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

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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.[1] 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.

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