

# Should eGFR and Albuminuria Be Added to the Framingham Risk Score? Chronic Kidney Disease and Cardiovascular Disease Risk Prediction

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## Key Words

Cystatin C · Creatinine · Chronic kidney disease · Cardiovascular disease · Risk prediction

## Abstract

Presence of chronic kidney disease (CKD) defined as decreased glomerular filtration rate (GFR) and/or increased urine albumin excretion is associated with heightened risk of cardiovascular disease (CVD) and all-cause as well as CVD mortality. Although CKD is strongly linked with CVD, it remains undetermined whether this strong association is simply due to shared CVD risk factors or unique traits consequential to CKD. The probability of future CVD events can be estimated with reasonable accuracy using the Framingham equation which was derived from the Framingham study, a community-based cohort of 5,209 white adults aged 30–62 years who were first examined in 1948. Efforts to capture excess CVD risk associated with CKD have been evaluated by adding estimated GFR, cystatin C, serum creatinine and measures of urinary albumin excretion to the Framingham equation which is based on traditional cardiovascular risk factors. Although decreased GFR and increased urine albumin excretion are consistently associated with cardiovascular outcomes, the addition of these factors to the Framingham equation has not been shown to substantially improve overall CVD risk prediction in populations not enriched with CKD.

Moreover, the Framingham equation itself underpredicts cardiovascular events among adults with stage 3 and 4 CKD without clinical CVD. Given the poor performance of the Framingham equation in adults with CKD, future studies should explore risk equations which include traditional CVD risk factors and the unique comorbidities associated with CKD for prediction of cardiovascular events in adults with CKD.

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## Introduction

Chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) <60 or a spot urine albumin/creatinine ratio  $\geq 30$  mg/g, affects roughly 1 in every 7 adults with the majority of CKD cases existing among adults at age >50 years [1]. The presence of CKD heightens an individual's risk for cardiovascular disease (CVD), death from cardiovascular disease (CVD) and all-cause mortality [2–12], and this risk increases once eGFR declines below a threshold of 45–60 ml/min/1.73 m<sup>2</sup> [12]. Increased levels of urinary albumin excretion confer increased CVD risk across all ranges of GFR, regardless of how urine albumin excretion is assessed [for example, spot urine albumin/creatinine ratios (ACR), timed urine collections or urine dipstick measurements]

[4, 10, 12–16]. It is important to note that low muscle mass may confound these associations as low urine creatinine excretion is independently associated with increased risk of CVD and mortality [17]. Likewise, muscle wasting, reflected as low serum creatinine, can result in falsely high eGFR.

The probability of future CVD can be estimated with reasonable accuracy in many different populations using equations derived from the Framingham study, which do not include measures of CKD [18–20]. Due to the strong association between CKD and CVD, it may seem intuitive to utilize CKD measures for CVD risk prediction. In this review, we discuss the association between CKD and CVD (events consequential to disease of coronary or peripheral arteries or veins, including coronary heart disease, CHD) and CHD (events consequential to disease of coronary circulation only), summarize studies which have explored the accuracy of the Framingham equation to predict CVD events in populations with CKD, and evaluate efforts to improve CVD risk prediction utilizing CKD measures.

### **Decreased GFR as an Independent Risk Factor for CVD**

The relationship between decreased GFR and CVD has been examined in numerous studies with the majority of studies involving high-risk populations (individuals with hypertension, heart failure, coronary artery disease, acute coronary syndrome, coronary artery bypass surgery, diabetes or age >65 years) [7, 16, 21–23] or low-risk populations [2–4, 7–9, 11, 12, 24] demonstrating increased CVD risk with decreased eGFR. The largest single study to date includes over 1.1 million adults enrolled in the Kaiser Permanente health plan with assessment of traditional CVD risk factors (blood pressure, lipids and smoking), serum creatinine and urinalysis [11]. GFR was estimated using the Modification of Diet in Renal Disease formula. Over a median follow-up of 2.4 years, a graded and inverse association was noted between eGFR and CVD events, hospitalizations and mortality, with 40, 100 and 180% higher adjusted risk in groups with eGFR 45–59, 30–44, and 15–29 ml/min/1.73 m<sup>2</sup>, respectively, compared to the groups with eGFR ≥60 ml/min/1.73 m<sup>2</sup>. These findings were supported by a recent collaborative meta-analysis that pooled data from 21 general population cohort studies to assess the relationship between CKD measures and CVD mortality [12].

