Research Open

Journal of Cardiology and Clinical Practice
Volume 3 Issue 1

Review article

Cardiovascular Disease and the Evidence for Cystatin C as a Cardiovascular Risk Predictor in Native and Kidney Transplant Populations

Leyton Galapia[1], Mira T Keddis[2]*

[1]Mayo Medical School, Arizona Campus

[2]Assistant Professor and Consultant in the Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic, Scottsdale, Arizona, United States of America

***Corresponding Author:** Mira T Keddis, Assistant Professor and Consultant in the Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic, Scottsdale, Arizona, United States of America; **Tel-** (480) 301-8000; **E-mail:** Keddis.Mira@mayo.edu

Received: December 30, 2019; **Accepted:** January 08, 2020; **Published:** January 15, 2020

Cardiovascular disease (CVD) in the form of coronary heart disease (CHD), stroke, or heart failure (HF) affects 9% of adults in the United States (U.S.) over the age of 20. When hypertension (HTN) is included in this grouping of CVD, its prevalence swells to 48% [1]. Meanwhile, peripheral arterial disease (PAD) has an estimated prevalence of 7.2% in American adults over the age of 40 [2]. Chronic kidney disease (CKD), defined as kidney injury or diminished glomerular filtration rate (GFR) lasting at least 3 months, is commonly associated with CVD and is an independent risk factor for CVD [3,4]. Furthermore, the risk of CVD in patients with CKD is significant, and patients with CKD are more likely to suffer from CVD than to progress to end stage renal disease (ESRD) [5]. There have been a number of pathophysiologic mechanisms posited with regards to the development of CVD in the setting of CKD. Abnormal vascular tone, hypertension, and endothelial injury can arise in CKD due to alterations in normal water and salt balance as well as activation of the renin, angiotensin, aldosterone system (RAAS) [6]. Runaway RAAS activity is also responsible for pathologic cardiac remodeling [6]. Hyperphosphatemia is a consequence of aberrant bone and mineral metabolism in CKD, and may cause direct vascular injury [7]. Hyperkalemia in the setting of CKD has been associated with cardiac conduction abnormalities [6]. The uremic milieu itself has been shown to contribute to CVD and anemia due to disruption of the erythropoietin (EPO) axis and functional iron deficiency have a correlative relationship to adverse cardiovascular outcomes [6,8]. In summary, there are numerous pathophysiologic mechanisms that may explain the increased CVD risk and events across various stages of CKD.

It stands to reason then that estimated GFR (eGFR), as a measure of kidney function, would have some predictive value for cardiovascular outcomes. Indeed, a relationship has been described between declining eGFR and worsening risk for CVD. A few representative studies are highlighted here. Lees et al. found an association between decreasing eGFR and increased adjusted hazard ratios for adverse outcomes consisting of all-cause mortality, CVD, and ESRD [9]. Specifically, hazard ratios for adverse outcomes tended to be highest among patients with eGFR ranging from 15–30 mL/min/1.73m^2, representing the group of patients with the lowest measured eGFR included in the study [9]. Guo et al. focused their investigation on the magnitude of eGFR decline over time and the effect of this change on risk for all-cause mortality and CVD events [10]. Their results had similar implications, as patients who experienced greater losses in GFR from one year to the next were at higher risk of mortality and CVD [10]. Therefore in addition to surveillance of renal function, it is imperative to define CV risk in CKD patients. In clinical practice, estimated GFR using creatinine (Cr) based eGFR equations has been the most commonly used approach to monitor renal function despite its limitations due to non-GFR determinants not accounted for in commonly used eGFR equations such as muscle mass and dietary protein intake for example [11,12]. Cystatin C (Cys C), another endogenous marker for estimating eGFR, is not influenced by body mass or dietary protein. It has been shown to have several non-GFR determinants including: elevated markers of inflammation, dyslipidemia, obesity, implying that inflammation and atherosclerosis may affect the accuracy of CysC-eGFR [12,13,14]. However the data has been overwhelmingly supportive of Cys C based eGFR as a better estimate of kidney function compared to Cr only eGFR in the native kidney population [15]. Furthermore, CysC and CysC eGFR have been shown to correlate with mortality and CVD [9,16,17]. Revisiting the study by Lees et al., though CVD risk was generally higher as Cr-eGFR and CysC-eGFR decreased CysC-eGFR was a more accurate predictor of mortality and cardiovascular events than Cr-eGFR [9]. Garcia-Carretero et al. found similar results with diminished CysC-eGFR being associated with higher hazard ratios of cardiovascular morbidity and mortality than Cr-eGFR [17].

In the kidney transplant (KTx) population, CVD remains the leading cause of death with a functioning graft [18]. Individuals in the KTx population remain subject to excess CVD risk due to recipient and donor characteristics which include: graft function, diabetes, history of dialysis prior to transplant, acute rejection events, and pre-transplant history of CVD [18,19]. Given significant differences between KTx patients and patients with native kidneys, it is appropriate to ask

whether or not the evidence in support of Cys C as a preferred marker of eGFR and predictor of CVD risk holds true in the KTx patient population. With regards to the first question, Yang et al. found no significant difference between measured GFR and eGFR based on Cys C, while eGFR based on Cr significantly underestimated measured GFR [20]. However, Keddis et al. also compared the accuracy of Cr-eGFR and CysC-eGFR in a cohort of stable KTx recipients [21]. They found that CysC-eGFR measurements showed greater bias than Cr-eGFR, with greater inaccuracy and underestimation of GFR compared to Cr-eGFR [21]. In fact, Cys C was found to have more non-eGFR determinants than Cr in the KTx population [12]. In another study, Foster et al. examined the association of diminished CysC-eGFR and Cr-eGFR with mortality, cardiovascular events, and kidney failure [22]. They found that diminished CysC-eGFR was associated with significantly increased risk for cardiovascular events after adjustment for known CV risk factors. Diminished Cr-eGFR was also significantly associated with an increased risk for cardiovascular events. However, this relationship was not continuous and disappeared with multivariable adjustment [22]. Further studies are needed to validate the relationship of CysC-eGFR with CV events and mortality in the KTx population. In conclusion, there is strong evidence to support that Cys C and CysC-eGFR provide better CV risk stratification in the native and transplant kidney populations compared to Cr. Further studies are needed to guide the value of routine measurements and the clinical implications of identified CV risk using Cys C.

