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Incremental prognostic information from kidney function in patients with new onset coronary heart disease

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Abstract

Background—Prognostic factors are usually evaluated by their statistical significance rather than by their clinical utility. Risk reclassification measures the extent to which a novel marker adds useful information to a prognostic model. The extent to which estimated glomerular filtration rate (eGFR) adds information about prognosis among patients with coronary heart disease is uncertain.

Methods—We studied patients in an integrated health care delivery system with newly diagnosed coronary heart disease. We developed a model of the risk of death over 2 years of follow-up and then added eGFR to the model and measured changes in C-index, net reclassification improvement, and integrated discrimination improvement.

Results—Almost half of the 31,533 study patients had reduced eGFR (<60 mL/min per 1.73 m²). Mortality was significantly higher among patients who had lower levels of eGFR, even after adjustment for baseline characteristics ($P < .0001$). The addition of eGFR to the prognostic model increased the C-index from 0.837 to 0.843, the net reclassification improvement by 3.2% ($P < .0001$), and integrated discrimination improvement by 1.3% ($P = .007$).

Conclusion—Estimated glomerular filtration rate is an informative prognostic factor among patients with incident coronary heart disease, independent of other clinical characteristics.

Chronic kidney disease (CKD) is associated with elevated mortality from cardiovascular disease and has been increasingly recognized as an independent risk factor for the development of coronary heart disease.^{1–3} Glomerular filtration rate (GFR) is a sensitive measure of kidney function, but in practice, GFR is seldom measured directly (eg, by iothalamate clearance). Instead, GFR is estimated using a formula, such as the CKD-EPI equation,⁴ which is based on the serum creatinine concentration and age, sex, and race. Estimated GFR (eGFR) may be substantially reduced in patients who have only modest

elevations in serum creatinine concentration, particularly in older subjects and women, which may impair recognition of early CKD.

Use of eGFR may improve cardiovascular risk assessment. Several studies have shown that eGFR has a significant relationship with subsequent outcome, even after adjusting statistically for other patient factors.¹⁻³ Consequently, eGFR could be regarded as a novel cardiac risk marker, one that is simple and inexpensive to measure and readily available from routinely collected laboratory data. The evaluation of novel risk markers should be conducted within a framework that assesses their potential clinical value by the degree to which they improve clinical predictions over and above standard clinical data.⁵ The degree to which risk estimates are changed correctly has been increasingly accepted as the measure of the potential clinical value of a risk marker.⁶ The change in risk estimates can be assessed using discrete risk categories (by the “net reclassification improvement” [NRI]) or by using continuous risk probabilities (by the “integrated discrimination improvement” [IDI]). The NRI and IDI have advantages over previously used measures such as the C-index (also known as the area under the receiver operating curve), which do not account for the degree of improvement in risk prediction or whether risk estimates have changed to a clinically meaningful degree.⁵

The purpose of this study was to assess eGFR as a “novel risk marker” and to judge the extent to which incorporating eGFR improves risk prediction over and above the predictive accuracy of standard clinical measures in a large, diverse cohort of adults with incident coronary heart disease.

Methods

Study population

The study population consisted of patients with newly diagnosed coronary heart disease in Kaiser Permanente Northern California, a large integrated health care delivery system that cares for >3.3 million individuals. The population is broadly representative of the local and statewide population, apart from slightly lower representation at the extremes of income and age. We identified all adult members (>30 years of age) with no prior history of coronary disease who were hospitalized between January 1, 2000, and December 31, 2006, for either acute coronary syndrome or for a coronary revascularization procedure (ie, coronary artery bypass surgery or percutaneous coronary intervention [PCI]). We excluded patients who did not have at least 12 months of continuous membership and drug benefit before index date. We also excluded patients who had end-stage renal disease treated with either chronic dialysis or renal transplant before the index date.

The study was approved by institutional review boards of the collaborating institutions and a waiver of consent was obtained due to the nature of the study. The study was funded by the American Heart Association, which had no role in the design and conduct of the study, the data analysis and interpretation, or in drafting and approving the manuscript.