### **ACR as an Independent Risk Factor for Mortality**

Higher ACR levels are directly associated with CVD outcomes and this risk begins at ACR levels below clinical thresholds for microalbuminuria (ACR ≥30–299 mg/g) [25]. The aforementioned CKD Prognosis Consortium meta-analysis included data from 14 studies and 105,872 individuals with baseline urine ACR measurements [12]. A linear association between ACR and CVD mortality was noted when ACR was examined on a logarithmic scale, and this heightened risk began with ACR levels >10 mg/g. Similar findings were noted when the analysis was limited to studies which used trace or ≥1+ urine dipstick results as the measure of increased urine albumin excretion [12]. While most previous studies focused solely on decreased GFR or increased urine albumin excretion as a predictor of CVD risk, this meta-analysis highlighted the importance of examining eGFR and urine albumin excretion concurrently for CVD mortality risk [12]. Associations between CVD mortality and eGFR <60 ml/min/1.73 m<sup>2</sup> appeared similar across all levels of ACR. Likewise, CVD mortality risk associated with increased levels of ACR and positive urine dipstick measurements was independent of eGFR level. Thus, the effects of decreased eGFR and increased ACR are multiplicative for CVD mortality risk [12]. Individuals with eGFR of 80 ml/min/1.73 m<sup>2</sup> and ACR >300 mg/g (stage 2 CKD) carry twice the risk of either death or myocardial infarction (MI) compared to individuals with eGFR 50 ml/min/1.73 m<sup>2</sup> and an ACR <30 mg/g (stage 3 CKD) [12].

### **What Factors Account for Excess CVD Risk Associated with CKD?**

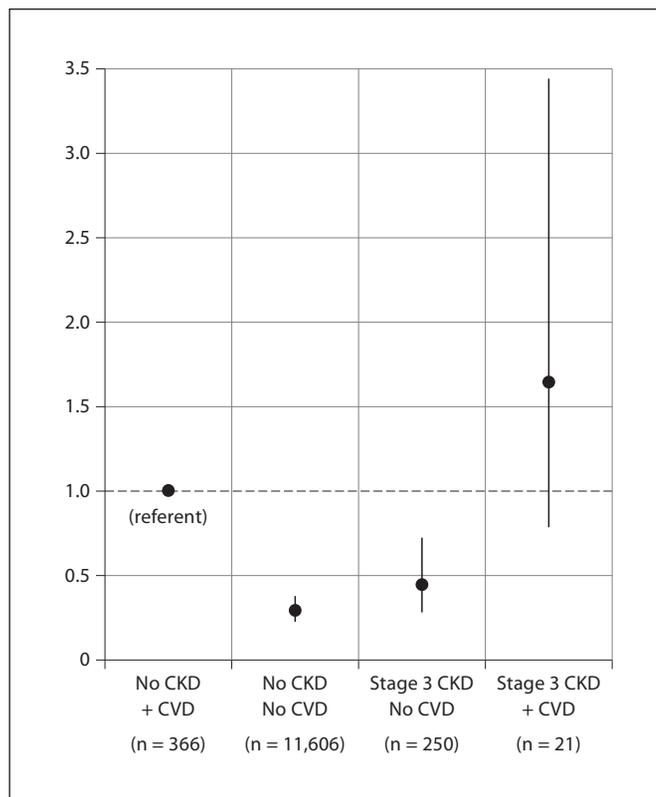
The increased CVD risk associated with CKD may simply reflect a longer duration or severity of traditional CVD risk factors such as hypertension, diabetes and dyslipidemia [5]. This is supported by a graded association between levels of subclinical cardiovascular disease and ACR among adults without established CVD [26]. Prevalence of left ventricular hypertrophy (LVH) is inversely related to eGFR and approximately 3 of 4 patients with stage 5 CKD have LVH at the time of dialysis initiation [27, 28]. Many posit that nontraditional risk factors consequential to CKD such as anemia, hyperphosphatemia, increased fibroblast growth factor-23 levels, inflammation and unmeasured uremic factors account for at least some of the excess cardiovascular risk [2, 29–33]. However, to date, no studies have demonstrated that these

unique factors improve the classification of CVD risk in adults with CKD above and beyond traditional cardiovascular risk factors.

