Canadian Journal of Cardiology 35 (2019) 1082–1084

Editorial

Is It Time to Recalibrate Cardiac Prediction Tools to Accommodate Chronic Kidney Disease?

Gregory L. Hundemer, MD, MPH, and Manish M. Sood, MD, MSc

Division of Nephrology, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

See article by Canney et al., pages 1106–1113 of this issue.

Cardiovascular disease disproportionately affects patients with chronic kidney disease (CKD) compared with the remainder of the population. In fact, CKD has historically been considered a cardiovascular disease "risk equivalent" along with other well known risk factors such as diabetes mellitus and peripheral vascular disease.[1] Moreover, there is a clear "dose-response" relationship with more advanced stages of CKD associated with progressively higher rates of cardiovascular disease.[2]

The Intertwined Nature of CKD and Cardiovascular Disease

The explanation for the heightened cardiovascular risk among the CKD population is multifactorial. There is substantial overlap among the underlying conditions that predispose to cardiovascular disease and CKD such as diabetes mellitus, hypertension, and vasculitis. Beyond these shared predisposing conditions, complications of CKD such as volume overload, anemia, and dysregulated bone and mineral metabolism further heighten cardiovascular risk among the CKD population.[3-5]

Currently measured primarily among symptomatic individuals, there has been a growing body of evidence showing that cardiac biomarkers, such as high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro B-type natriuretic peptide (NT-proBNP), are predictive of future cardiovascular events among asymptomatic individuals in the general population.[6-9] This raises the possibility of using these biomarkers to generate prognostic models for predicting future cardiovascular risk. Because of the substantially heightened cardiovascular risk among the CKD population, important issues to address are: (1) the prognostic value of these biomarkers in the setting of CKD; and (2) whether different thresholds for these biomarkers should be used in the CKD vs the non-CKD population.

Complexities With Cardiovascular Disease Prognostication in CKD

Interpretation of cardiac biomarkers in the CKD population represents a common challenge for the clinician. Among asymptomatic individuals, CKD patients generally have higher levels of hs-cTnT and NT-proBNP compared with the non-CKD population. Additionally, the more advanced the CKD, the higher the levels of these biomarkers even among asymptomatic patients.[10,11] The reasons behind the elevations in hs-cTnT and NT-proBNP are likely multifactorial. First, reduced renal clearance might contribute to elevation in each of these biomarkers.[12,13] Second, these cardiac biomarkers in the CKD population might signify the presence of subclinical levels of myocardial ischemia and cardiac volume overload.[14,15] These differences in baseline values of hs-cTnT and NT-proBNP in CKD vs non-CKD patients ultimately make clinical interpretation of their prognostic meaning extremely challenging. Key questions that remain include: Should different thresholds for hs-cTnT and NT-proBNP be used in CKD? Should these thresholds vary further according to CKD stage?

Cardiac Biomarkers for Cardiovascular Disease Prognostication in CKD: How to Interpret?

The article in this issue of the *Canadian Journal of Cardiology* by Canney et al. explores different thresholds for hs-cTnT and NT-proBNP by degree of CKD in regard to cardiovascular risk prognostication.[16] The authors performed a retrospective 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) cohort. CanPREDDICT was a unique multicentre prospective cohort of individuals with nondialysis CKD with baseline estimated glomerular filtration rate (eGFR) between 15 and 45 mL/min/1.73 m^2.[17] These participants had hs-cTnT and NT-proBNP measured at baseline and were followed for a median of 4 years. Adjudicated information on cardiovascular outcomes including acute coronary syndrome (unstable angina or myocardial infarction), congestive heart failure, stroke, and cardiovascular death was collected. Participants were stratified according to the degree of CKD at the time of study entry on the basis of baseline eGFR category: < 20, 20-29, or 30-44 mL/min/1.73 m^2.

Received for publication June 27, 2019. Accepted June 30, 2019.

Corresponding author: Dr Gregory L. Hundemer, The Ottawa Hospital, Riverside Campus, 1967 Riverside Dr, Ottawa, Ontario K1H 7W9, Canada. Tel.: +1-613-738-8400 ×82716; fax: +1-613-738-8337.

E-mail: ghundemer@toh.ca

See page 1083 for disclosure information.

https://doi.org/10.1016/j.cjca.2019.06.026

Of 1956 participants from CanPREDDICT, a total of 401 cardiovascular events occurred during the study period.[16] In accordance with previous studies,[6-11] levels of hs-cTnT and NT-proBNP showed a stepwise increased association with: (1) severity of CKD; and (2) risk of future cardiovascular events. Unique to this study, the investigators assessed what the optimal cut point was for each level of CKD with regard to cardiovascular risk prognostication. They defined "standard" cutoffs for hs-cTnT and NT-proBNP as 14 ng/L and 125 pg/mL, respectively. It is worth mentioning that these are generally considered cutoffs for diagnostic purposes (eg, acute myocardial infarction or acute heart failure exacerbation) rather than for prognostic purposes,[18,19] as was the current study's[16] focus. Nevertheless, the optimal prognostic cutoff for hs-cTnT increased in a stepwise fashion on the basis of the degree of baseline CKD: 22.7 ng/L for eGFR 30-44 mL/min/1.73 m^2, 26.8 ng/L for eGFR 20-29 mL/min/1.73 m^2, and 35.5 ng/L for eGFR < 20 mL/min/1.73 m^2. This relationship between degree of baseline CKD and optimal prognostic cutoff was less clear for NT-proBNP using the following optimal cutoffs: 584 pg/mL for eGFR 30-44 mL/min/1.73 m^2, 459 pg/mL for eGFR 20-29 mL/min/1.73 m^2, and 765 pg/mL for eGFR < 20 mL/min/1.73 m^2. Using these prognostic eGFR-specific cutoffs, as opposed to the aforementioned existing cutoffs for these cardiac biomarkers, not only improved the C-statistic of their prognostic models but also appropriately reclassified a large percentage of participants who experienced a cardiovascular event as being at "high risk" and those who did not as being at "low risk."

