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Cystatin C versus Creatinine in Determining Risk Based on Kidney Function

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Abstract

BACKGROUND—Adding the measurement of cystatin C to that of serum creatinine to determine the estimated glomerular filtration rate (eGFR) improves accuracy, but the effect on detection, staging, and risk classification of chronic kidney disease across diverse populations has not been determined.

METHODS—We performed a meta-analysis of 11 general-population studies (with 90,750 participants) and 5 studies of cohorts with chronic kidney disease (2960 participants) for whom standardized measurements of serum creatinine and cystatin C were available. We compared the association of the eGFR, as calculated by the measurement of creatinine or cystatin C alone or in combination with creatinine, with the rates of death (13,202 deaths in 15 cohorts), death from cardiovascular causes (3471 in 12 cohorts), and end-stage renal disease (1654 cases in 7 cohorts) and assessed improvement in reclassification with the use of cystatin C.

RESULTS—In the general-population cohorts, the prevalence of an eGFR of less than 60 ml per minute per 1.73 m^2 of body-surface area was higher with the cystatin C–based eGFR than with the creatinine-based eGFR (13.7% vs. 9.7%). Across all eGFR categories, the reclassification of the eGFR to a higher value with the measurement of cystatin C, as compared with creatinine, was associated with a reduced risk of all three study outcomes, and reclassification to a lower eGFR was associated with an increased risk. The net reclassification improvement with the measurement of cystatin C, as compared with creatinine, was 0.23 (95% confidence interval [CI], 0.18 to 0.28) for death and 0.10 (95% CI, 0.00 to 0.21) for end-stage renal disease. Results were generally similar for the five cohorts with chronic kidney disease and when both creatinine and cystatin C were used to calculate the eGFR.

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CONCLUSIONS—The use of cystatin C alone or in combination with creatinine strengthens the association between the eGFR and the risks of death and end-stage renal disease across diverse populations. (Funded by the National Kidney Foundation and others.)

The estimated glomerular filtration rate (eGFR) is the clinical standard for the assessment of kidney function.[1–3] The eGFR thresholds for the definition and staging of chronic kidney disease are based on risk,[3] but measurement of creatinine to determine the eGFR has limitations in risk prediction, particularly in patients with reduced muscle mass.[4] Cystatin C has received much attention as an alternative filtration marker with stronger and more linear risk relationships than creatinine.[5–7] Several studies have suggested that the addition of cystatin C measurements to creatinine measurements in calculating the eGFR significantly improves the risk classification for death, cardiovascular disease, and end-stage renal disease.[8–10]

However, existing evidence has been limited by the lack of a reference standard for cystatin C to calibrate the measures across studies and by the absence of cystatin C–based equations that are derived from a broad population with a wide range of kidney function. The development of an international reference standard for cystatin C and the publication of improved GFR-estimating equations by the Chronic Kidney Disease Epidemiology Collaboration[11] prompted the current meta-analysis of 16 studies across a diverse population of participants. The objectives of this study, which was conducted by the Chronic Kidney Disease Prognosis Consortium (CKD-PC), were to determine whether the addition of an eGFR that was calculated with the use of the recently developed cystatin C equations would strengthen the relationships between various eGFR categories and adjusted risks of death from any cause, death from cardiovascular causes, and end-stage renal disease, as compared with the use of creatinine-based eGFR.

METHODS

STUDY DESIGN AND PARTICIPANTS

Detailed descriptions of the CKD-PC have been reported previously.[12–15] To be eligible for inclusion in the meta-analysis, studies had to include at least 1000 participants (with the exception of studies that enrolled only patients with chronic kidney disease)[14] for whom data on baseline serum creatinine and albuminuria were available. In addition, studies had to include reports of at least 50 events for any outcome of interest. This meta-analysis included 11 general-population studies (with 90,750 participants) and 5 studies of patients with chronic kidney disease (with 2960 participants) for whom measurements of serum cystatin C were available.

We calculated the eGFR using the latest equations from the Chronic Kidney Disease Epidemiology Collaboration, with measurement of serum creatinine, cystatin C, or both creatinine and cystatin C (combination).[11,16–18] All three eGFR equations incorporated kidney-filtration markers (serum creatinine or cystatin C) as well as age, sex, and race (black vs. nonblack), except for the cystatin C–based eGFR, for which data on race were not required.

For each study cohort, we attempted to calibrate cystatin C measurements to the reference standard by evaluating the year and measurement method used (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[11,19] We first used the cystatin C–based eGFR to reclassify participants who were initially classified according to the creatinine-based eGFR. Comparing the cystatin C–based eGFR with the creatinine-based eGFR had the advantage of providing the clearest contrast, since each equation includes only one filtration marker. We then compared the creatinine equation with the combination equation.

STUDY OUTCOMES

The outcomes of interest were death from any cause, death from cardiovascular causes, and end-stage renal disease. Death from cardiovascular causes was defined as death from myocardial infarction, heart failure, or stroke. End-stage renal disease was defined by the need for renal-replacement therapy or death from chronic kidney disease.

We first performed analyses within each study cohort and then performed meta-analyses across all studies, using random-effects models. We restricted our analysis to participants who were at least 18 years of age. Primary analyses were conducted in the general-population cohorts, since participants were not selected on the basis of serum creatinine levels. Secondary analyses were performed in the cohorts with chronic kidney disease.