### Framingham Risk Score

Various risk scores predicting coronary heart disease (CHD), meaning events consequential to disease affecting the coronary circulation, have been derived using data from the Framingham Heart Study, a community-based cohort of 5,209 white adults aged 30–62 years living in the Boston suburb of Framingham who were first examined in 1948 [34]. The inclusion of several variables into a risk prediction model enhances the predictive ability for CHD, a complex disease consequential to the interactions between multiple risk factors. In 1976, Kannel [35] first created a CHD risk score, which incorporated age, gender, smoking, systolic blood pressure, total cholesterol, electrocardiogram evidence of LVH, and diabetes. Subsequently, several iterations of this CHD risk score have been validated in differing populations [35]. A sex-specific CHD risk prediction model based on the Fifth Joint National Committee on Hypertension blood pressure categories and National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) II cholesterol categories was created in 1998 [20]. This risk model predicts ‘hard’ CHD (MI and CHD death) using age, sex, blood pressure, total cholesterol, low-density cholesterol, high-density cholesterol, smoking status and diabetes, and has been incorporated into the NCEP-ATP III guidelines, in which lipid-lowering therapy is based on estimated 10-year risk of hard CHD [36]. Individuals with <10% and 10–20% risk over the next 10 years are considered low and intermediate risk, respectively, while those with >20% risk or existing CHD or CHD risk equivalents are considered high risk. Diseases listed by the NCEP-ATP III that are CHD risk equivalents include diabetes, symptomatic carotid artery disease, peripheral artery disease and abdominal aortic aneurysm [34].

The National Kidney Foundation has suggested in its Kidney Disease Outcomes Quality Initiative guidelines that CKD be considered a CHD risk equivalent, which they acknowledge is only supported by grade ‘B’, or moderate evidence [37]. This concept of CHD risk equivalency was examined in the Atherosclerosis Risk in Communities (ARIC) study, where the presence of stage 3 CKD did not confer the same hard CHD risk as existing CHD among adults aged 45–64 years (fig. 1) [38, 39]. In contrast, a similar study in elderly adults >65 years in the



**Fig. 1.** Relative risk of fatal CHD or myocardial infarction by presence of stage 3 CKD and/or CVD. Adapted from Wattanakit et al. [39].

Cardiovascular Health Study (CHS) found that CKD stage 3–4 conferred equivalent 10-year cardiovascular mortality risk as history of MI [38, 39]. Better classification methods accounting for both decreased GFR and increased urine albumin excretion simultaneously could help identify individuals truly at high risk for CHD events.

### Evaluation of a Multivariate Model

Efforts to improve upon the existing Framingham risk score should either identify new individuals with high CVD risk or reclassify individuals into more appropriate categories. Several methods may be used to assess the performance of a risk prediction model [19, 40–42]. The area under the receiver-operating characteristic curve (AUC) measures the probability that a given individual with disease will have a higher risk prediction score than an individual without disease, termed ‘discrimination’.

Higher AUC values with the addition of a biomarker such as serum creatinine or ACR to the Framingham equation would equate to improved discrimination between individuals who do and do not develop CVD. However, to improve CVD discrimination, a biomarker must be strongly associated with CVD yet very poorly correlated with traditional CVD risk factors, including age [43–45].

Another measure of risk prediction performance is calibration, which refers to the agreement between observed and predicted outcomes. The addition of a new biomarker should improve classification of individuals as low or high CVD risk because risk management for individuals classified as intermediate risk remains controversial. The net reclassification index (NRI) assesses the difference in proportion of individuals with and without events who move to a low- or high-risk category; a significantly high NRI indicates classification improvement with the addition of the biomarker(s) [39].

### **Framingham Risk Score and CKD**

The Framingham equation was created using data from a population-based cohort in which the majority of individuals did not have CKD. Thus, the generalizability of this equation for adults with CKD deserves scrutiny. Weiner [46] investigated the utility of the Framingham equation to predict incident MI or CHD mortality among individuals with stage 3 and 4 CKD and no pre-existing CVD utilizing data from the ARIC and CHS studies. In this study, the association between CHD events and traditional risk factors was not consistent with known associations in the general population. For example, HDL levels were not associated with CHD events. The Framingham equation demonstrated poor discrimination in men and underpredicted events in both men and women with CKD, and this was attributed to high competing 10-year mortality risk of 35% in men and 20% in women [41].

