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Editorial Comment

EDITORIAL COMMENT

Estimation of glomerular filtration rate in cardiorenal patients: a step forward

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ABSTRACT

The progressive reduction in estimated glomerular filtration rate (eGFR) resulting in chronic kidney disease (CKD) is associated with increased risk of cardiovascular disease (CVD) (i.e., cardiorenal disease). Cardiorenal disease is associated with poor outcomes, mainly due to increased cardiovascular (CV) complications and CV death. Data from general population–based studies and studies of cohorts with CKD and/or CVD show that compared with creatinine-based eGFR, cystatin C–based eGFR and creatinine plus cystatin C–based eGFR detect higher risks of adverse CV outcomes and add predictive discrimination to current CVD risk scores. On the other hand, growing clinical evidence supports kidney and CV protective effects of sodium–glucose cotransporter-2 (SGLT2) inhibitors in cardiorenal patients. However, recent data suggest that some detrimental effects of SGLT2 inhibitors on skeletal muscle mass may lead to overestimation of creatinine-based eGFR and subsequent misinterpretation of associated CV risk in patients treated with these agents. Within this framework, we suggest the advisability of using cystatin C and/or creatinine plus cystatin C–based eGFR for routine clinical practice in cardiorenal patients to more accurately stratify CV risk and evaluate the kidney and CV protective effects of SGLT2 inhibitors. In this regard, we make a call to action to investigate the protective effects of these pharmacological agents using cystatin C–based eGFR.

Keywords: cardiovascular disease, chronic kidney disease, creatinine, cystatin C, estimated glomerular filtration rate

THE GROWING BURDEN OF CARDIOVASCULAR DISEASE (CVD) IN CHRONIC KIDNEY DISEASE (CKD)

CKD has a major effect on global health, both as a direct cause of global morbidity and mortality and as an important risk factor for CVD either atherosclerotic (e.g. ischaemic heart disease and cerebrovascular disease) or non-atherosclerotic [e.g. heart failure (HF) and cardiac arrhythmias] [1]. In fact, the prevalence of CVD in people with CKD is ≈65% [2]. Therefore, CKD, defined as decreased kidney function and/or increased albuminuria, is now recognized as a cardiovascular (CV) risk factor in routine clinical practice [3].

Many are the factors that facilitate CVD in CKD (Fig. 1). Among patients with CKD, there is a high prevalence of traditional atherosclerotic risk factors, including diabetes mellitus, hypertension, dyslipidaemia and obesity [4, 5]. Furthermore, patients with CKD are also particularly exposed to other emerging CV damaging factors, including oxidative stress, inflammation and fibrosis, as well as arterial stiffening and

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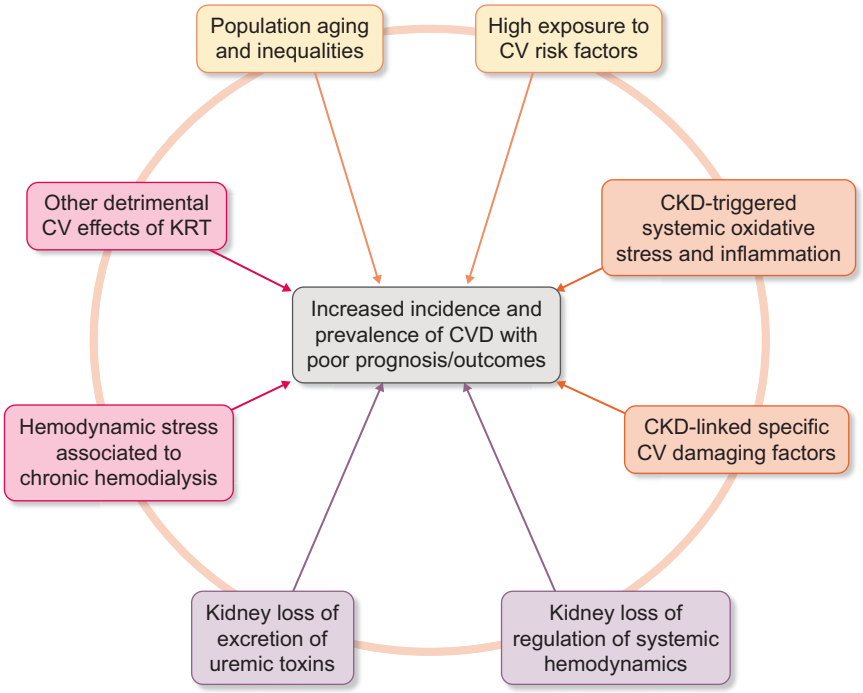

Figure 1: Groups of factors that facilitate the development of CVD in patients with CKD.

calcification. Additionally, in cases of advanced CKD, neurohumoral activation and fluid retention as well as uraemia-related toxins play a major role in the severity of CVD, namely HF [4, 6]. Finally, factors related to kidney replacement therapy, in particular to haemodialysis, also increase the risk of CVD [7].