STUDY OVERSIGHT

The study was designed by the CKD-PC steering committee. Data were collected within each of the 16 cohorts and analyzed centrally at the coordinating center.

STATISTICAL ANALYSIS

We first evaluated the distributions for each eGFR equation. Subsequently, we constructed Cox proportional-hazards models fitted with eGFR linear splines, with adjustment for age, sex, race (black vs. nonblack), smoking status, status with respect to a history of cardiovascular disease, systolic blood pressure, presence or absence of diabetes, total cholesterol level, body-mass index, and the level of albuminuria. From these models, we computed and pooled hazard ratios for each increment in the eGFR of 1 ml per minute per 1.73 m^2 of body-surface area for eGFR values from 15 to 120, with a reference point at 95 ml per minute per 1.73 m^2 (50 ml per minute per 1.73 m^2 for cohorts with chronic kidney disease), as in previous CKD-PC meta-analyses.[12–14,16,20,21] The reference point was moved to 65 ml per minute per 1.73 m^2 for the end point of end-stage renal disease in the general-population cohorts in order to ensure that there were sufficient events at an eGFR value above the reference point. Details about the statistical analysis are provided in Appendix 1 in the Supplementary Appendix.

We cross-tabulated the eGFR that was calculated by means of each equation, using clinical categories of volume per minute per 1.73 m^2 (<15 ml, 15 to 29 ml, 30 to 44 ml, 45 to 59 ml, 60 to 89 ml, and ≥90 ml).[1,22] We then evaluated the proportion of participants in each creatinine-calculated eGFR category for whom the eGFR was reclassified on the basis of the cystatin C measurement or the combined measurement.[1,16,22–25] For each outcome, we used

multivariable Cox proportional-hazards models to assess risks of adverse outcomes among participants for whom the eGFR was reclassified to a higher value (i.e., to higher categories of cystatin C–calculated eGFR or combination-calculated eGFR) or a lower eGFR value (i.e., to lower categories of the two sets of GFR estimates), as compared with participants for whom the eGFR was not reclassified.

We assessed the overall improvement in reclassification on the basis of clinical eGFR categories by applying the net-reclassification-improvement approach,[25,26] a method involving the use of predefined risk categories to assess improved risk prediction. To assess generalizability, we calculated the net reclassification improvement in subgroups according to age (<65 vs. ≥65 years), sex, race (black vs. nonblack), eGFR category, and status with respect to diabetes, hypertension, and albuminuria, with a correction for bias when appropriate.[27] All analyses were conducted with the use of Stata/MP software, version 11.2.

RESULTS

STUDY OUTCOMES

The mean values for the eGFR as measured with creatinine, cystatin C, and a combination of both for volume per minute per 1.73 m^2 were 85 ml, 85 ml, and 84 ml, respectively, among the general-population cohorts and 38 ml, 39 ml, and 38 ml, respectively, among the cohorts with chronic kidney disease (Table 1).[28–43] In the general-population cohorts, the prevalence of an eGFR of less than 60 ml per minute per 1.73 m^2 was 9.7% with the creatinine equation, 13.7% with the cystatin C equation, and 10.0% with the combination (Fig. 1), values that were consistent across subgroups (Fig. S1 in the Supplementary Appendix).

Death from Any Cause—In the 11 general-population cohorts, 12,351 of 90,750 participants (13.6%) died during a mean follow-up of 7.7 years. With a cystatin C–based eGFR, the risk of death from any cause was increased at eGFR values that were below the reference point of 95 ml per minute per 1.73 m^2, with a threshold of 88 ml per minute per 1.73 m^2 (i.e., the point at which the risk was significantly higher than the risk at the reference point) (Fig. 2A). The corresponding thresholds were 59 ml and 83 ml per minute per 1.73 m^2 for the creatinine-based eGFR and the combination-based eGFR, respectively. There was a reverse J-shaped association for the creatinine and combination measurements of eGFR, with a significantly elevated risk of death at higher eGFR values, as has been reported previously.[6]

Among the cohorts of patients with chronic kidney disease, eGFR values based on cystatin C and combination measurements also had more linear associations with the risk of death than did the values based on creatinine measurement, although no reverse J-shaped association was observed for the creatinine-based eGFR values (Fig. S2A in the Supplementary Appendix).

In the general-population cohorts, across all the creatinine-based eGFR categories, reclassification to a lower eGFR was associated with a significantly higher adjusted risk of death (Table 2). For example, among participants with a creatinine-based eGFR of 60 to 89 ml per minute per 1.73 m^2 (48% of participants overall), 14% were reclassified to a cystatin

C–based eGFR of less than 60 ml per minute per 1.73 m^2 and had a relative increase of 57% in the adjusted risk of death during follow-up. Within the smaller category of a createnine-based eGFR of 60 to 74 ml per minute per 1.73 m^2 (18% of all participants), the 23% who were reclassified to a cystatin C–based eGFR of less than 60 ml per minute per 1.73 m^2 also had a significantly higher adjusted risk of death (hazard ratio, 1.54; 95% confidence interval [CI], 1.33 to 1.79) (Table S2 in the Supplementary Appendix).