### **Adding eGFR, Creatinine, Cystatin C or ACR to the Framingham Equation**

Efforts to capture excess CVD risk associated with CKD have been evaluated by adding eGFR, cystatin C and ACR to models with traditional CVD risk factors [10, 41, 46–48]. Hallan et al. [10] investigated the use of eGFR and ACR (composite variable combining 4 categories of eGFR and ACR) to improve prediction of cardiovascular mortality in a Norwegian community-based study. There

was minimal improvement in risk prediction after adding these terms to a model that included age, sex, diabetes mellitus, prevalent CVD, systolic blood pressure, cholesterol levels and smoking [49]. A similar study by Weiner et al. [50] investigated whether presence of eGFR <60 ml/min/1.73 m<sup>2</sup> improves the discrimination and calibration of the Framingham equation (based on JNC and NCEP categories) for the composite outcome of MI or fatal CAD. Although CKD was an important predictor of the composite outcome, particularly in African Americans, it did not improve discrimination of cardiac events or mortality. Another study utilized a population-based cohort of elderly men (average age 71) living in Sweden and demonstrated significant improvement in prediction of cardiovascular mortality when 4 biomarkers (troponin I, N-terminal pro-brain natriuretic peptide, cystatin C and C-reactive protein) were added to traditional CVD risk factors (table 1) [41]. Cystatin C alone increased the AUC by 0.027 in the entire cohort but not when the analysis was restricted to participants without baseline CVD. Moreover, serum levels of cystatin C are correlated with inflammation which could confound its association with CVD and mortality [51, 52].

In collaboration with investigators from the Multiethnic Study of Atherosclerosis (MESA), we previously evaluated the addition of serum cystatin C and creatinine to the Framingham risk score variables to predict a wide spectrum of incident CVD events including CHD, heart failure, stroke and peripheral arterial disease in a cohort without baseline CVD [48]. No significant change in risk prediction was noted with the addition of serum cystatin C or creatinine to the Framingham equation. Similar to the study by Hallan et al. [10], approximately 11% of MESA participants classified as intermediate risk with the Framingham equation were reclassified as high risk with the addition of cystatin C. However, the NRI was very low (1.6%;  $p = 0.48$ ) with the addition of cystatin C and negative with the addition of serum creatinine (–0.9%;  $p = 0.49$ ).

In contrast to CKD measures, the coronary artery calcification (CAC) score improves risk stratification for individuals classified as intermediate risk with the Framingham equation [53–55]. In the MESA cohort, addition of the CAC score to the Framingham equation reclassified 23% of individuals with incident CVD events as high risk and an additional 13% without events as low risk with an overall NRI of 23% [53]. However, CAC is not routinely measured, and its cost-effectiveness and role in improving risk prediction in populations enriched with CKD deserves additional evaluation.

**Table 1.** Description of studies examining CKD measures to improve CVD risk prediction

Author year	Population	Primary outcome	Model predictors	Added biomarkers	Original AUC	Change in AUC with biomarkers
Wang et al., 2006 [40]	Framingham Offspring study	Fatal and nonfatal MI, coronary insufficiency, CHF, stroke	Age, sex, DM, smoking status, BP categories, TC, HDL, BMI, creatinine	ACR, BNP	0.76	+0.01
Hallan et al., 2007 [10]	Population-based Norwegian study	Cardiovascular death (ICD-10 codes I10-I15, I20-I25, I44-I49, I50, I60-I69, I70-I77)	Age, sex, DM, smoking status, SBP, BP medication, TC, HDL, prevalent CVD	eGFR and ACR categories	Age <70 years 0.91 Age ≥70 years 0.76	Age <70 +0.002 Age ≥70 +0.01
Olsen et al., 2007 [56]	Population-based Danish study	Cardiovascular death, non-fatal MI, stroke	Age, sex, DM, smoking status, SBP, LDL, heart rate, glucose, LVEF, prior MI, prior stroke	ACR, hsCRP, NT-proBNP	0.82	+0.01 (ACR) +0.02 (all 3 biomarkers)
Weiner et al., 2007 [46]	Pooled from 2 population-based US studies, 1 study with adults >65 years age	CHD death, nonfatal MI	Age, sex, DM, smoking status, BP categories, TC, HDL	eGFR <60	White men 0.74 AA men 0.64 White women 0.78 AA women 0.75	White men +0.002 AA men -0.002 White women +0.001 AA women +0.004
Zethelius et al., 2008 [41]	Community-based cohort of elderly Swedish men (subsample without CVD)	Cardiovascular death (ICD-10 codes I00-I99)	Age, DM, smoking status, SBP, BP medication, TC, HDL, cholesterol medication, BMI	Cystatin C, troponin, CRP, NT-proBNP	0.69	+0.01 (cystatin C) +0.06 (all 4 biomarkers)
Shlipak et al., 2008 [47]	Adults with pre-existing CHD	CHD death, nonfatal MI, stroke	Age, sex, race, DM, smoking status, HTN, BMI, creatinine, aspirin use, LVEF <50, prior MI, prior stroke	ACR, CRP, NT-proBNP	0.73	+0.04 (all 3 biomarkers)
Ito et al., 2010 [48]	Population-based multiethnic US study without clinical CVD	CVD death, resuscitated cardiac arrest, nonfatal MI, stroke, angina, PAD, CHF	Age, sex, DM, smoking status, SBP, BP medication, TC, HDL, cholesterol medication, BMI	Creatinine or cystatin C	0.72	-0.01 (creatinine) +0.02 (cystatin C)