References

1. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, et al. (2019) Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation* 139: 56–528. [Crossref]
2. Allison MA, Ho E, Denenberg JO, Langer RD, Newman AB, et al. (2007) Ethnic-specific prevalence of peripheral arterial disease in the United States. *Am J Prev Med* 32: 328–333. [Crossref]
3. (2013) Chapter 1: Definition and classification of CKD. *Kidney Int Suppl (2011)* 3: 19–62. [Crossref]
4. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, et al. (2003) 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* 108: 2154–2169. [Crossref]
5. Sarnak MJ (2003) Cardiovascular complications in chronic kidney disease. *Am J Kidney Dis* 41: 11–17. [Crossref]
6. Tomey MI, Winston JA (2014) Cardiovascular pathophysiology in chronic kidney disease: opportunities to transition from disease to health. *Ann Glob Health* 80: 69–76. [Crossref]
7. Tonelli M, Pannu N, Manns B (2010) Oral phosphate binders in patients with kidney failure. *N Engl J Med* 362: 1312–1324. [Crossref]
8. Vanholder R, Glorieux G, Lameire N, European Uremic Toxin Work G (2003) Uraemic toxins and cardiovascular disease. *Nephrol Dial Transplant* 18: 463–466. [Crossref]
9. Lees JS, Welsh CE, Celis-Morales CA, Mackay D, Lewsey J, et al. (2019) Glomerular filtration rate by differing measures, albuminuria and prediction of cardiovascular disease, mortality and end-stage kidney disease. *Nat Med* 25: 1753–1760. [Crossref]
10. Guo Y, Cui L, Ye P, Li J, Wu S, et al. (2018) Change of Kidney Function Is Associated With All-Cause Mortality and Cardiovascular Diseases: Results From the Kailuan Study. *J Am Heart Assoc* 7: e010596.
11. Tangri N, Stevens LA, Schmid CH, Zhang YL, Beck GJ, et al. (2011) Changes in dietary protein intake has no effect on serum cystatin C levels independent of the glomerular filtration rate. *Kidney Int* 79: 471–477. [Crossref]
12. Foster MC, Levey AS, Inker LA, Shafi T, Fan L, et al. (2017) Non-GFR Determinants of Low-Molecular-Weight Serum Protein Filtration Markers in the Elderly: AGES-Kidney and MESA-Kidney. *Am J Kidney Dis* 70: 406–414. [Crossref]
13. Ferguson TW, Komenda P, Tangri N (2015) Cystatin C as a biomarker for estimating glomerular filtration rate. *Curr Opin Nephrol Hypertens* 24: 295–300. [Crossref]
14. Rule AD, Bailey KR, Lieske JC, Peyser PA, Tuner ST (2013) Estimating the glomerular filtration rate from serum creatinine is better than cystatin C for evaluating risk factors associated with chronic kidney disease. *Kidney Int* 83: 1169–1176. [Crossref]
15. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, et al. (2012) Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Eng J Med* 367: 20–29. [Crossref]
16. Luo J, Wang LP, Hu HF, Zhang L, Li YL, et al. (2015) Cystatin C and cardiovascular or all-cause mortality risk in the general population: A meta-analysis. *Clin Chim Acta* 450: 39–45. [Crossref]
17. Garcia-Carretero R, Vigil-Medina L, Barquero-Perez O, Goya-Esteban R, Mora-Jimenez I, et al. (2017) Cystatin C as a predictor of cardiovascular outcomes in a hypertensive population. *J Hum Hypertens* 31: 801–807. [Crossref]
18. Stoumpos S, Jardine AG, Mark PB (2015) Cardiovascular morbidity and mortality after kidney transplantation. *Transpl Int* 28: 10–21. [Crossref]
19. Kasiske BL, Chakkera HA, Roel J (2000) Explained and unexplained ischemic heart disease risk after renal transplantation. *J Am Soc Nephrol* 11: 1735–1743. [Crossref]
20. Yang Y, Kim KY, Hwang I, Yim T, Do W, et al. (2017) Cystatin C-Based Equation for Predicting the Glomerular Filtration Rate in Kidney Transplant Recipients. *Transplant Proc* 49: 1018–1022. [Crossref]
21. Keddis MT, Amer H, Voskoboev N, Kremers WK, Rule AD, et al. (2016) Creatinine-Based and Cystatin C-Based GFR Estimating Equations and Their Non-GFR Determinants in Kidney Transplant Recipients. *Clin J Am Soc Nephrol* 11: 1640–1649. [Crossref]
22. Foster MC, Weiner DE, Bostom AG, Carpenter MA, Inker LA, et al. (2017) Filtration Markers, Cardiovascular Disease, Mortality, and Kidney Outcomes in Stable Kidney Transplant Recipients: The FAVORIT Trial. *Am J Transplant* 17: 2390–2399. [Crossref]

Citation:
Galapia L, Keddis MT (2020) Cardiovascular Disease in Kidney Disease and the Evidence for Cystatin C as A Cardiovascular Risk Predictor in Native and Kidney Transplant Populations. *J Cardiol Clin Pract* Volume 3(1): 1–2.