	584 pg/mL
20-29 mL/min	26.8 ng/L	459 pg/mL
< 20 mL/min	35.5 ng/L	765 pg/mL

GFR, glomerular filtration rate; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Despite the recognition that patients with CKD are at high cardiovascular risk,[1] with a magnitude of risk similar to patients with diabetes mellitus,[27] accurate prediction of cardiovascular events in CKD has proven to be challenging. Patients with advanced CKD represent a particularly complex subgroup in whom to predict cardiovascular outcomes. Established risk prediction models for cardiovascular disease in the general population have not been well validated in patients with CKD, and do not include important CKD-related risk factors. It is important to accurately predict which CKD patients are at higher risk of cardiovascular events to identify those who require more intensive surveillance, additional investigations, or more aggressive treatment. Equally important is the identification of patients at lower risk of cardiovascular events, with the aims of limiting polypharmacy, avoiding unnecessary investigations, and reducing patient anxiety. Although hs-cTnT and NT-proBNP appear to be strong predictors of cardiovascular events in advanced CKD, clinicians need meaningful cutoffs to assign a positive or negative test result for patients. Current standard thresholds, which are fixed across the range of GFR, appear to have limited utility for risk discrimination in this population because most patients have a positive test result. It should be acknowledged that it is not known if using cardiac biomarkers for risk discrimination in asymptomatic patients with CKD will improve outcomes, or lead to more streamlined cardiac evaluation in these patients. However, our findings could inform future studies seeking to investigate these questions.

Similar problems in the interpretation of hs-cTnT have been encountered in patients who present to the emergency room with symptoms suggestive of acute myocardial infarction. Among patients with GFR < 60 mL/min/1.73 m^2, current thresholds show high sensitivity and negative

Table 3. Association between hs-cTnT and NT-proBNP and cardiovascular events, comparing uniform with GFR-specific cutoffs

Cutoff	Hs-cTnT	n (%)	Events (%)	Unadjusted	Adjusted*
Uniform	Negative	473 (24)	25 (5.3)	Reference	Reference
	Positive	1483 (76)	376 (25.4)	5.86 (3.90-8.78)	2.63 (1.71-4.04)
GFR-specific	Negative	1072 (55)	106 (9.9)	Reference	Reference
	Positive	884 (45)	295 (33.4)	4.28 (3.42-5.34)	2.66 (2.08-3.42)
	NT-proBNP				
Uniform	Negative	334 (17)	19 (5.7)	Reference	Reference
	Positive	1622 (83)	382 (23.6)	5.29 (3.34-8.39)	1.94 (1.20-3.14)
GFR-specific	Negative	1096 (56)	97 (8.9)	Reference	Reference
	Positive	860 (44)	304 (35.4)	5.67 (4.51-7.14)	3.17 (2.45-4.11)

Estimates are hazard ratios (95% confidence interval).

GFR, glomerular filtration rate; Hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro-B type natriuretic peptide.

*Model adjusted for age, sex, diabetes, cardiovascular disease, pulse pressure, hemoglobin, estimated GFR, urinary albumin to creatinine ratio, phosphate, and high sensitivity C-reactive protein.

predictive value, but low specificity and positive predictive value.[28,29] It has been suggested that, in the acute setting, optimal cutoffs for hs-cTnT might be higher in CKD patients compared with those without CKD.[28] Whether GFR-specific cutoffs would improve the positive predictive value of hs-cTnT for acute myocardial infarction in patients with CKD cannot be answered by the present study, because all patients were asymptomatic at the time of testing. In this asymptomatic cohort, GFR-specific cutoffs for hs-cTnT and NT-proBNP performed better than standard cutoffs for the prediction of subsequent cardiovascular events, thereby offering the potential to refine the cardiovascular risk profile of an individual patient with CKD. For instance, the use of GFR-specific cutoffs for hs-cTnT appropriately reclassified 52% and 21% of patients into a higher and lower risk profile, respectively, compared with 39% into higher risk and no patients into lower risk using the standard threshold. The standard threshold for NT-proBNP did not appreciably add to the base model, whereas the addition of NT-proBNP using GFR-specific cutoffs substantially improved the model C-statistic and reclassification for events and nonevents. We propose that this approach could prove useful for inclusion of CKD patients into event-driven clinical trials, by using GFR-specific thresholds of hs-cTnT or NT-proBNP to stratify cardiovascular risk at the time of enrollment.