Predictor variables

The primary predictor of interest was level of kidney function, as assessed by eGFR. We estimated GFR based on the most recent outpatient, non-emergency department serum creatinine concentration (calibrated based on a serum creatinine assay traceable to an isotope dilution mass spectroscopy reference measurement procedure) found in a comprehensive health plan laboratory database up to 365 days before a patient's index date; qualifying results were available in 75% of patients, at a median interval of 22 days (interquartile range 2-119 days) before the index date. We estimated GFR using the CKD-EPI equation⁴:

$$eGFR = 141 \times \text{minimum}(Cr/\kappa, 1)^\alpha \times \text{maximum}(Cr/\kappa, 1)^{-1.029} \\ \times 0.993^{\text{age}} \times 1.018 [\text{if female}] \times 1.159 [\text{if black}]$$

where Cr = serum creatinine concentration;

$\kappa = 0.7$ for females and $\kappa = 0.9$ for males; and

$\alpha = -0.329$ for females, and $\alpha = -0.411$ for males.

Outcome

The primary outcome was death from any cause during follow-up through December 31, 2008. Deaths were ascertained from health plan data sources, Social Security Administration vital status files, and California state death certificate records. Patients were censored if they were alive at the time of disenrollment from the health plan or at the end of follow-up on December 31, 2008.

Covariates

We gathered data on baseline demographic characteristics, clinical history, ambulatory laboratory results, and outpatient drug prescriptions by linking multiple health plan electronic databases and electronic health records to form an integrated record for each patient, using previously validated methods.⁷⁻¹¹ Longitudinal medication exposure for relevant drugs was characterized based on detailed information from dispensed prescriptions, as previously described.^{8,10,12}

Analytic approach

We developed models of subsequent death over 2 years of follow-up using multivariable logistic regression. To avoid bias in risk estimates due to informative censoring, we restricted the study population to patients who had complete follow-up data for the full 2 years. For each patient, we estimated the probability of death during follow-up based on demographics, clinical characteristics, and initial treatments for coronary disease: age, sex, race (white, black, Asian, other), calendar year of presentation; diabetes, smoking, hypertension, dyslipidemia; history of peripheral artery disease, valvular disease, dementia, depression, liver disease, lung disease, cancer, stroke or transient ischemic attack; acute coronary syndrome, heart failure, atrial fibrillation, ventricular tachycardia or fibrillation; and treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β -blockers, statins, clopidogrel, or PCI. We then updated the risk estimate by

adding eGFR to the model, which we coded as an ordinal variable, based on recommendations of the National Kidney Foundation¹³:

- eGFR ≥ 90 mL/min per 1.73 m²
- eGFR 60 and <90 mL/min per 1.73 m²
- eGFR 45 and <60 mL/min per 1.73 m²
- eGFR 30 and <45 mL/min per 1.73 m²
- eGFR 15 and <30 mL/min per 1.73 m²
- eGFR <15 mL/min per 1.73 m²

We assessed in several ways the contribution of adding eGFR categories to the baseline prognostic model in several ways. We calculated the NRI described by Pencina et al⁶ using a set of risk categories that were clinically meaningful for patients with established coronary disease: low risk of <1% per year, medium risk of between 1% and <2% per year, high risk of between 2% and <5% per year, and very high risk of ≥ 5% per year. Although the choice of these 4 risk levels was clinically reasonable, the particular cut points between categories were arbitrary, so we also performed a sensitivity analysis that divided the cohort into 4 equally sized risk quartiles.

In a second set of analyses, we treated the estimated probability of death as a continuous variable and calculated the IDI measure⁶ of improved risk prediction from adding eGFR categories to the multivariable risk model that included baseline demographic, clinical, and treatment variables.

All analyses were performed using R Version 2.8.1 software.

Results

A total of 34,727 patients who developed incident coronary heart disease between 2000 and 2006 met the eligibility criteria and had a qualifying eGFR, 31,533 (91%) of whom were continuously enrolled in the health plan for at least 2 years during follow-up and formed the analysis population. Almost half (47%) of the patients had a baseline eGFR <60 mL/min per 1.73 m², indicative of reduced kidney function. Baseline characteristics of patients with lower eGFR levels were progressively less favorable, particularly with older age and higher prevalence of comorbid conditions (Table I).