Conversely, across all categories of creatinine-based eGFR values, reclassification to a higher eGFR with the measurement of cystatin C was associated with a reduction in the adjusted risk of death, as compared with the group with eGFR values that were not reclassified, although the findings were significant only for creatinine-based eGFR categories of 30 to 44 ml and 45 to 59 ml per minute per 1.73 m^2. In the latter category, 42% of participants were reclassified to a cystatin C–based eGFR of 60 ml per minute per 1.73 m^2 or more and had a relative reduction of 34% in the adjusted risk of death. Similar results were observed when findings were unadjusted or further adjusted for the creatinine-based eGFR (Tables S3 and S4 in the Supplementary Appendix).

Across all categories of creatinine-based eGFR values, the overall net reclassification improvement for death from any cause was 0.21 (95% CI, 0.17 to 0.26; P<0.001) and was greater in the general-population cohorts than in those with chronic kidney disease (Fig. 3). Among the 15 cohorts for which mortality data were available, all had positive net reclassification improvements. The bias-corrected estimates of net reclassification improvement were highest for the creatinine-based eGFR categories of 45 to 59 ml per minute per 1.73 m^2 (0.28; 95% CI, 0.19 to 0.36), 30 to 44 ml per minute per 1.73 m^2 (0.32; 95% CI, 0.25 to 0.39), and 15 to 29 ml per minute per 1.73 m^2 (0.27; 95% CI, 0.18 to 0.37) (Table S5 in the Supplementary Appendix). In sensitivity analyses that were stratified according to age, sex, race, and status with respect to diabetes, hypertension, and albuminuria, estimates of net reclassification improvement varied minimally (Fig. S3 and Table S6 in the Supplementary Appendix). Meta-regression analyses showed no cohort-specific factors that were significantly associated with the net reclassification improvement (Table S7 in the Supplementary Appendix).

Death from Cardiovascular Causes—The 10 general-population cohorts with data on deaths from cardiovascular causes included 64,010 participants, with 3193 events during a mean follow-up period of 8.8 years. For the creatinine-based eGFR, there was no reverse J-shaped association for the risk of death from cardiovascular causes, but the risk gradient was steeper for eGFR values based on cystatin C measurements and those based on combined measurements than for the creatinine-based eGFR values; threshold values for significant elevations in risk were 69 ml per minute per 1.73 m^2 for the creatinine equation, 86 ml per minute per 1.73 m^2 for the cystatin C equation, and 83 ml per minute per 1.73 m^2 for the combination equation (Fig. 2B).

In analyses according to eGFR category, reclassification to a lower eGFR was consistently associated with an increased risk in each creatinine-based eGFR category, but point estimates were significant only for the creatinine-based eGFR categories of 45 to 59 ml, 60 to 89 ml, and 90 ml per minute per 1.73 m^2 or more. Reclassification to a higher eGFR was

associated with a decreased risk in each category of creatinine-based eGFR but was significant only for a creatinine-based eGFR of 15 to 29 ml per minute per 1.73 m^2 (Table 2). Overall, the net reclassification improvement was 0.16 (95% CI, 0.12 to 0.21; P<0.001), including the two cohorts with chronic kidney disease, and point estimates favored the cystatin C–based eGFR within each cohort (Fig. 3) and within each subgroup tested (Fig. S3 and Table S7 in the Supplementary Appendix).

End-Stage Renal Disease—In two of the general-population cohorts, with a total of 37,872 participants, there were 357 events of incident end-stage renal disease, and in the five cohorts with chronic kidney disease, comprising 2955 participants, there were 1297 such events over a mean follow-up of 9.3 years. The risk associations for creatinine-based eGFR, cystatin C–based eGFR, and eGFR based on combined measurements were similar in the general-population cohorts (Fig. 2C) and cohorts with chronic kidney disease (Fig. S2B in the Supplementary Appendix). Nonetheless, in all categories of creatinine-based eGFR, reclassification to a lower eGFR with measurement of cystatin C was associated with an increased risk of end-stage renal disease, and reclassification to a higher eGFR was generally associated with a lower risk (Table 2). The overall net reclassification improvement was not significant (0.03; 95% CI, −0.03 to 0.08; P = 0.46), although it had borderline significance in the general-population cohorts (0.10; 95% CI, 0.00 to 0.21; P = 0.05) (Fig. 3).

Use of Combined Calculations—Reclassification to a lower eGFR with the combination equation was strongly associated with an increased risk of all three outcomes (Table S8 in the Supplementary Appendix), with effect sizes that were similar to those for cystatin C–based eGFR, but smaller proportions of participants were reclassified with the combination equation. Similarly, reclassification to a higher eGFR with the combination equation was associated with reductions in risks that were similar to those with the cystatin C equation.

The net reclassification improvement with the combination eGFR equation over the creatinine equation was smaller than the improvement with the cystatin C equation for death from any cause (0.13; 95% CI, 0.12 to 0.15; P<0.001) and death from cardiovascular causes (0.11; 95% CI, 0.09 to 0.13; P<0.001) but was larger for end-stage renal disease (0.07; 95% CI, 0.02 to 0.12; P = 0.01) (Fig. 3, and Fig. S4 in the Supplementary Appendix). We found that the net reclassification improvement with the cystatin C equation, as compared with the combination equation, was moderately strong and significant for death from any cause (0.13; 95% CI, 0.09 to 0.18; P<0.001) and for death from cardiovascular causes (0.10; 95% CI, 0.06 to 0.14; P<0.001) but was essentially equivalent for end-stage renal disease (−0.02; 95% CI, 0.16 to 0.13; P = 0.82).

