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Cardiovascular Risk Prediction in People with CKD

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Abstract

Purpose of review—Clinical guidelines are not consistent regarding whether or how to utilize information on measures of chronic kidney disease (CKD) for predicting the risk of cardiovascular disease (CVD). This review summarizes recent literature regarding CVD prediction in the context of CKD.

Recent findings—Previous studies used different definitions of CKD measures and CVD outcomes and applied distinct statistical approaches. A recent individual-level meta-analysis from the CKD Prognosis Consortium is of value since it has uniformly investigated creatinine-based estimated glomerular filtration rate (eGFR) and albuminuria as CKD measures and applied the same statistical approach across 24 cohorts with >630,000 participants. In this meta-analysis, eGFR and albuminuria improve CVD risk prediction beyond traditional CVD risk factors, particularly for CVD mortality and heart failure. Albuminuria demonstrates more evident improvement than eGFR. Moreover, several recent studies have shown that other filtration markers, e.g., cystatin C and β_2 -microglobulin, and measures of atherosclerosis or cardiac damage (e.g., coronary artery calcium and cardiac troponins) can further improve CVD prediction in CKD population.

Summary—Future clinical guidelines may require updates regarding whether/how to incorporate CKD measures and other biomarkers in CVD prediction, depending on CVD outcomes of interest, target population, and availability of those measures/biomarkers in that population.

Keywords

estimated glomerular filtration rate; albuminuria; cardiovascular disease; risk prediction

Introduction

Chronic kidney disease (CKD) is recognized as an important public health issue.¹ CKD affects 10%-15% of adults around the globe and increases the risk of various clinical adverse outcomes.^{1, 2} Cardiovascular disease (CVD) is one of the most important complications of

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Conflicts of interest:

None

CKD. Indeed, up to 50% of people with CKD die due to CVD even before most of them reach end-stage renal disease requiring renal replacement therapy.

Risk prediction is central for decision making for primary prevention of CVD such as statin or aspirin therapy.^{3, 4} However, there are several challenges in predicting CVD risk in persons with CKD. First of all, traditional risk factors have been shown to perform poorly in this clinical population.⁵ In addition, although numerous studies have demonstrated that persons with CKD are at high risk of CVD, interestingly, clinical guidelines are not consistent regarding how to utilize information on CKD measures for predicting CVD risk. This review summarizes current literature regarding CVD prediction with CKD measures as well as CVD prediction among those with CKD, with emphasis on recent studies.

Two key CKD measures for CVD prediction: representative individual studies

Two key measures of CKD, glomerular filtration rate (GFR) and albuminuria, have been consistently associated with high cardiovascular risk across a range of populations with different demographic, geographic, and clinical backgrounds.^{2, 6} However, the significant association does not necessarily indicate better prediction of CVD with CKD measures beyond traditional cardiovascular risk factors. Indeed, inconsistent results have been seen regarding whether CKD measures can improve CVD prediction beyond traditional risk factors (Table 1).⁷⁻¹³ These studies have used different definitions of CKD measures and CVD outcomes and have applied different statistical approaches, making it difficult to infer definite conclusions.

Two key CKD measures for CVD prediction: representative clinical guidelines

Reflecting these conflicting data, clinical guidelines take considerably different positions as to whether or how to incorporate the two CKD measures for CVD prediction (Table 2). Specifically, the American Heart Association (AHA) and the American College of Cardiology (ACC) 2013 Guideline on the Assessment of Cardiovascular Risk¹⁴ does not take into account either GFR or albuminuria because “The contribution to risk assessment for a first ASCVD [atherosclerotic CVD] event using ApoB [apolipoprotein B], CKD, albuminuria, or cardiorespiratory fitness is uncertain at present.”¹⁴