Few prospective studies have simultaneously investigated the prognostic value of hs-cTnT and NT-proBNP in individuals with kidney disease. A large population-based study (n = 8121) from the Netherlands showed that both biomarkers were statistically significant predictors of incident cardiovascular morbidity and mortality, after adjusting for GFR and albuminuria.[6] These findings were not generalizable to a CKD sample. The mean GFR in this cohort was 84 mL/min/1.73 m^2 and only 55 participants had a GFR < 45 mL/min/1.73 m^2. The Chronic Renal Insufficiency Cohort (CRIC) investigators extended these observations to individuals with mild to moderate CKD (mean GFR 45.7 mL/min/1.73 m^2).[5] In a death-censored analysis, the investigators reported that hs-cTnT and NT-proBNP were independently associated with higher risk of incident heart failure. The present analysis further advances the literature by describing the risk relationships of these biomarkers with cardiovascular events in patients with more severe CKD. We have shown that hs-cTnT and NT-proBNP are independent predictors of cardiovascular events among asymptomatic CKD patients, even at a relatively advanced stage of disease and accounting for the competing risk of death. Although cardiac biomarkers are not yet used for cardiovascular risk stratification among asymptomatic CKD patients, our data suggest that their capacity for prognostication could be maximized by adopting

Table 4. Added prognostic value of hs-cTnT and NT-proBNP for risk of a cardiovascular event at 3 years

	Base model*	Base and hs-cTnT	Base and NT-proBNP
Addition of biomarkers using standard cutoffs			
C-statistics (95% CI)	0.763 (0.746-0.788)	0.771 (0.752-0.792)	0.765 (0.748-0.790)
Δ C-statistics (95% CI)		0.009 (0.003-0.013)	0.003 (0.0004-0.006)
cNRI (95% CI)		0.108 (−0.009 to 0.226)	−0.018 (−0.124 to 0.105)
cNRI for event		0.389 (0.273-0.491)	0.439 (0.332-0.559)
cNRI for nonevent		−0.281 (−0.318 to −0.222)	−0.457 (−0.513 to −0.375)
IDI (95% CI)		0.004 (0.0002-0.007)	−0.0007 (−0.002 to 0.002)
Addition of biomarkers using GFR-specific cutoffs			
C-statistics (95% CI)	0.763 (0.746-0.788)	0.787 (0.767-0.808)	0.795 (0.774-0.815)
Δ C-statistics (95% CI)		0.024 (0.015-0.038)	0.032 (0.02-0.045)
cNRI (95% CI)		0.73 (0.630-0.863)	0.817 (0.632-0.925)
cNRI for event		0.52 (0.436-0.616)	0.563 (0.416-0.648)
cNRI for nonevent		0.21 (0.164-0.263)	0.253 (0.182-0.291)
IDI (95% CI)		0.028 (0.016-0.044)	0.035 (0.019-0.049)

CI, confidence interval; cNRI, continuous net reclassification index; GFR, glomerular filtration rate; hs-cTnT, high sensitivity cardiac troponin T; IDI, integrated discrimination index; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Base model adjusted for age, sex, diabetes, cardiac disease, pulse pressure, hemoglobin, GFR, urinary albumin to creatinine ratio, phosphate, high sensitivity C-reactive protein.

clinical cutoffs that are specific to the level of GFR, for example, in risk prediction models for cardiovascular events.

The mechanism by which hs-cTnT and NT-proBNP are elevated in patients with CKD is not fully understood. A small study in patients with heart failure showed a similar transcardiac gradient for troponin T in patients with and without CKD, suggesting that higher circulating levels of troponin T in CKD patients are attributable to reduced renal clearance.[30] Both biomarkers are also increased in individuals with albuminuria and preserved GFR,[6,7] which argues against reduced clearance being the sole explanatory mechanism. Cross-sectional studies have shown correlations between both biomarkers and objective evidence of structural heart disease in asymptomatic CKD patients, indicating that they might be surrogates for underlying subclinical cardiac dysfunction. Data from CRIC showed a higher likelihood of left ventricular hypertrophy and systolic dysfunction among CKD patients with detectable hs-cTnT levels.[31] Smaller studies have identified associations with other indices of structural cardiac abnormalities such as left ventricular mass index.[32]

The findings of our study should be interpreted in the context of its potential limitations. Cardiac biomarkers were measured once at baseline, which might have led to misclassification of study participants. Outcome definitions for myocardial infarction and heart failure did not include objective criteria for cardiac dysfunction. There remains the potential for residual measured or unmeasured confounding. Data regarding history of cigarette smoking were not available. The cohort was predominantly Caucasian, limiting generalizability. The identified cut points were specific to the observed outcomes in this sample and will need to be validated in other cohorts. These limitations are balanced by several strengths. The cohort was a contemporary sample of CKD patients undergoing nephrology care. Although this limits generalizability to a referred sample of CKD patients, the cohort included patients at an advanced stage of disease, a previously under-represented population in studies of hs-cTnT and NT-proBNP. We applied a novel approach to the identification of clinical cutoffs for each biomarker according to level of kidney function, underpinned by the risk of centrally adjudicated hard outcomes.

We have shown that optimal risk-based cutoffs for hs-cTnT and NT-proBNP differ according to the level of GFR among asymptomatic patients with advanced CKD, are strongly associated with cardiovascular events, and improve prognostication of cardiovascular events compared with existing standard thresholds. We propose that GFR-specific cutoffs could provide clinicians with a more meaningful interpretation of hs-cTnT and NT-proBNP, as an alternative to standard thresholds derived from healthy adults in the general population.

Acknowledgements

See the *Acknowledgements* section of the Supplementary Material.

Funding Sources

This work was supported by Janssen Ortho Inc with an unrestricted, investigator-initiated grant.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2019.06.014.