DISCUSSION

Accurate detection and staging of chronic kidney disease are integral components of clinical medicine, since such evaluations have a major effect on disease labeling, interventions, drug doses, and risk stratification for clinical procedures.[3] Our study provides evidence that the use of cystatin C improves the role of eGFR in risk categorization, as judged by the risk of

death from any cause and to a lesser extent the risks of death from cardiovascular causes and end-stage renal disease. Most notably, reduced values for cystatin C–based eGFR and eGFR based on combined measurements of creatinine and cystatin C had a consistent linear association with increased risks of death from any cause and from cardiovascular causes for all eGFR levels below approximately 85 ml per minute per 1.73 m^2, which is well above the threshold of 60 ml per minute per 1.73 m^2 for the detection of chronic kidney disease with a creatinine-based eGFR. These findings show that eGFR equations that are based on the measurement of cystatin C can be used to detect increased risks of adverse outcomes that are not detected with creatinine-based calculation of the eGFR.

Differences among the eGFR values with respect to risk relationships probably reflect confounding by non-GFR determinants of the filtration markers. We observed that the creatinine-based eGFR had the weakest association with death from any cause among the three GFR estimates and had a marked reverse J-shaped association. It is well known that the non-GFR determinants of serum creatinine, including muscle mass, diet, and physical activity, can confound the associations between the creatinine-based eGFR and outcomes.[44] The hypothesized mechanism is that serum creatinine levels are lower than expected for the level of GFR in patients who are in poor health and who are most likely to die. Non-GFR determinants of cystatin C also exist, though they are quantifiably smaller than those of creatinine.[45] It is therefore possible that confounding by non-GFR determinants of cystatin C may enhance the association between cystatin C–based eGFR and the risk of death.[29] Hypothesized mechanisms include the potential influences of obesity, inflammation, and diabetes in raising cystatin C levels.[46–48]

Recent studies have shown that calculation of the eGFR with a combination of creatinine and cystatin C more accurately reflects measured GFR than either marker alone, findings that are probably due to the lesser overall effects of non-GFR determinants of either marker when both markers are included.[11,49] However, we found that eGFR calculated with the use of both markers had a weaker association with the risk of death from any cause than did the cystatin C–based eGFR. Because analyses of prognosis are most heavily influenced by the events (in this case, deaths), the confounding by non-GFR determinants of creatinine in persons who are most susceptible to illness may particularly weaken the association between eGFR based on combined measurements and longitudinal outcomes as compared with the effect in cross-sectional comparisons with measured GFR. Thus, calculation of the eGFR with the use of combined measurements may provide the most accurate eGFR overall but not in some subgroups of patients in whom creatinine levels are reduced and risk is high. Alternatively, if non-GFR determinants of cystatin C augment its association with the risk of death, then they will have a greater effect on the cystatin C–based eGFR than on the eGFR that is based on combined measurements. We cannot distinguish among these possibilities, since the strength of our study is in establishing firm associations, with limited ability to determine causal mechanisms.

Recent guidelines suggest the use of cystatin C to validate the diagnosis of chronic kidney disease in patients who are currently considered to have chronic kidney disease solely on the basis of a creatinine-based eGFR of less than 60 ml per minute per 1.73 m^2, without albuminuria or other markers of kidney damage.[3] In our study, 42% of participants with a

creatinine-based eGFR of 45 to 59 ml per minute per 1.73 m^2 had a cystatin C–based eGFR of 60 ml per minute per 1.73 m^2 or more, and those participants had a 34% reduction in the risk of death and an 80% reduction in the risk of end-stage renal disease, as compared with participants for whom the eGFR was not reclassified. Persons with a creatinine-based eGFR of 45 to 59 ml per minute per 1.73 m^2 in the absence of albuminuria account for 4% of all persons in the United States and for 54% of patients with a creatinine-based eGFR of less than 60 ml per minute per 1.73 m^2 (the typical threshold for a diagnosis of chronic kidney disease).[50] Confirmatory testing with the use of cystatin C could allow substantial reclassification in this group, with more appropriate resource utilization for patients at increased risk for complications of chronic kidney disease. Although the use of two different calculations of the eGFR (the creatinine-based eGFR and the cystatin C–based eGFR) allows for an examination of the average of the two values as well as the difference between them, our results indicate that a single calculation of the eGFR based on the combined measurements performs well for risk classification in addition to its proven advantage in GFR estimation.

Our study examined prognosis on the basis of eGFR values calculated with the use of cystatin C as compared with creatinine-based eGFR values in more than 90,000 study participants. We examined a variety of clinically useful methods for GFR estimation, included a broad range of kidney function, and standardized the measurements of cystatin C and creatinine across studies to the extent possible. Nonetheless, we had less information to evaluate reclassification according to the cystatin C–based eGFR for end-stage renal disease. The available results suggest that cystatin C adds less value to creatinine for the prediction of end-stage renal disease than for the prediction of death, but these findings should be interpreted with caution, since the diagnosis of end-stage renal disease is based on the serum creatinine level in addition to signs and symptoms of uremia.