On the other hand, the 2012 European guidelines on CVD¹⁵ incorporate both GFR and albuminuria, with some prioritization on GFR over albuminuria. Specifically, the European guidelines consider individuals with GFR <30 ml/min/1.73m² as very high risk (equivalent to 10-year predicted risk of CVD mortality 10%) and those with GFR 30-59 ml/min/1.73m² as high risk (10-year CVD mortality risk 5% to <10%) (Table 1).¹⁵ Albuminuria is only discussed in the context of diabetes, and diabetic patients with albuminuria are categorized as very high risk.¹⁵ The 2013 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Lipid Management in CKD¹⁶ takes a more extreme approach and considers everyone aged 50 years with CKD (i.e., GFR <60 ml/min/

1.73m² and/or albuminuria ≥30 mg/day) as high CVD risk.¹⁶ For younger individuals with CKD, the KDIGO Guideline recommends estimating 10-year risk of coronary heart disease (i.e., coronary death or non-fatal myocardial infarction) and considering 10% or greater as high risk, a group that would benefit from statin therapy.¹⁶

A recent individual-level data meta-analysis for CKD measures improving CVD risk prediction

As aforementioned, previous studies have investigated different CKD measures and CVD outcomes and applied distinct statistical approaches. In this context, a recent individual-level data meta-analysis from the CKD Prognosis Consortium is of value since it has uniformly investigated estimated GFR (eGFR) based on creatinine and urine albumin-to-creatinine ratio (ACR) as CKD measures and applied the same statistical approach across 24 cohorts with >630,000 participants.¹⁷

This meta-analysis demonstrated that both eGFR and ACR were independently and significantly associated with four subtypes of CVD, i.e., CVD mortality, coronary heart disease, stroke, and heart failure.¹⁷ Of these, the two CKD measures were particularly strongly associated with CVD mortality and heart failure. Consistently, the addition of either or both of CKD measures more evidently improved the prediction (assessed by Harrell's c-statistic and net reclassification improvement) of CVD mortality and heart failure as compared to that of coronary disease and stroke (Figure 1¹⁷). The improvement was more evident with ACR than with eGFR.

The assessment of whether the addition of a biomarker can improve prediction, described above, is implicitly linked to a clinical question about whether we would benefit from newly assessing that biomarker. However, in CKD population, by definition, data on eGFR and albuminuria are likely to be readily available. In such a situation, a practical question is which data of CKD measures and traditional risk factors should be kept in consideration for CVD prediction. From this perspective, this meta-analysis has evaluated the drop in c-statistic by subtracting each predictor (or some combinations) in turn and demonstrated that the combination of both eGFR and ACR contributed to better risk discrimination more than any single traditional risk factors for almost all CVD subtypes (Figure 2¹⁷).

What would be key implications from this individual-level data meta-analysis to the representative clinical guidelines? The answer would depend on the CVD outcomes of interest, target population, and availability of CKD measures in that population. The AHA/ACC Guideline currently focuses on the risk of coronary heart disease and stroke, and for these two CVD outcomes, the addition of eGFR and ACR has only modestly improved the prediction. However, this AHA/ACC Guideline recognizes the importance of including heart failure as an outcome of interest. If such a modification occurs in the future, it is worth considering the addition of GFR and ACR. The European Guideline is based on the risk of CVD mortality and now takes into account both GFR and ACR. However, as mentioned above, this European Guideline prioritizes GFR over ACR in this context. Our data suggest the need for more emphasis on ACR for better classification of CVD mortality risk. For the KDIGO Lipid Guideline, this meta-analysis demonstrates that both GFR and ACR are useful

to classify the risk of CVD in the CKD population. This KDIGO Lipid Guideline fundamentally focuses on statin therapy, but new treatment options of controlling cholesterol increasingly attract attention. Thus, refinement of the CVD risk within the CKD population may be needed. In such a situation, both GFR and ACR would be of value.

Other biomarkers for predicting CVD risk in individuals with CKD

The KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of CKD recommends evaluating general clinical risk (e.g., mortality and the risk of end-stage renal disease) with GFR and ACR. As described in the prior section, this approach will be generally useful for CVD risk prediction as well. However, in case finer risk classification is needed, there are several promising biomarkers as summarized below.