The Future of Cardiac Biomarkers in the CKD Population

The findings by Canney et al.[16] add to the existing literature showing that baseline levels of hs-cTnT and NT-proBNP associate with future incident cardiovascular disease.[20] The demonstrated optimal cutoffs for each of these biomarkers (when used for prognostic purposes) were found to vary according to severity of underlying CKD. These results beg the question of whether CKD, and its severity, should be incorporated into existing cardiovascular risk prediction models. Alternatively, do CKD patients fundamentally differ so much with regard to cardiac risk that they warrant their own CKD-specific risk prediction tools?

Key areas for future study are to determine whether cardiac (eg, blood pressure control, lipid-lowering interventions, etc) and kidney risk reduction strategies (eg, antiproteinuric therapies) might be effective in reducing levels of these cardiac biomarkers, which might potentially signify an improved future cardiovascular risk profile. In other words, can we intervene when we discover elevations in these cardiac biomarkers to make a long-term difference in cardiovascular risk? Finally, Canney et al. focused on the prognostic cutoffs for hs-cTnT and NT-proBNP in asymptomatic individuals.[16] Far more commonly, these biomarkers are used for diagnostic purposes in the settings of acute coronary syndrome or a heart failure exacerbation. Identifying what the optimal diagnostic cutoffs are (according to CKD severity) for these biomarkers in the acute setting might have a much more direct effect on medical practice.

Disclosures

The authors have no conflicts of interest to disclose.

References

1. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation 2003;108:2154-69.
2. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296-305.
3. Astor BC, Arnett DK, Brown A, Coresh J. Association of kidney function and hemoglobin with left ventricular morphology among African Americans: the Atherosclerosis Risk in Communities (ARIC) study. Am J Kidney Dis 2004;43:836-45.
4. Paloian NJ, Giachelli CM. A current understanding of vascular calcification in CKD. Am J Physiol Renal Physiol 2014;307:F891-900.
5. Tsai YC, Chiu YW, Tsai JC, et al. Association of fluid overload with cardiovascular morbidity and all-cause mortality in stages 4 and 5 CKD. Clin J Am Soc Nephrol 2015;10:39-46.
6. de Lemos JA, Drazner MH, Omland T, et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. JAMA 2010;304:2503-12.
7. Linssen GC, Bakker SJ, Voors AA, et al. N-terminal pro-B-type natriuretic peptide is an independent predictor of cardiovascular morbidity and mortality in the general population. Eur Heart J 2010;31:120-7.
8. Saunders JT, Nambi V, de Lemos JA, et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. Circulation 2011;123:1367-76.
9. Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med 2004;350:655-63.
10. Dubin RF, Li Y, He J, et al. Predictors of high sensitivity cardiac troponin T in chronic kidney disease patients: a cross-sectional study in the chronic renal insufficiency cohort (CRIC). BMC Nephrol 2013;14:229.
11. Takase H, Dohi Y. Kidney function crucially affects B-type natriuretic peptide (BNP), N-terminal proBNP and their relationship. Eur J Clin Invest 2014;44:303-8.
12. de Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. Lancet 2003;362:316-22.
13. Tsutamoto T, Kawahara C, Yamaji M, et al. Relationship between renal function and serum cardiac troponin T in patients with chronic heart failure. Eur J Heart Fail 2009;11:653-8.
14. Ooi DS, Isotalo PA, Veinot JP. Correlation of antemortem serum creatine kinase, creatine kinase-MB, troponin I, and troponin T with cardiac pathology. Clin Chem 2000;46:338-44.
15. DeFilippi CR, Fink JC, Nass CM, Chen H, Christenson R. N-terminal pro-B-type natriuretic peptide for predicting coronary disease and left ventricular hypertrophy in asymptomatic CKD not requiring dialysis. Am J Kidney Dis 2005;46:35-44.
16. Canney M, Tang M, Er L, Barbour SJ, Djurdjev O, Levin A. Glomerular filtration rate-specific cutoffs can refine the prognostic value of circulating cardiac biomarkers in advanced chronic kidney disease. Can J Cardiol 2019;35:1106-13.

17. Levin A, Rigatto C, Brendan B, et al. Cohort profile: Canadian study of prediction of death, dialysis and interim cardiovascular events (CanPREDDICT). BMC Nephrol 2013;14:121.

18. Januzzi JL, van Kimmenade R, Lainchbury J, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. Eur Heart J 2006;27:330-7.

19. Kavsak PA, Worster A, Ma J, et al. High-sensitivity cardiac troponin risk cutoffs for acute cardiac outcomes at emergency department presentation. Can J Cardiol 2017;33:898-903.

20. 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. J Am Soc Nephrol 2015;26:946-56.