We acknowledge additional limitations of our study. First, the GFR was not measured. However, we are aware of no diverse, population-based cohort study that has measured GFR. Methods for measurement of creatinine and cystatin C varied across the studies, as did the efforts to calibrate these measures to reference standards. We cannot determine whether any measurement bias would have favored creatinine or cystatin C, nor can we determine the effects of any bias on the thresholds reported for significant elevations in risks. In addition, although the general-population cohorts were broadly representative, the cohorts with chronic kidney disease were not completely generalizable, since only two of the five cohorts included patients with diabetes and none included kidney-transplant recipients. Our results may be influenced by the presence of residual confounding, which could have an effect on the eGFR thresholds for elevated risk. Finally, most participants were either white or black; therefore, caution should be used in extrapolating our results to other racial or ethnic groups.

In conclusion, the use of cystatin C to calculate the eGFR strengthened the associations between eGFR categories and the risks of death and end-stage renal disease across diverse populations. We also found that the risk of death was increased when values for both cystatin C–based eGFR and eGFR based on combined creatinine and cystatin C measurements were below a threshold of approximately 85 ml per minute per 1.73 m^2.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX

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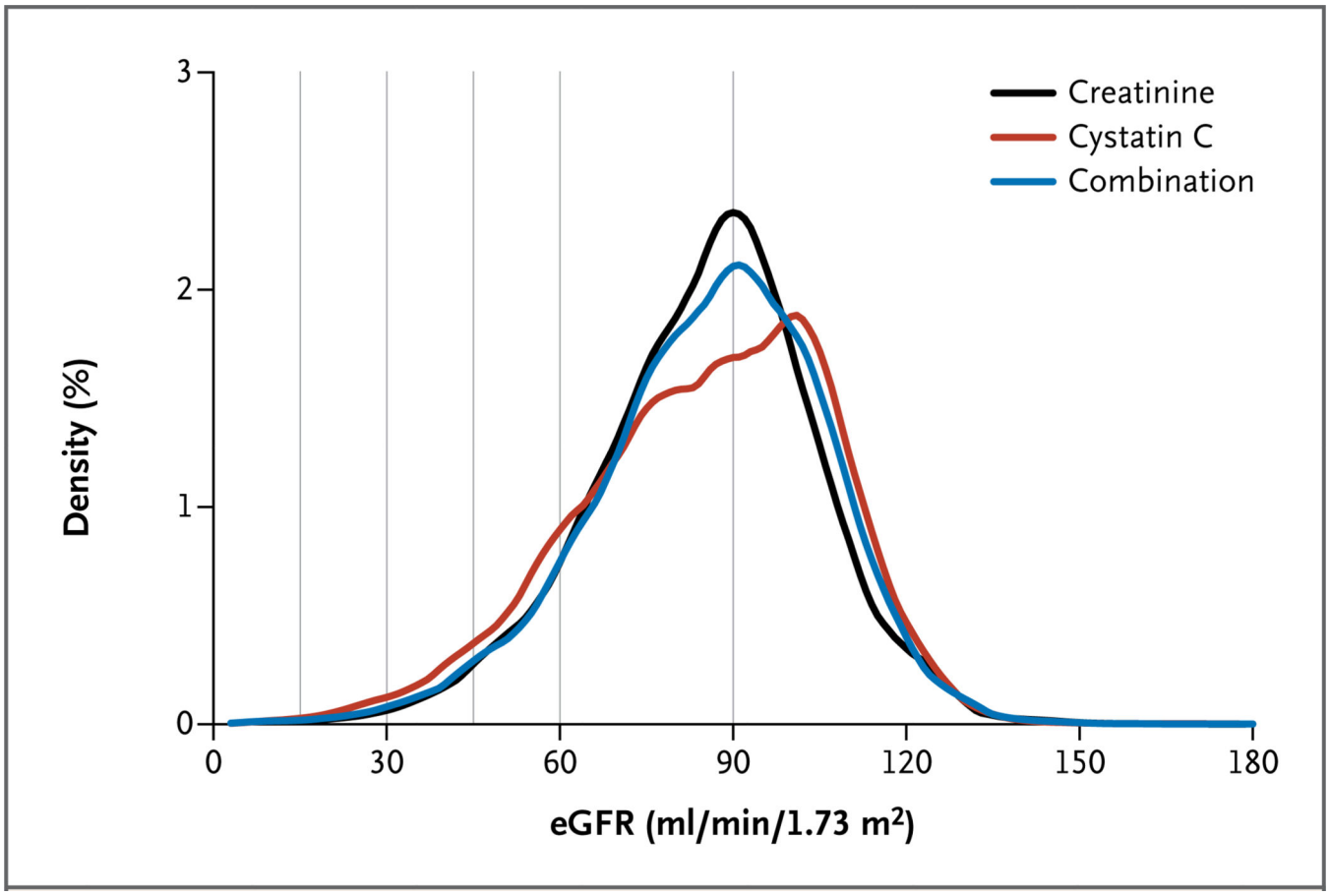

Figure 1. Distribution of the Estimated Glomerular Filtration Rate (eGFR) as Calculated with the Measurement of Creatinine, Cystatin C, or Both in 11 General-Population Cohort Studies

A total of 90,750 participants were included in the meta-analysis of 11 studies, with a kernel-density estimate showing the smoothed frequency for each 1 ml of the eGFR value. The vertical lines indicate current clinical thresholds for eGFR categories.