Filtration markers other than serum creatinine

The most studied alternative filtration marker is likely cystatin C. Several studies have consistently demonstrated that eGFR based on cystatin C predicts CVD risk better than eGFR based on serum creatinine.^{18, 19} Although eGFR based on both serum creatinine and cystatin C is shown to best estimate measured GFR, of interest, often eGFR based on cystatin C predicts clinical outcomes better than eGFR based on the combination of those two filtration markers. The contribution of non-GFR determinants of cystatin C such as inflammation to CVD prediction may account for this observation.¹⁸

β_2 -microglobulin (B2M) and β -trace protein (BTP) are other alternative filtration markers. Of these, a few studies have demonstrated particularly strong associations of B2M with CVD outcomes. For example, using data from the Chronic Renal Insufficiency Cohort, Foster et al. recently reported that in patients with CKD, only B2M, but not creatinine-based eGFR or BTP, was significantly associated with CVD events (myocardial infarction, heart failure, and stroke).²⁰ Similarly, among cystatin C, B2M, and BTP, only B2M significantly improved the prediction of a composite of CVD outcomes beyond traditional risk factors among participants with CKD in the Atherosclerosis Risk in Communities Study.²¹ This strong association of B2M with CVD may reflect its property as a good filtration marker and/or a molecule damaging vasculature through amyloid formation.^{21, 22}

Measures of subclinical atherosclerosis or cardiac damage/overload

Theoretically it seems reasonable that measures reflecting the disease process in the cardiovascular system predict clinical CVD events well. In this context, the AHA/ACC Cholesterol Guideline recommends the assessment of coronary artery calcium (CAC) or ankle brachial index (ABI) to refine CVD risk.⁴ Of these, a body of evidence demonstrates CAC as one of the strongest predictor of CVD in the general population.²³ Despite some concerns about the clinical implications of CAC in patients with CKD due to their unique calcium-phosphate metabolism,²⁴ our group recently confirmed the usefulness of CAC over two other measures of subclinical atherosclerosis, ABI and carotid intima-media thickness, for predicting CVD events in persons with CKD.²⁵

Blood levels of cardiac troponins and natriuretic peptides are commonly used to diagnose myocardial infarction and heart failure, respectively, in clinical practice. A growing body of

evidence suggests that these cardiac markers can also inform future risk of incident CVD events. Of interest, high-sensitivity cardiac troponin T levels are detected in the majority of the middle-aged and older general population and are shown to be more strongly associated with heart failure than coronary heart disease.²⁶ There have been some concerns about how to interpret cardiac troponin T and natriuretic peptides in patients with CKD, as these markers may be elevated due to reduced kidney function but not necessarily cardiac damage or overload. Nonetheless, several studies, including ours, have demonstrated that both cardiac troponin T and natriuretic peptides improve the prediction of CVD events, particularly heart failure, beyond traditional risk factors even in the CKD population.²¹

Areas of future research

A risk-centered approach is currently incorporated for lipid management and aspirin therapy.^{3, 4} For blood pressure management, although not yet implemented in U.S. guidelines,²⁷ a recent meta-analysis from the Blood Pressure Lowering Treatment Trialists' Collaboration²⁸ has demonstrated that such a risk-centered approach may also be advantageous for hypertension management. Since hypertension is prevalent among those with CKD, future studies would be warranted to determine whether predicted risk can guide blood pressure control in persons with CKD.

The AHA/ACC Guideline on the Assessment of Cardiovascular Risk¹⁴ emphasizes the importance of “risk discussion” between patients and physicians for shared decision making. Such a discussion would include the patient's predicted risk for CVD, potential benefits/harms of treatments, and patient preferences of preventive therapies.¹⁴ However, to our best knowledge, data on these aspects for patients with CKD are sparse.

Most previous studies have investigated the risk prediction of CVD mortality, coronary heart disease, stroke, and heart failure. However, there are some other CVD subtypes relevant to individuals with CKD such as sudden cardiac death, atrial fibrillation, and peripheral artery disease including ischemic limb amputation. Statin and/or aspirin therapy based on risk of CHD and stroke may modify the risk of these understudied CVD subtypes or their complications as well. However, since there are specific preventive and therapeutic options available for sudden cardiac death, atrial fibrillation, and peripheral artery disease, specific investigations for these CVD subtypes are needed.