CVD is the leading cause of morbidity and death in CKD patients [8, 9]. Even after adjustment for known CVD risk factors, CVD morbidity and mortality risk progressively increases with worsening CKD [10], especially as estimated glomerular filtration rate (eGFR) declines below 60 ml/min/1.73 m^2 [11]. This independent association has been confirmed recently using Mendelian randomization analyses [12]. Finally, the additional costs associated with management of the associated CV morbidity and related hospitalizations in patients with CKD are substantial and increase with disease severity [13].

As recently estimated in the USA [14], with an ageing population, the number of patients with multimorbid CKD and CVD will increase, making clinical management more complex and increasing the economic and social burdens on healthcare systems. Prevalence is predicted to increase across all comorbid disease states, with CKD and comorbid HF having the largest percentage increase of 101% between 2021 and 2030 [14]. In parallel, cumulative total direct healthcare costs from 2021 to 2025 and 2030 in patients with CKD and HF have been estimated at $4.2 billion and $10.2 billion, respectively, which gives an idea of the growing economic impact of the concurrence of these conditions on the healthcare system [14].

Therefore, early and accurate CV risk stratification and proactive management in CKD patients, namely in those with HF, should be a priority for healthcare providers to alleviate its clinical, economic and societal burdens [15]. As recently emphasised in a position statement by the Council of the European Renal Association, this requires not only estimation of GFR, but also assessment of albumin in urine [16]. In this conceptual framework, we propose to reconsider the routine estimation of the GFR, using cystatin C as a marker instead of creatinine. The proposal is based on accumulated evidence that suggests eGFR calculated with creatinine offers poorer CV prognostic performance in CKD patients than eGFR calculated with cystatin C alone or with creatinine plus cystatin C and that this difference may impact on the way CV and kidney protective effects of recently incorporated agents such as sodium–glucose cotransporter-2 (SGLT2) inhibitors are evaluated.

EQUATIONS FOR GFR ESTIMATION AND CVD RISK STRATIFICATION

The eGFR is the clinical standard parameter for the assessment and staging of kidney dysfunction in CKD [17, 18]. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations have been widely used to estimate GFR, measuring serum creatinine only ($eGFR_{cr}$), serum cystatin C only ($eGFR_{cys}$) or measuring the two serum markers ($eGFR_{cr/cys}$) [19, 20].

Several observational studies have been performed in general populations [13, 21–23] and in cohorts of patients with CKD and/or CVD [21, 24–27] to assess the CV prognostic value of the CKD-EPI $eGFR_{cys}$ and $eGFR_{cr/cys}$ equations and compare them with $eGFR_{cr}$. The findings of these studies show that both $eGFR_{cys}$ and $eGFR_{cr/cys}$ yielded better measurements of performance (discrimination, calibration and reclassification) [28]. These results have been confirmed in a meta-analysis including 11 general population studies and 5 studies in CKD patients [29]. Collectively, these data suggest that eGFR measuring cystatin C may be preferred to accurately estimate the risk of CVD and associated outcomes in patients with CKD.

Regarding the risk of HF, a single example analysing the data from the Cardiovascular Health Study [24] can support the

Table 1: Associations of decreased eGFR (<60 ml/min/1.73 m^2) by creatinine and cystatin C with HF in the Cardiovascular Heart Study.

Demographic-adjusted HR (95% CI)[a]				Fully adjusted HR (95% CI)[b]			
CKD-EPI eGFR not decreased	Decreased CKD-EPI $eGFR_{cr}$	Decreased CKD-EPI $eGFR_{cys}$	Decreased CKD-EPI $eGFR_{cr/cys}$	CKD-EPI eGFR not decreased	Decreased CKD-EEPI $eGFR_{cr}$	Decreased CKD-EPI $eGFR_{cys}$	Decreased CKD-EPI $eGFR_{cr/cys}$
1.00 (reference)	1.08 (0.91–1.27)	2.12 (1.68–2.66)	1.91 (1.64–2.23)	1.00 (reference)	0.99 (0.84–1.18)	1.69 (1.33–2.13)	1.43 (1.22–1.67)

[a]Adjusted for age, race and gender.
[b]Adjusted for age, race, gender, prevalent diabetes, prevalent hypertension, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, C-reactive protein and prevalent CVD.
The data were adapted from Peralta *et al.* [24].