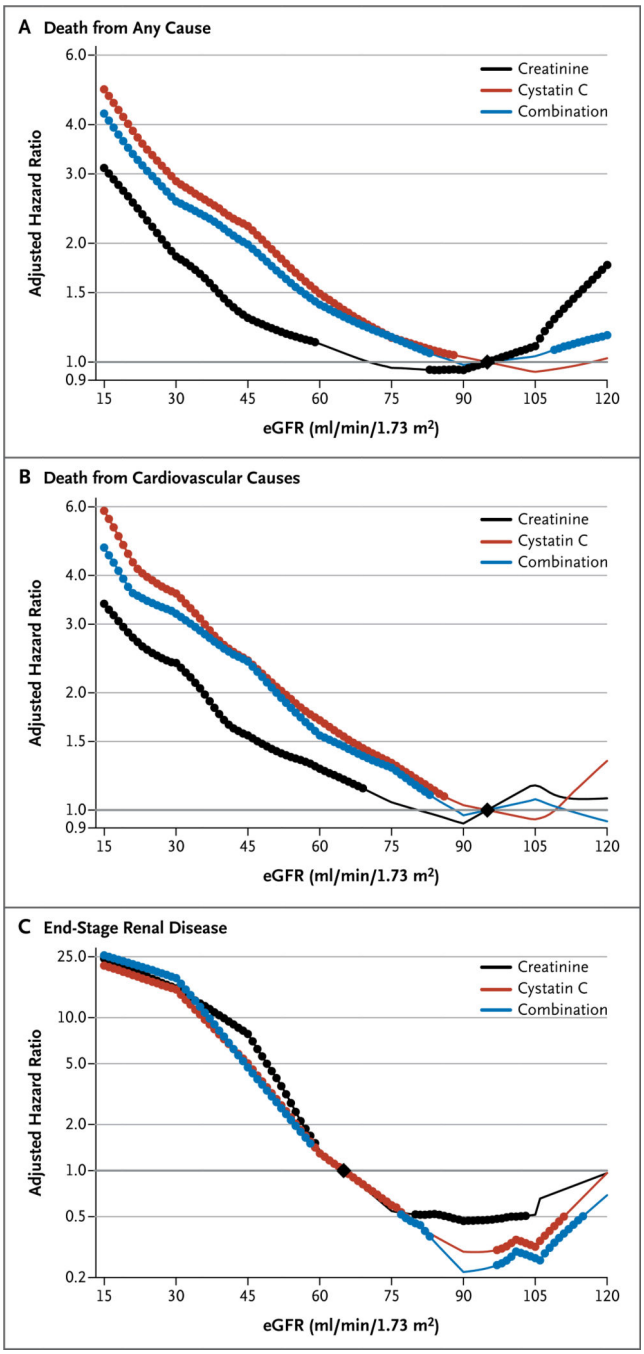

Figure 2. Adjusted Hazard Ratios for the Three Study Outcomes in the General-Population Cohort Studies

Shown are hazard ratios for death from any cause (Panel A), death from cardiovascular causes (Panel B), and end-stage renal disease (Panel C), according to whether the eGFR was calculated with the measurement of creatinine, cystatin C, or both. The graphs show associations by plotting the adjusted hazard ratio versus the reference points, which are indicated by black diamonds (at 95 ml per minute per 1.73 $m^2$of body-surface area for death from any cause and death from cardiovascular causes and at 65 ml per minute per 1.73 $m^2$for end-stage renal disease). The hazard ratios were adjusted for age, sex, race, body-mass index, systolic blood pressure, total cholesterol, presence or absence of a history of cardiovascular disease, smoking status, presence or absence of diabetes, and level of albuminuria. In each panel, solid circles indicate that the adjusted hazard ratio at

the indicated eGFR level was significant, as compared with the reference point. For death from any cause, the meta-analysis included 11 general-population cohorts with 90,750 participants, of whom 12,351 died during follow-up. For death from cardiovascular causes, the meta-analysis included 10 general-population cohorts with 64,010 participants, of whom 3193 died from cardiovascular causes during follow-up. For incident end-stage renal disease, the meta-analysis included 2 general-population cohorts with 37,872 participants, in 357 of whom end-stage renal disease occurred during follow-up. Because there were fewer events of end-stage renal disease than deaths, several eGFR levels had nonsignificant associations with the outcome, despite point estimates that were similar to those for other eGFR levels that had significant associations with end-stage renal disease.

