Renal Dysfunction in Patients With Heart Failure With Preserved Versus Reduced Ejection Fraction
Impact of the New Chronic Kidney Disease-Epidemiology Collaboration Group Formula

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Background—Prior studies in heart failure (HF) have used the Modification of Diet in Renal Disease (MDRD) equation to calculate estimated glomerular filtration rate (eGFR). The Chronic Kidney Disease-Epidemiology Collaboration Group (CKD-EPI) equation provides a more-accurate eGFR than the MDRD when compared against the radionuclide gold standard. The prevalence and prognostic import of renal dysfunction in HF if the CKD-EPI equation is used rather than the MDRD is uncertain.

Methods and Results—We used individual patient data from 25 prospective studies to stratify patients with HF by eGFR using the CKD-EPI and the MDRD equations and examined survival across eGFR strata. In 20 754 patients (15 962 with HF with reduced ejection fraction [HF-REF] and 4792 with HF with preserved ejection fraction [HF-PEF]; mean age, 68 years; deaths per 1000 patient-years, 151; 95% CI, 146–155), 10 589 (51%) and 11 422 (55%) had an eGFR < 60 mL/min using the MDRD and CKD-EPI equations, respectively. Use of the CKD-EPI equation resulted in 3760 (18%) patients being reclassified into different eGFR risk strata; 3089 (82%) were placed in a lower eGFR category and exhibited higher all-cause mortality rates (net reclassification improvement with CKD-EPI, 3.7%; 95% CI, 1.5%–5.9%). Reduced eGFR was a stronger predictor of all-cause mortality in HF-REF than in HF-PEF.

Conclusions—Use of the CKD-EPI rather than the MDRD equation to calculate eGFR leads to higher estimates of renal dysfunction in HF and a more-accurate categorization of mortality risk. Renal function is more closely related to outcomes in HF-REF than in HF-PEF. (Circ Heart Fail. 2012;5:309-314.)

Key Words: kidney disease chronic ■ heart failure ■ prognosis

It is well recognized that renal dysfunction is common in patients with heart failure (HF) and is an adverse prognostic factor.1–8 Although prior studies examining the prevalence and prognostic import of renal dysfunction in HF have used the Modification of Diet in Renal Disease (MDRD) equation to calculate the estimated glomerular filtration rate (eGFR),9 recent studies comparing MDRD-generated eGFRs against radionuclide gold standards have demonstrated that the MDRD systematically underestimates true eGFR, particularly in patients with an eGFR > 60 mL/min.10 Thus, studies using the MDRD equation to calculate eGFR may overestimate the prevalence of renal dysfunction in study participants.11 In clinical practice, patients misclassified as having renal dysfunction may be exposed to potential harms because such patients often are treated with lower doses of drugs, and diagnostic tests using contrast media are avoided.

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In 2009, the Chronic Kidney Disease-Epidemiology Collaboration Group (CKD-EPI) developed and validated

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in 8254 patients a new equation for calculating the eGFR, which is more accurate than the MDRD when compared against the radionuclide gold standard.12 However, few patients in the CKD-EPI validation studies had HF, and the true prevalence and prognostic import of renal dysfunction in HF if the CKD-EPI equation is used rather than the MDRD equation is uncertain. In addition, it is unknown whether renal dysfunction prevalence and prognostic importance differs between patients with HF with reduced ejection fraction (HF-REF) and those with HF with preserved ejection fraction (HF-PEF) and whether renal dysfunction prevalence and prognostic importance differs between patients with HF with reduced ejection fraction (HF-REF) and those with HF with preserved ejection fraction (HF-PEF) and whether lower eGFR levels might be a more appropriate cut point to identify at-risk individuals because most patients with HF are elderly and eGFR declines with age.11

We designed the present study to examine the frequency of renal dysfunction in patients with HF using the CKD-EPI and the MDRD formulas. We also examined the association between renal dysfunction and mortality in patients with HF-REF and HF-PEF.

### Methods

The methods, including details about study selection criteria and the flow of included studies, and main results of the MAGGIC (Meta-analysis Global Group in Chronic Heart Failure) meta-analysis have been described in full elsewhere.13 For this analysis, we pooled individual patient data from the 25 studies in the MAGGIC meta-analysis (2 pharmacotherapy randomized controlled trials, 4 management strategy randomized controlled trials, and 19 observational studies) that included data on serum creatinine (SCr) levels and collected all-cause mortality outcomes prospectively in patients with HF and did not restrict their study entry criteria by left ventricular ejection fraction. The meta-analysis protocol was approved by The University of Auckland Human Subjects Ethics Committee. Data (demographics, comorbidities, therapy, symptom status, clinical variables, laboratory variables, and outcomes) from the individual studies were recoded into a uniform format at the Central Coordinating Centre at The University of Auckland and incorporated into 1 database.