DM = Diabetes mellitus; TC = total cholesterol; HDL = high-density cholesterol; LDL = low-density cholesterol; BMI = body mass index; BNP = brain natriuretic peptide; PAD = peripheral arterial disease; CHF = congestive heart failure; ICD = International Statistical Classification of Diseases; LVEF = left ventricular ejection fraction; hsCRP = high-sensitivity C-reactive protein; NT-proBNP = N-terminal pro-brain natriuretic peptide.

## Conclusion

Increased ACR or decreased eGFR is associated with higher CVD risk, yet the presence of traditional CVD risk factors does not entirely account for this excess risk. The Framingham equation underpredicts CVD risk in adults with CKD. However, incorporation of CKD markers such as eGFR, serum creatinine, cystatin C and ACR have so far shown minimal improvement in CVD risk discrimination. Future studies should evaluate CVD risk equations that account for the unique comorbidities associated with CKD in addition to traditional CVD risk factors.

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## Editorial Comment

Meguid El Nahas, Sheffield

The mini review by Chang and Kramer addresses the taxing issue of prediction of CVD in CKD patients. A rising number of reports confirm the high morbidity and mortality risks associated with albuminuria and low eGFR. This has led some to advocate universal screening of communities for these renal-related variables in an attempt to identify those at higher risk of CVD mortality as well as all-cause mortality. Others, including myself, feel that microalbuminuria and reduced eGFR in the community are a reflection of ageing and underlying CVD. With that in mind, it is not too surprising that CKD, as a manifestation of underlying CVD, predicts CVD outcomes! So the logical task within the community would be to focus on the prevention of CVD to prevent CKD; protect your heart to protect your kidneys! This is all the more relevant since recent reports from the Global Burden of Metabolic Risk Factors of the Chronic Diseases Collaborating Group point to the fact that obesity, diabetes, hypertension, dyslipidemia and smoking are on the increase worldwide [1–3].

This will undoubtedly be associated, over the next decade, with a rising number of CKD in the older individuals; the bulk of those suffering from CKD in the commu-

nity are over 60. Emphasis should therefore be on the early detection of those at risk of CVD within the community. Addressing and minimizing their risk factors may in turn reduce the incidence of CKD. There are a number of prediction tools to identify those at increased CVD risk, including the Framingham Risk Score. Unfortunately, current prediction tools, including Framingham Risk Score, perform poorly in CKD patients. The review by Chang and Kramer shows that adding albuminuria, cystatin C or eGFR to conventional risk scores adds little to their predictability and showed minimal improvement in CVD risk discrimination. It concludes that future studies should evaluate CVD risk equations that account for the unique comorbidities associated with CKD in addition to traditional CVD risk factors. Perhaps, one major renal-related risk factor that seems to be overlooked is anemia! This could be the case in spite of a number of studies pointing to its major impact on CVD outcomes in CKD patients [4] as well as its negative impact on CKD progression in those with underlying CVD [5]. Perhaps a CVD risk prediction equation incorporating hemoglobin level may be all that is needed?

## References

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