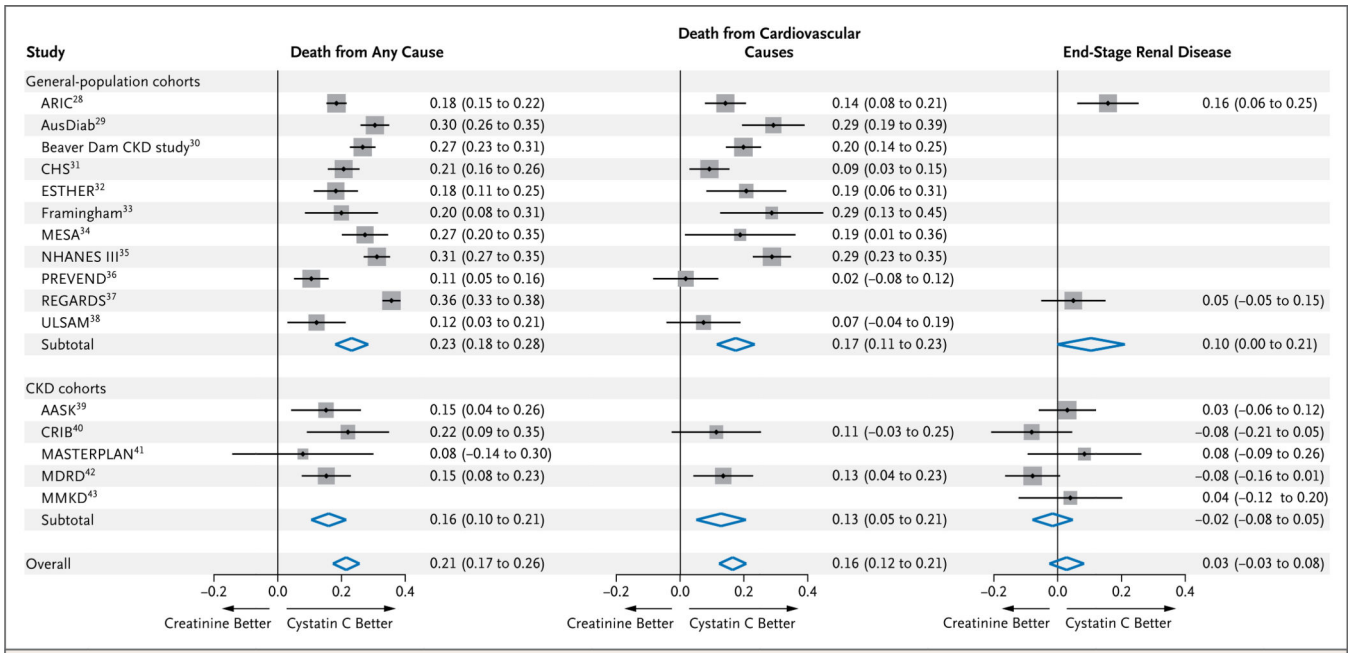

Figure 3. Net Reclassification Improvement in eGFR Based on the Measurement of Cystatin C, as Compared with Creatinine-Based eGFR, for the Three Study Outcomes in the 16 Study Cohorts

Shown are values for net reclassification improvement, a measure of the overall improvement in the association between the reclassified eGFR based on the measurement of cystatin C, as compared with the creatinine-based eGFR, and the study outcomes of death from any cause, death from cardiovascular causes, and end-stage renal disease. The size of the squares is proportional to the inverse of the variance of the net reclassification improvements. The horizontal line indicates the 95% confidence interval. A similar analysis of the net reclassification improvement in eGFR as calculated with the measurement of both creatinine and cystatin C (combination group) is provided in Figure S4 in the Supplementary Appendix. The full study names are provided in Table 1. CKD denotes chronic kidney disease.

Table 1

Baseline Characteristics of Participants in 11 General-Population Studies and 5 Studies of Chronic Kidney Disease.*

Study	Country	No. of Participants	Mean Age	Female Sex	Black Race	Estimated Creatinine	Glomerular Cystatin C	Filtration Rate Combination	Albumin uria†	Smoking (%)	History of CVD	Hypercholes-terolemia	Hyper-tension	Diabetes	Mean Follow-up	Death		End-Stage Renal Disease
																Any Cause	CVD	
			yr	*% of participants*			*ml/min/1.73 m²*					*% of participants*			yr	*no. of participants*		
General population																		
All studies		90,750	60	54	20	85	85	84	12	18	15	32	50	16	7.7	12,351	3193	357
ARIC[28]	United States	11,215	63±6	56	22	84±16	83±18	85±16	8	15	14	34	48	17	10.6	1,884	383	186
AusDiab[29]	Australia	10,507	51±14	55	0	86±17	90±20	88±17	6	16	8	44	32	6	9.9	832	172	NA
Beaver Dam CKD[30]	United States	4,617	62±11	56	<1	80±18	79±21	79±19	4	20	15	54	50	10	11.5	1,462	647	NA
CHS[31]	United States	2,984	78±5	59	17	74±17	63±19	69±18	20	8	31	38	64	16	8.4	1,729	655	NA
ESTHER[32]	Germany	9,607	62±7	55	0	84±20	83±18	84±17	12	16	17	46	60	19	5.0	487	159	NA
Framingham[33]	United States	2,596	58±10	54	0	89±18	83±19	86±17	11	15	6	22	39	9	10.7	186	92	NA
MESA[34]	United States	6,693	62±10	53	28	82±16	89±20	86±18	10	13	0	28	45	12	6.2	322	70	NA
NHANES III[35]	United States	6,748	56±20	52	25	90±25	84±28	87±26	16	22	16	NA	42	16	8.0	1,438	635	NA
PREVEND[36]	Netherlands	7,982	49±13	50	1	89±16	103±21	97±19	11	34	5	39	34	4	9.7	602	170	NA
REGARDS[37]	United States	26,698	64±10	54	43	87±21	84±21	84±21	16	16	22	16	60	23	5.0	2,947	NA	171
ULSAM[38]	Sweden	1,103	71±1	0	0	76±11	59±14	67±12	16	20	36	58	75	19	11.6	462	210	NA
Chronic kidney disease																		
All studies		2,960	55	37	37	38	39	38	78	19	30	52	97	9	9.3	851	278	1297
AASK[39]	United States	949	55±11	39	100	46±15	45±18	44±15	61	29	51	43	100	0	8.8	216	NA	273
CRIB[40]	United Kingdom	292	62±14	34	6	22±11	22±12	21±11	86	14	44	57	95	18	6.1	110	55	138
MASTERPLAN[41]‡	Netherlands	473	59±13	31	3	36±14	46±21	40±17	86	23	25	72	95	32	4.1	52	NA	66
MDRD[42]	United States	1,044	52±13	39	10	35±15	32±14	32±14	84	10	13	NA	NA	6	14.0	473	223	749
MMKD[43]	Austria	202	47±12	34	0	47±30	50±33	48±32	95	21	12	39	89	0	4.0	NA	NA	71