Mortality was higher among patients with lower levels of baseline eGFR (Figure 1). Two-year mortality ranged from 4.1% among patients with an eGFR ≥ 90 mL/min per 1.73 m² to 46% among patients with an eGFR <15 mL/min per 1.73 m² ($P < .0001$). Estimated GFR remained a significant predictor ($P < .0001$) of 2-year mortality even after adjustment for other baseline clinical characteristics and for treatment (Figure 2). The logistic model of 2-year death from any cause using baseline characteristics, but without eGFR, had a C-index of 0.837. The addition of eGFR to this model increased the C-index to 0.843, an improvement of 0.006 (95% CI 0.005-0.008).

Using the 4 risk categories demarcated by clinical boundaries at 1%, 2%, and 5% annual mortality rates, eGFR reclassified patient risk upwards (correctly) for 99 patients who died but reclassified patient risk downward (incorrectly) for 103 patients who died (Table II). Among patients who survived the 2 years of follow-up, eGFR reclassified risk downward (correctly) in 1,864 patients and upward (incorrectly) in 976 patients (Table II). Overall, the number of patients reclassified correctly exceeded the number reclassified incorrectly by 884 individuals, and the net reclassification improvement was 3.2% ($P < .0001$).

In a sensitivity analysis, we recalculated the NRI using quartiles of estimated 2-year risk, with categories demarcated by boundaries at 1.4%, 3.6%, and 9.5% annual mortality rates. Using these empirically determined categories, predicted risk was reclassified upwards (correctly) for 242 patients who died and downward (incorrectly) for 191 patients who died, while among patients who survived, risk was reclassified downwards (correctly) in 2,036 patients and upwards (incorrectly) in 1,181 patients (Table III). Overall, the number of patients reclassified correctly exceeded the number reclassified incorrectly by 906 individuals, and the net reclassification improvement based on empirical quartiles of risk was 4.3% ($P < .0001$).

The integrated discrimination index assesses the net change in predicted probability among patients who survived and among those who died. Among patients who died, adding eGFR to a model of 2-year risk increased the predicted probability of death for 43% of patients and increased the mean probability of death by 1.2%. Among patients who survived, the predicted probability of death decreased in 65% of patients, and the mean predicted probability of death decreased by 0.2% (Figure 3). Overall, the addition of eGFR to the risk model yielded an integrated discrimination improvement of 1.3% ($P = .007$).

Discussion

This study demonstrates that eGFR is an informative prognostic marker among patients with newly diagnosed coronary heart disease that is independent of other clinical characteristics. Adding baseline eGFR to a detailed prognostic model changed predicted risk categories for 10% to 12% of patients and did so correctly in most cases. Interestingly, eGFR appeared to identify lower risk patients more often than higher risk patients.

Impaired kidney function has been identified as an adverse prognostic factor for patients with coronary disease in many prior studies, but these studies have usually used serum creatinine concentration rather than eGFR as the measure of kidney function and did not assess the effect of eGFR on risk reclassification, which is increasingly recognized as a key measure of the clinical utility of novel risk markers.⁵ The PREDICT score for prognosis after acute coronary syndrome used elevations of blood urea nitrogen as a marker of kidney function.¹⁴ The Ontario Acute Myocardial Infarction Mortality Prediction Rules included “acute renal failure” rather than prior kidney function as an adverse predictor and that identified patients with a 3.9 times higher risk of death over the subsequent year.¹⁵ Procedural mortality for PCIs has been shown to be increased among patients with a serum creatinine level of >1.5 mg/dL¹⁶ and among those with “renal insufficiency.”¹⁷ The National Cardiovascular Disease Registry found that eGFR categories (<30 , 30-60, 60-90,

and >90) predicted the risk of procedural death for contemporary PCI,¹⁸ as did Parikh and associates.¹⁹ The Mayo Clinic risk scores for PCI used 6 categories of renal function based on serum creatinine levels.²⁰ The EuroSCORE II includes eGFR categories as predictors for cardiac surgery risk,²¹ whereas the age, creatinine, ejection fraction cardiac surgery risk score uses serum creatinine levels,²² as does the Society of Thoracic Surgeons online risk calculator.²³ Although evidence of CKD has been a reasonably consistent predictor of adverse outcome among patients with coronary disease, investigators have used many different approaches to assess renal function, which has made this evidence difficult to apply in clinical practice.