For this analysis, HF-PEF was prespecified as a baseline left ventricular ejection fraction of ≥50%, and we defined renal dysfunction as an eGFR of <60 mL/min, which corresponds to National Kidney Foundation KDOQI (Kidney Disease Outcomes Quality Initiative) stage 3 and 4 kidney disease.14 Covariates were all defined at baseline, including anemia (hemoglobin <120 g/L in women and <130 g/L in men). We calculated eGFR by 2 methods. For the MDRD equation, none of the studies used isothe dilution to measure SCr, and thus, we used 186 × (SCr)^−1.154 × age (in years)^−0.203 × 0.742 (if female) × 1.212 (if black). For the CKD-EPI equation, we used the following: eGFR = 141 × min (SCr/0.1a × max (SCrk,1)−1.209 × 0.993age × 1.159 (if black), where k is 0.7 for female patients and 0.9 for male patients, a is −0.329 for female patients and −0.411 for male patients, min
Results

In 20,754 patients with HF (15,962 with HF-REF; 4,792 with HF-PEF; mean age, 68 years; men, 66%), all-cause mortality was 24% over a median follow-up of 2 years (deaths per 1000 patient-years, 150.5; 95% CI, 146.3–154.7). There were 136.7 (95% CI, 128.2–145.7) deaths per 1000 patient-years in those with HF-PEF and 154.1 (95% CI, 149.4–158.9) in those with HF-REF.

Patients with HF-REF were more likely to be men and to have ischemic etiology and diabetes mellitus (comparisons done using χ² tests) (Table 1). The distribution of eGFR was similar in patients with HF-PEF and HF-REF (Figure 1). Patients with lower eGFRs exhibited worse HF symptom status, higher comorbidity burden, and lower use of cardiovascular medications (all P<0.001) (Table 1).

Using the MDRD equation, 10,589 (51%) patients had an eGFR <60 mL/min (meeting the National Kidney Foundation KDOQI definition of stage 3 or 4 kidney disease); using the CKD-EPI equation, 11,422 (55%) patients had an eGFR <60 mL/min (Figure 1). However, using the CKD-EPI formula resulted in 3,760 (18%) patients being reclassified between KDOQI categories (Figure 2, Table 2), with reclassification occurring across all categories of eGFR. Eighteen percent (n=671) of those reclassified were placed in a higher eGFR category with the CKD-EPI than with the MDRD equation (ie, they were reclassified to a higher risk group). Although the CKD-EPI and MDRD equations demonstrated similar discrimination in predicting all-cause mortality in patients with HF, the CKD-EPI-derived eGFR performed statistically significantly better than the model using MDRD (Table 3), and review of the misclassification matrix (Table 2) confirmed that the all-cause mortality rates in the reclassified patients more closely reflected their CKD-EPI-based risk categorization than their MDRD-based risk stratification (net reclassification improvement, 3.7%; 95% CI, 1.5%–5.9%).

Although the adjusted Cox proportional hazard ratio for the association between renal dysfunction and mortality in patients with HF-REF increased sequentially as eGFR declined to <60 mL/min (Figure 3A), the association was less evident in HF-PEF, where there were fewer patients and lower event rates in each category (P=0.048 for interaction between ejection fraction groups) (Figure 3B). Indeed, perusal of the adjusted hazard ratios in Figure 3A and 3B reveals that renal dysfunction was a stronger predictor of all-cause mortality in patients with HF-REF than in those with HF-PEF. Of note, the hazard ratios were adjusted for age; sex; etiology; and presence or absence of anemia, atrial fibrillation, hypertension, or diabetes and were stratified by study, and the adjusted hazard ratios were almost identical when baseline medication use was included in the models (data not shown). The association between gradients of CKD-EPI-defined eGFR and mortality was similar irrespective of age (Figure 4).

Discussion

This large meta-analysis based on individual patient data from >20,000 individuals confirms previous reports of...
greater symptom burden, reduced likelihood of being prescribed evidence-based therapies, and poorer adjusted survival in patients with renal dysfunction and HF.7–15 An important novel finding is that the use of the CKD-EPI equation to calculate the eGFR rather than use of the MDRD equation increases the apparent prevalence of renal dysfunction in both patients with HF-PEF and patients with HF-REF. This finding is contrary to prior studies conducted in healthier and younger patient populations, which suggested higher prevalence of renal dysfunction using the MDRD equation compared to the CKD-EPI equation.9–12,16–18 However, the present data are consistent with a recent report from the Nijmegen Biomedical Study, which found that the CKD-EPI formula provided lower eGFR values of eGFR than the MDRD formula in older sub-