previous statement. The study included 5160 participants (mean age 72 ± 5 years, 84% White, 57% women and 24% with prevalent CVD) followed for a mean period of 12.2 years. Compared with subjects without CKD (eGFR ≥60 ml/min/1.73 m^2), both the demographic and the fully adjusted hazard ratios (HRs) for incident HF in subjects with CKD (eGFR <60 ml/min/1.73 m^2) changed non-significantly for $eGFR_{cr}$ (+8% and −1%, respectively) but increased significantly for $eGFR_{cys}$ (+112% and +68%, respectively) and for $eGFR_{cr/cys}$ (+91% and +43%, respectively) (Table 1) [24]. These data suggest that among adults diagnosed with CKD, the long-term risk of HF is better identified using the $eGFR_{cys}$ or $eGFR_{cr/cys}$ equations than the $eGFR_{cr}$ equation.

There are methodological and mechanistic data to argue that reduced $eGFR_{cys}$ values may have an important role in identifying CKD patients who are at the highest risk of HF. First, cystatin C is a marker of kidney function that approximates direct measures of GFR more precisely than creatinine because its serum concentrations are independent of muscle mass or diet [30, 31]. In the setting of patients with CKD and HF this can be particularly relevant because muscle wasting and sarcopenia are highly prevalent in both conditions [32, 33]. Second, it is known that higher levels of serum cystatin C, but not serum creatinine, are associated with an increased risk of HF [34–36]. Third, it has been reported that in patients with HF with preserved ejection fraction (HFpEF), increased serum cystatin C is associated with diastolic dysfunction and alterations in collagen metabolism (i.e. reduced extracellular degradation of collagen fibres by metalloproteinases) involved in myocardial fibrosis independent of eGFR [37]. Finally, the shrunken pore syndrome (SPS) has been found to be related to poor outcomes (i.e. mortality rate and HF hospitalization) in HFpEF, where it can occur in up to 25% of patients [38]. SPS is a phenotype of glomerular filtration dysfunction mainly manifested by the impaired filtration of moderate-sized molecules (e.g. cystatin C, a 13-kDa protein) due to the narrowing pore size between endothelial cells [39] and defined by $eGFR_{cys}$ being <60% of $eGFR_{cr}$ in the absence of extrarenal influences on the serum levels of cystatin C or creatinine [40].

There is an additional aspect that deserves to be considered. Available data beginning at age 18 years through age 80 years indicate that males and African Americans have more skeletal muscle mass than females and other ethnic groups across the entire age range, even adjusting for weight and height [41]. In this regard, it has been reported recently that whereas the use of serum creatinine to estimate GFR without race (or genetic ancestry) introduced systematic misclassification, the estimation of GFR with the use of cystatin C generated similar results while eliminating the negative consequences of the current race-based approaches [42]. Therefore, the use of $eGFR_{cys}$ without the inclusion of race in the equation may be especially indicated to accurately assess the very high CVD risk reported in African Americans with CKD [43]. Finally, a recent published study including 227 643 patients in Sweden showed that GFR estimation using the European Kidney Function Consortium equation with serum cystatin C instead of serum creatinine presented similar accuracy but allowed one to safely exclude not only race, but also sex, thus allowing for a more complete exclusion of the potential influence of these two aspects in skeletal muscle mass [44].

EQUATIONS FOR GFR ESTIMATION AND ORGAN-PROTECTIVE EFFECTS OF SGLT2 INHIBITORS

Considering the expense and limited availability of cystatin C assays in routine laboratories, and that its serum level can be influenced by non-eGFR-dependent factors (e.g. steroid treatment, thyroid dysfunction, adiposity and active inflammation), one should balance the cost and benefits of cystatin C–based equations to estimate CV risk. This aspect can be a limiting factor when considering the general population under the perspective of public health, but in the cardiorenal population, accurate CV risk stratification is required and this limitation is overcome by its potential advantages. One example may illustrate this notion.

Increasing observations from clinical trials and subsequent detailed analyses have shown that the kidney- and CV-protective effects of SGLT2 inhibitors are consistent across many patient subgroups, including those with and without type 2 diabetes mellitus, at different stages of CKD and in patients with and without HF [45–47]. A recent analysis has shown that extrapolating the results of reported CV and kidney outcomes trials for SGLT2 inhibitors to a representative US population would likely result in a substantial reduction in disease prevalence, the number of hospitalizations and the associated costs over the next decade, especially in the case of CKD with HF [14]. Thus SGLT2 inhibitors emerge as a foundational therapy for preventing CKD progression and its associated risk of CVD.