Estimated GFR has several potential advantages over other measures of CKD, including serum creatinine concentration. Directly measured GFR is the reference standard for measuring kidney function, but it is not performed in most clinical studies because it requires injection of radioactively labeled iothalamate and collection of serum and urine samples over a prolonged period. Because serum creatinine concentration is inversely related to actual GFR, kidney function can be considerably reduced before serum creatinine levels are clearly elevated, particularly in older patients with lower muscle mass. However, GFR can be estimated using formulas such as the CKD-EPI equation using readily available clinical data (serum creatinine concentration, age, sex, and race). Estimated GFR is arguably the best and most readily available measure of kidney function for most patients. Despite its superiority to serum creatinine concentration, eGFR is not routinely assessed in most prognostic studies, particularly in studies of patients with established cardiovascular disease. Our data confirm that eGFR is a powerful predictor of mortality in patients with coronary heart disease (Figure 1) and remains so even after accounting for known prognostic factors (Figure 2).

Many putative novel risk markers have been developed in recent years, based on advances in biomarkers, genetics, genomics, and medical imaging. It has been difficult for many clinicians to determine, based on published data, just how good these novel risk markers really are and whether they are worth measuring in clinical practice. An American Heart Association task force developed guidance on the conceptual framework that should be used to assess the value of novel risk markers.⁵ These guidelines emphasize the concept of incremental value—how much a new marker adds to the information readily available from standard clinical evaluation. The Committee also endorsed the use of risk reclassification as a tool to measure the degree to which prognostic predictors were improved by the addition of a risk marker. Net reclassification improvement^{5,6} has considerable face validity as a measure of whether a marker changes predictions sufficiently to move a patient across a clinically meaningful risk category. The related integrated discrimination improvement metric does not rely upon risk categories and instead measures the “distance” that an individual’s predicted risk is moved “correctly” by addition of a new risk marker. These measures are gaining currency and have several advantages over alternatives such as the C-index or risk ratios for statistical models.

In this study, the addition of eGFR to standard risk markers reclassified patient risk frequently and correctly more often than incorrectly. Baseline eGFR significantly improved the NRI scores over and above an already strong prognostic model (C-index 0.837) whether

a priori clinical risk categories were used (Table II) or empirical risk quartiles were used (Table III). This suggests that eGFR is a robust predictor of prognosis among patients with coronary disease. This conclusion is buttressed by the significant improvements in the IDI metric by the addition of eGFR, a category-free measure of improved risk predictors. Our results suggest that eGFR is a potentially useful marker of patient risk that could be used in clinical risk scores.

We have not, however, evaluated how much the provision of eGFR levels to clinicians might affect actual clinical decision making. Most clinicians are aware of a patient's serum creatinine concentration and use that information in an intuitive fashion to assess patient risk. Because eGFR is simple to calculate and is becoming part of standard reporting by laboratories nationally, there should be few barriers to incorporating it in clinical decision making and more accurately estimating the prognosis of patients with coronary heart disease.

Patients with impaired kidney function are less likely to receive many evidence-based therapies, including drugs and procedures.²⁴ Concerns about aggravating kidney function may lead to lower use of angiotensin-converting enzyme inhibitors, for instance, or statins. Coronary angiography may be avoided in patients with reduced kidney function for fear of inducing contrast nephropathy. Our data show clear reductions in the use of coronary revascularization procedures, angiotensin-converting enzyme inhibitors, and statins among patients with reduced baseline levels of eGFR (Table I). Our prognostic models adjusted for the lower use of evidence-based treatments among patients with reduced eGFR, but our data confirm that patients with CKD often receive less aggressive treatment for coronary disease, despite their increased risk.

Although our study has several strengths, it also has several limitations. First, we eGFR based on a single outpatient, non-emergency department serum creatinine measurement that was nearest to the index date, which may have led to misclassification of some of the patients. Second, because very few patients in the study population had proteinuria measured, we were unable to incorporate proteinuria into our risk prediction model, although proteinuria has been shown to be associated with mortality and cardiovascular morbidity independent of eGFR.^{2,25,26} Third, patients were followed up for a shorter period than in other risk prediction models, which have often followed up patients for up to 10 years.² However, the patients in this study had an adequate number of outcome events over the 2 years of follow-up to permit analysis of prognostic factors.

In conclusion, this study underscores the importance of impaired kidney function as an adverse prognostic marker among patients with incident coronary heart disease. Our results suggest that eGFR reclassifies patient risk frequently and correctly and is a potentially valuable risk marker.