Conclusions

Two key CKD measures, eGFR and albuminuria, improve CVD risk prediction beyond traditional risk factors, particularly for CVD mortality and heart failure. Overall, albuminuria demonstrates more evident improvement than eGFR based on serum creatinine. It seems reasonable to take into account these CKD measures for CVD prediction, particularly when the data have been already measure for some clinical indications (e.g., CKD patients). When the risk prediction should be further refined other biomarkers can be also useful, and measures reflecting pathophysiological process of CVD such as coronary artery calcium and high-sensitivity cardiac troponin T seem particularly promising. Future clinical guidelines may require updates regarding whether/how to incorporate CKD

measures and other biomarkers in CVD prediction, depending on the CVD outcomes of interest, target population, and availability of those measures and biomarkers in that population.

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KEY POINTS

- A recent international meta-analysis of individual-level data demonstrates that eGFR and albuminuria improve CVD risk prediction beyond traditional CVD risk factors, particularly for CVD mortality and heart failure.
- This meta-analysis also shows that albuminuria contributes to better CVD risk prediction more than eGFR and most modifiable traditional risk factors.
- Filtration markers other than serum creatinine, e.g., cystatin C and β_2 -microglobulin, lead to better CVD risk prediction beyond creatinine-based eGFR.
- If the goal is to predict CVD risk, measures of CVD process, e.g., coronary artery calcium and cardiac troponins, are promising in the CKD population.

Figure 1.

Difference in C-statistic for cardiovascular outcomes by adding kidney measure(s) to traditional models in the combined general population and high-risk cohorts.

Figure 2.

C-statistic difference for four cardiovascular outcomes by omitting kidney disease measures and traditional risk factors from a model with all risk factors in a CKD population

Table 1
Representative individual studies exploring either or both of key CKD measures (GFR and albuminuria) for CVD prediction

Lead author	Published year	Population	CKD measures	CVD outcomes	Authors' conclusion about prediction improvement
Hallan ⁷	2007	General	eGFR _{cre} & ACR	CVD mortality	Yes
Weiner ⁸	2007	General	eGFR _{cre}	CHD	No
Clase ⁹	2011	High risk	eGFR & ACR	CVD composite (CVD death, MI, stroke, HF)	No
Ito ¹⁰	2011	General	Serum creatinine & cystatin C	CVD composite (CHD, stroke, HF, PAD)	No
Nerpin ¹¹	2011	General	eGFR & ACR	CVD mortality	Yes
Chen ¹²	2013	CKD	eGFR & dipstick proteinuria	CVD composite (CHD, TIA, stroke, ventricular arrhythmia, HF)	Yes
Bittencourt ¹³	2015	High risk	Serum creatinine (dipstick proteinuria in subsample)	CVD composite (CVD death or non-fatal MI)	Yes

ACR: urine albumin to creatinine ratio; CHD: coronary heart disease; CKD: chronic kidney disease; CV: cardiovascular; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; eGFR_{cre}: eGFR based on creatinine; HF: heart failure; MI: myocardial infarction; PAD: peripheral artery disease; TIA: transient ischemia attack.

Table 2

Representative clinical guidelines and their position for incorporating CKD measures in CVD risk prediction

	AHA/ACC ¹⁴	European ¹⁵	KDIGO ¹⁶
Published year	2013	2012	2013
Outcome(s) of interest	CHD (coronary death and non-fatal myocardial infarction) + stroke	CVD mortality	CHD (coronary death and non-fatal myocardial infarction)
CKD measures for risk classification	Not included due to uncertainty	very high (≤ 10 -year CVD mortality risk $> 10\%$): GFR < 30 ; diabetes plus elevated albuminuria high (≤ 10 -year CVD mortality risk 5-10%): GFR 30-59	high risk: all persons with CKD aged ≥ 50 years and persons with CKD < 50 years with predicted 10-year CHD risk $> 10\%$