However, most studies reporting the beneficial kidney and CV effects of SGLT2 inhibitors have used $eGFR_{cr}$, and recent available clinical evidence suggests that treatment with these agents may result in a loss of skeletal muscle mass (Table 2) [48–55]. These results should be interpreted with caution, as the association between SGLT2 inhibitors and the loss of skeletal muscle derives from small observational and mostly single-arm studies that have mainly used electrical bioimpedance for body composition assessment [48–55]. Nevertheless, it is important to mention that a recent meta-analysis of seven randomized clinical trials in patients with type 2 diabetes mellitus, including 206

Table 2: Effects of treatment with SGLT2 inhibitors on skeletal muscle mass in patients with type 2 diabetes mellitus.

Studies showing a significant reduction in skeletal muscle mass				Studies showing non-significant changes in skeletal muscle mass	
Study with canagliflozin[a]	Study with empagliflozin[a]	Studies with ipragliflozin[a]	Studies with luseogliflozin[b]	Studies with dapagliflozin[a]	Study with ipragliflozin[a]
Seko *et al.* [48]	Goto *et al.* [49]	Seko *et al.* [48] Yamamoto *et al.* [50]	Bouchi *et al.* [51] Sasaki *et al.* [52]	Tobita *et al.* [53] Sugiyama *et al.* [54]	Miyake *et al.* [55]

Skeletal muscle mass was assessed by [a]bioelectrical impedance or by [b]dual-energy X-ray absorptiometry.

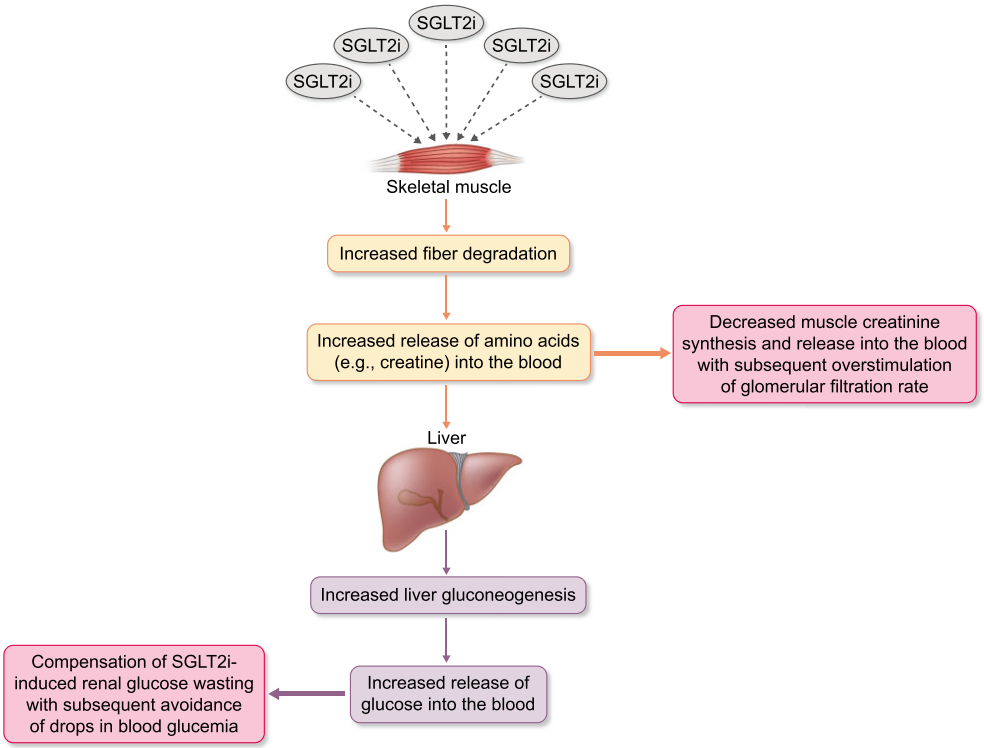

Figure 2: Effects of SGLT2 inhibitors on skeletal muscle that may result in creatinine-based overestimation of GFR.