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Figure 1.
Kaplan-Meier survival rates of baseline eGFR category.

Figure 2.

Adjusted odds ratios and 95% CIs for death within 2 years based on eGFR. The model also adjusted for age, sex, race (white, black, Asian, other), calendar year of presentation; diabetes, smoking, hypertension, dyslipidemia; history of peripheral artery disease, valvular disease, dementia, depression, liver disease, lung disease, cancer, stroke or transient ischemic attack; acute coronary syndrome, heart failure, atrial fibrillation, ventricular tachycardia or fibrillation; treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β -blockers, statins, clopidogrel, or PCI.

Figure 3.

Change in predicted risk of death after addition of eGFR to a risk model. The change in probability is shown separately for patients who died within 2 years (left panel) and for patients who survived 2 years (right panel). The line in the center of the box indicates the median change, the top of the box indicates the 75th percentile, the bottom of the box indicates the 25th percentile, the top of the whisker indicates the 95th percentile, and the bottom whisker indicates the 5th percentile. In the “no event group,” 65% of the predictions decreased, with a mean change of -0.0019 and a median change of -0.0020 . In the “event group,” 43% of predictions increased, with a mean change of 0.0116 and a median change of -0.0050 .

Table I

Baseline characteristics by level of kidney function (%)

	Baseline eGFR category (mL/min per 1.73 m ²)					
	90	60 to <90	45 to <60	30 to <45	15 to <30	<15
Patients (n)	2441	14412	8266	4520	1622	272
Age (y) (mean)	55.3	65.4	73.1	77.2	77.8	73.3
Male gender	69.9	69.3	60.8	49.9	44.8	49.6
Black race	12.2	6.8	5.8	5.9	7.0	12.1
Diabetes mellitus	44.1	31.8	30.4	38.2	50	62.5
Hypertension	48.6	56.9	69.4	78.6	83.3	91.5
Current or former smoker	42.2	32.9	28.3	27.1	26.7	32.7
Acute coronary syndrome	69.1	68.9	71.6	79.5	86.8	89.3
Heart failure	2.7	5.4	10.8	21.6	32.4	30.9
Atrial fibrillation	3.8	7.2	12.2	16.9	16.6	14.7
Peripheral artery disease	1.5	2.5	4.2	6.0	7.7	9.2
Ischemic stroke or TIA	1.6	3.4	5.1	7.3	9.1	12.1
Initial treatment						
CABG	13.5	14.3	14.9	10.9	6.0	5.9
PCI	17.4	16.8	13.5	9.6	7.2	4.8
ACEI	60.9	60.9	63.7	65.0	53.8	44.9
ARB	7.5	8.2	10.8	12.3	15.3	11.4
β-Blocker	87.9	87.8	86.5	84.9	85.0	86.8
Statin	83.3	83.4	79.7	76.7	72.2	71.0

TIA, Transient ischemic attack; CABG, coronary artery bypass graft; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table II

Effect of eGFR in reclassifying patients from initial clinical categories of baseline risk

Annual risk category (without eGFR)	Annual risk category (with eGFR)				Reclassified	
	<1%/y	1%-2%/y	2%-5%/y	5%/y	Correctly	Incorrectly
<1%/y						
Died	56	9	1	0	10	0
Survived	5388	237	7	0	0	244
1%-2%/y						
Died	6	114	16	3	19	6
Survived	343	4330	286	11	343	297
2%-5%/y						
Died	0	23	373	70	70	23
Survived	0	652	6160	435	652	435
5%/y						
Died	0	0	74	3609	0	74
Survived	0	0	869	8461	869	0

Table III

Effect of eGFR in reclassifying patients from initial quartiles of baseline risk

Annual risk category (without eGFR)	Annual risk category (with eGFR)				Reclassified	
	1.4%/y	1.4%-3.6%/y	3.6%-9.5%/y	9.5%/y	Correctly	Incorrectly
1.4%/y						
Died	98	18	1	0	19	0
Survived	7460	301	6	0	0	307
1.4%-3.6%/y						
Died	10	268	53	4	57	10
Survived	535	6614	388	10	535	398
3.6%-9.5%/y						
Died	0	50	703	166	166	50
Survived	0	896	5593	476	896	476
9.5%/y						
Died	0	0	131	2852	0	131
Survived	0	0	605	4295	605	0