Table 2. Comparison of All-Cause Mortality Rates (Expressed as Incidence per 1000 Person-Years) in MDRD-Defined and CKD-EPI-Defined Subgroups

<table>
<thead>
<tr>
<th>CKD-EPI eGFR, mL/min</th>
<th>MDRD eGFR, mL/min</th>
<th>Whole Group</th>
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Data are presented as n or median (95% CI). Reclassification downward indicates that eGFR risk strata are lower with CKD-EPI than with MDRD, and reclassification upward indicates that eGFR risk strata are higher with CKD-EPI than with MDRD. CKD-EPI indicates Chronic Kidney Disease-Epidemiology Collaboration Group; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

A second important observation from the current analysis is that eGFR is a stronger predictor of all-cause mortality in HF-REF than in HF-PEF, and for any given eGFR category, mortality is higher in patients with HF-REF than in patients with HF-PEF. The stronger relationship between mortality and eGFR in HF-REF emphasizes the relevance of the cardiorenal syndrome to prognosis in these patients. Indeed, it is likely that reduction in eGFR is a marker for reduced cardiac output, which is a more-important prognostic factor in patients with HF-REF than in those with HF-PEF. Further, competing mortality risks from comorbid conditions, such as cancer and chronic obstructive lung disease, are likely to play a larger role in prognosis in HF-PEF.24

Although the present study reports on a large, well-categorized, and heterogeneous cohort of patients with HF who are similar to other population-based HF cohorts,25 there are some limitations. First, we only have renal function and covariate data at baseline. Use of a single baseline SCr level to calculate each patient’s eGFR (by either the MDRD or the CKD-EPI equation) may overestimate the prevalence of kidney disease.11,26 However, this would have introduced a null bias into the study, leading to an underestimation of the magnitude of the association between renal dysfunction and outcomes, and the QICKD (Quality Improvement in Chronic Kidney Disease) study recently reported that using 2 eGFR measurements at least 3 months apart rather than just a single measurement only reduced the prevalence estimates for CKD by ≈1%.27
Second, we do not have any data on unmeasured covariates, such as body mass index and levels of brain natriuretic peptide, parathyroid hormone, C-reactive protein, or cholesterol; studies comparing these levels in patients with and without renal dysfunction and the effects of interventions on these levels and subsequent clinical outcomes clearly are needed. However, we did adjust for anemia in the multivariable analyses and showed in a cohort of 754 patients followed at a specialized HF clinic (in whom we had hemoglobin data) that renal insufficiency is an independent prognostic factor, even after adjusting for hemoglobin values.7 In the same vein, we do not have data on other renal function metrics, such as albuminuria,22 rate of change in eGFR,28 or cystatin C levels,21,29 which appear to be prognostically important in patients regardless of eGFR level; however, this mimics clinical practice in that the majority of patients with HF are managed without access to cystatin C levels. Finally, we acknowledge that there is variability between laboratories in measurement of SCr levels before the introduction of isotope-dilution mass spectrometry standardization in the mid-2000s; however, this variability was shown to predominantly introduce error at higher eGFR levels (ie, >60 mL/min), which were not the focus of the present study.

In conclusion, despite the limitations, the study demonstrates that reduced renal function is even more common than previously appreciated in HF, regardless of ejection fraction. We also confirm that reduced eGFR is a stronger predictor of death in patients with HF-REF than in those with HF-PEF. Finally, mirroring the findings from the KEEP in subjects at high risk of kidney disease,18 we demonstrate that in patients with HF, use of the CKD-EPI formula to calculate eGFR appears to offer better mortality risk stratification than the MDRD formula.

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Disclosures

None.

References


**CLINICAL PERSPECTIVE**

Compared to the radionuclide gold standard for the assessment of renal function, the Chronic Kidney Disease-Epidemiology Collaboration Group equation more accurately calculates estimated glomerular filtration rate than the Modification of Diet in Renal Disease equation. In an analysis of 20,754 patients (15,962 with heart failure with reduced ejection fraction and 4,792 with heart failure with preserved ejection fraction), we found that using the Chronic Kidney Disease-Epidemiology Collaboration Group equation rather than the Modification of Diet in Renal Disease equation results in higher estimates of renal dysfunction (55% versus 51%) and better mortality risk stratification. Regardless of which equation was used, reduced estimated glomerular filtration rate was a stronger predictor of all-cause mortality in patients with heart failure with reduced ejection fraction than those with heart failure with preserved ejection fraction.
Renal Dysfunction in Patients With Heart Failure With Preserved Versus Reduced Ejection Fraction: Impact of the New Chronic Kidney Disease-Epidemiology Collaboration Group Formula

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Supplemental Material

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