SGLT2 inhibitor users and 201 non-users, showed that SGLT2 inhibitors significantly reduced skeletal muscle mass compared with other anti-hyperglycaemic agents [56]. In fact, as a catabolic response to renal glucose loss and reduction of glycaemia, SGLT2 inhibitors may induce skeletal muscle degradation to increase the release of amino acids into the systemic circulation, which are transported to the liver as substrates for gluconeogenesis, thereby preventing hypoglycaemia [57] (Fig. 2). Assuming this hypothesis, the effect of SGLT2 inhibitors on skeletal muscle mass renders serum creatinine (a surrogate of muscle mass)-based kidney endpoints questionable (i.e. due to overestimation of eGFR), especially in cardiorenal patients that exhibit loss of muscle mass and sarcopenia [58] (Fig. 2). In support of this possibility, it has been recently reported in patients with type 2 diabetes mellitus, presenting with and without CKD and CVD, that those treated during a mean 69.5 ± 36.2 weeks with SGLT2 inhibitors (i.e. dapagliflozin or empagliflozin) exhibited after treatment significantly higher $eGFR_{cr}$ but similar $eGFR_{cys}$ when compared with the control group not treated with SGLT2 inhibitors [59]. Although this study has an observational design with a small sample size (90 patients with type 2 diabetes mellitus) and an important imbalance between groups in terms of history of CVD and CKD staging, the discrepancy between $eGFR_{cr}$ and $eGFR_{cys}$ offers intriguing possibilities on the real kidney function effects of SGLT2 inhibitors that will need further confirmation in clinical trials focused on this mechanism [59]. Of interest, the landmark outcome trials of empagliflozin [60], canagliflozin [61] and dapagliflozin [62] found that at the end of the studies, the values of $eGFR_{cr}$ in the treatment groups were 2–4 ml/min/1.73 m^2 higher than those in the placebo groups and could be declared to be statistically significant.

These aspects may influence the interpretation of the true effects of SGLT2 inhibitors on CV risk and outcomes. In fact, in the study previously mentioned [59], the post-treatment distribution of CKD stages based on $eGFR_{cr}$ was different between the SGLT2 inhibitors group and the non-SGLT2 inhibitors group, where the SGLT2 inhibitors group had a lower CKD stage. In contrast, there was no statistical difference in CKD stage based on $eGFR_{cys}$ between these two groups. The relevance of this issue is given by the data reported by Shlipak *et al.* [28] showing in 11 general population studies (with 90 750 participants) and 5 studies of cohorts with CKD (2960 participants) that the

categorization of CKD stages by $eGFR_{cys}$ detected increased risks of adverse CV and other outcomes that are not detected with $eGFR_{cr}$-based stratification.

CONCLUSIONS AND PERSPECTIVES

Accumulating evidence suggests that the use of cystatin C (alone or in combination with creatinine) to calculate the eGFR provides a more accurate detection and staging of CKD and strengthens the associations between CKD stages and the risks of CVD and CV death, as well as of total death and kidney failure, across diverse populations. These aspects have a major effect on disease labelling, risk stratification, diagnostic procedures and therapeutic interventions, thus becoming an integral component of clinical nephrology [63]. Beyond the expenses due to the use of cystatin C to estimate GFR, its incorporation in routine clinical practice should be considered as a more efficient strategy, as more patients will benefit from early management of their cardiorenal risks. Where costs are an issue, $eGFR_{cys}$ should be chosen in specific situations such as $eGFR_{cr}$ >60 ml/min/1.73 m^2 or 45–59 ml/min/1.73 m^2 at the initial diagnosis of CKD and in patients with intense sarcopenia, chronic illness or malnutrition, as suggested by the KDIGO Controversies Conference 2021 [15, 63].

SGLT2 inhibitors have emerged as practice-changing treatments for cardiorenal patients with or without type 2 diabetes mellitus. However, post hoc analyses of existing trials or new trials based on estimations of GFR independent of muscle mass (i.e. calculation of eGFR based on cystatin C) may provide a more accurate assessment of the proposed kidney and CV protective effects of SGLT2 inhibitors. Although some work has been carried out in this regard, further studies are greatly needed and we thus make a call to action to investigate in this field.

These considerations fit well with strategies of precision medicine that have been proposed to improve kidney patient care on the basis of exploring novel or incorporating existing biomarkers that stratify patients with greater accuracy with respect to their future kidney and CV risk (prognostic) and that are also able to predict the response to nephroprotective and cardioprotective treatments (predictive) [64, 65]. The content of this review supports the notion that the time has come to step forward and consider cystatin C–based eGFR as one of the biomarkers for precision medicine in cardiorenal patients. We anticipate that routine use of cystatin C to estimate GFR will help in obtaining more robust conclusions on the effects of novel kidney and cardioprotective drugs and, as a consequence, facilitate better personalization of their prescription.

CONFLICT OF INTEREST STATEMENT

The authors declare no financial conflicts of interest. The views expressed here are solely their own. This work has not been published elsewhere and is not under consideration by another publication.

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