*Plus–minus values are means ±SD. AASK denotes African American Study of Kidney Disease and Hypertension, ARIC Atherosclerosis Risk in Communities, AusDiab Australian Diabetes, Obesity, and Lifestyle, Beaver Dam CKD Beaver Dam Chronic Kidney Disease Study, CHS Cardiovascular Health Study, CRIB Chronic Renal Impairment in Birmingham, CVD cardiovascular disease, ESTHER Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung, Framingham Framingham Heart Study, MASTERPLAN Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of a Nurse Practitioner, MDRD Modification of Diet in Renal Disease, MESA Multi-Ethnic Study of Atherosclerosis, MMKD Mild to Moderate Kidney Disease, NA not available, NHANES III Third U.S. National Health and Nutrition Examination Survey, PREVEND Prevention of Renal and Vascular End-Stage Disease, REGARDS Reasons for Geographic and Racial Differences in Stroke, and ULSAM Uppsala Longitudinal Study of Adult Men.

†Listed are the proportions of participants with an albumin:creatinine ratio of 30 or more (with albumin measured in milligrams per deciliter and creatinine in grams per deciliter), a protein:creatinine ratio of 50 or more (with protein measured in milligrams per deciliter and creatinine in grams per deciliter), or a dipstick protein value of 1+ or higher.

‡Five participants were excluded from the analysis of incident end-stage renal disease.

Table 2

Risk of Clinical Outcomes According to Reclassification of the eGFR with the Measurement of Cystatin C, as Compared with Creatinine, in the 11 General-Population Cohorts.*

Outcome and Category of Creatinine-Based eGFR (ml/min/1.73 m^2)	Total No. of Participants Evaluated	Reclassification to Higher eGFR		No Reclassification		Reclassification to Lower eGFR	
		%of Participants	Adjusted Hazard Ratio (95% CI)	%of Participants	Adjusted Hazard Ratio (95% CI)	%of Participants	Adjusted Hazard Ratio (95% CI)
Death from any cause		1260 events		6110 events		4981 events	
≥90	38,287	NA	NA	70	Reference	30	1.36 (1.24–1.48)
60–89	43,630	32	0.88 (0.76–1.01)	55	Reference	14	1.57 (1.39–1.78)
45–59	6,358	42	0.66 (0.57–0.77)	34	Reference	24	1.67 (1.49–1.88)
30–44	1,917	38	0.77 (0.61–0.98)	44	Reference	19	1.72 (1.24–2.37)
15–29	427	24	0.60 (0.27–1.36)	65	Reference	11	3.04 (1.87–4.95)
0–14	131	20	0.44 (0.14–1.36)	80	Reference	NA	NA
Death from cardiovascular causes		340 events		1572 events		1281 events	
≥90	25,691	NA	NA	71	Reference	29	1.37(1.09–1.71)
60–89	32,283	33	0.94 (0.70–1.28)	54	Reference	13	1.44(1.19–1.74)
45–59	4,458	47	0.79 (0.61–1.04)	33	Reference	21	1.60 (1.30–1.95)
30–44	1,276	43	0.66 (0.42–1.02)	39	Reference	18	1.19(0.77–1.83)
15–29	231	23	0.15 (0.03–0.74)	66	Reference	12	2.83 (0.79–10.18)
0–14	71	17	ND	83	Reference	NA	NA
End-stage renal disease		52 events		198 events		107 events	
≥90	16,898	NA	NA	68	Reference	32	3.37(0.93–12.15)
60–89	17,453	29	0.71 (0.34–1.48)	58	Reference	13	2.66 (1.52–4.67)
45–59	2,468	35	0.20 (0.08–0.53)	37	Reference	27	1.72 (0.91–3.27)
30–44	758	28	0.39 (0.16–0.90)	53	Reference	20	2.04 (1.14–3.65)
15–29	220	26	7.15 (0.04–1257)†	64	Reference	10	2.23 (0.74–6.78)
0–14	75	20	2.39 (0.72–7.87)	80	Reference	NA	NA

*Reclassification of the eGFR to a higher value with the measurement of cystatin C was associated with a decreased risk of a study outcome. Conversely, reclassification of the eGFR to a lower value was associated with an increased risk. Hazard ratios were adjusted for age, sex, race, smoking status, systolic blood pressure, total cholesterol level, presence or absence of diabetes, presence or absence of a history of cardiovascular disease, body-mass index, and the level of albuminuria. NA denotes not applicable, and ND not done because of small sample size.

† The 95% confidence interval is very wide in this category.