Drawbacks and Prognostic Value of Formulas Estimating Renal Function in Patients With Chronic Heart Failure and Systolic Dysfunction

Tom D.J. Smilde, MD, PhD; Dirk J. van Veldhuisen, MD, PhD; Gerjan Navis, MD, PhD; Adriaan A. Voors, MD, PhD; Hans L. Hillege, MD, PhD

Background—Renal function is an important risk marker for morbidity and mortality in chronic heart failure (CHF) and is often estimated with the use of creatinine-based formulas. However, these formulas have never been validated in a wide range of CHF patients. We validated 3 commonly used formulas estimating glomerular filtration rate (GFR) with true GFR in CHF patients. Furthermore, we compared the prognostic value of these formulas for cardiovascular outcome with that of true GFR during 12 months of follow-up.

Methods and Results—In 110 CHF patients (age, 57±11.7 years; left ventricular ejection fraction, 0.27±0.09; NYHA class, 2.5±0.9), we measured 125I-iothalamate clearance. Cockcroft-Gault (GFRcg), Modification of Diet in Renal Disease (MDRD), and simplified MDRD (sMDRD) equations were used as creatinine-based renal function estimations. Furthermore, 24-hour creatinine clearance (CrCl) was determined. CrCl and GFRcg were the most accurate. MDRD was most precise formula, although it was also highly biased. All formulas overestimated in the lower ranges and underestimated in the upper ranges of the GFR corrected for body surface area. The predictive performance of the formulas was best in severe CHF (NYHA classes III and IV). The prognostic value of CrCl and MDRD for cardiovascular outcome was comparable to that of GFR, the sMDRD was slightly less, and the GFRcg had a significantly worse prognostic value.

Conclusions—In the more severe ranges of CHF, creatinine-based formulas and CrCl corrected for body surface area appeared to be more precise and accurate in estimating true GFR corrected for body surface area. The MDRD formula is the most precise and has a good prognostic value, whereas the sMDRD is slightly less accurate but uses fewer parameters, which makes this formula a practical alternative in clinical practice. (Circulation. 2006;114:1572-1580.)

Key Words: glomerular filtration rate | heart failure | prognostic value | renal function | validation

Over the last decade, the prognostic and clinical value of renal function in chronic heart failure (CHF) has generally been recognized. Glomerular filtration rate (GFR) measures the filtration capacity of the kidneys and is considered the best overall index of renal function. Exact quantitative assessment of GFR requires the determination of the renal clearance of an exogenous marker such as inulin or 125I-iothalamate. However, these are expensive, time-consuming, and not applicable in a setting in which a large number of measurements of GFR are required. Renal creatinine clearance (CrCl) can also be used as a tool to measure renal function. However, for the measurement of CrCl a 24-hour urine collection is required, which is inconvenient for the patient and prone to collection failure. Therefore, in clinical practice GFR is usually estimated by creatinine-based equations that incorporate demographic characteristics, such as age, gender, race, and weight to account for differences in muscle mass and hence creatinine generation. The most commonly used formulas are the Cockcroft-Gault (GFRcg) and the simplified Modification of Diet in Renal Disease (sMDRD) equations. The aforementioned renal function equations have been developed and validated against exact or true GFR measurements in populations with renal disease, in which they prove to be a reasonable to good estimate of renal function.

However, in several studies in nonrenal patient populations, their predictive performance was disappointing. Although several important studies in CHF used renal function estimations by creatinine-based formulas, none of these formulas have been validated in a wide range of CHF patients. A
number of factors specific to this group of patients may influence the accuracy and precision of these formulas, such as the predominantly hemodynamic nature of renal function impairment, medication interfering with renal function, sodium retention leading to volume expansion, and loss of muscle mass due to inactivity.

Although the estimated renal function is commonly used as a prognostic cardiovascular risk marker, the prognostic value has never been compared with the true renal function. In the present study we validated the predictive performance of several creatinine-based formulas estimating GFR in patients with CHF by the "gold standard" of iothalamate clearance, examined sources related to accuracy and precision,\textsuperscript{11,12} and compared the prognostic value of renal function estimated by the different equations for cardiovascular outcome with the prognostic value of true renal function.

Methods

Patient Population

This study was performed at the University Medical Center of Groningen, Groningen, Netherlands. CHF patients aged $ \geq $18 years, with left ventricular ejection fraction (LVEF) $ < $0.45, and clinically stable were asked to participate at the outdoor clinic. For ethical reasons, all patients had to use renin-angiotensin system inhibitors. All medications had been stable for at least 1 month. Exclusion criteria were a myocardial infarction within the last 3 months, cardiac surgery or angioplasty within the last 3 months or scheduled to undergo these procedures, unstable angina pectoris, primary renal disease, prior organ transplantation, or chronic use of renal function–compromising medication. Special care was taken to include patients over the full range of severity of CHF.

Study Design

All patients underwent the same study protocol. On the first day, renal function was measured by iothalamate clearance as described below. Body weight and length were determined just before renal function measurement started. Two hours after the beginning of the renal measurements, venous blood was drawn to determine serum creatinine, serum urea, and serum albumin. In addition, during renal measurements, blood pressure and heart rate were determined. Systolic and diastolic blood pressure measurements were calculated as the mean of the last 2 of 10 consecutive measurements during 10 minutes with the patient in the sitting position with an automatic Dinamap XL model 9300 series device (Johnson-Johnson Medical Inc, Tampa, Fla). After the renal function measurements by iothalamate were finished, patients were given 2 containers for two 24-hour urine collections. After return of these containers, samples were taken to determine urine creatinine concentration for calculation of 24-hour creatinine clearance.

Renal Function Measurement by Iothalamate Clearance

GFR and effective renal plasma flow (ERPF) were measured by constant infusion of the radiolabeled tracers \textsuperscript{125}I-iothalamate and \textsuperscript{131}I-hippuran.\textsuperscript{11} After a blank sample was drawn, a priming solution containing 0.4 MBq/kg body wt of the infusion solution (0.04 MBq of \textsuperscript{125}I-iothalamate and 0.03 MBq of \textsuperscript{131}I-hippuran) plus an extra 0.6 MBq of \textsuperscript{125}I-iothalamate was given at 8 AM, followed by infusion at 12 mL/h. To attain stable plasma levels of both tracers, a 2-hour stabilization period followed, after which baseline measurements were started at 10 AM. The clearances were calculated as \((U \times V)/P\) and \((\times V)/P\), respectively, where \(U\) is the urinary excretion of the tracer, \(I \times V\) is the infusion rate of the tracer, and \(P\) is the tracer value in plasma at the end of each clearance period. This method corrects for incomplete bladder emptying and dead space by multiplying the urinary clearance of \textsuperscript{125}I-iothalamate with the ratio of the plasma and urinary clearance of \textsuperscript{131}I-hippuran. The filtration fraction (FF) was calculated as the ratio of GFR and ERPF and expressed as a percentage. This method has a day-to-day variation coefficient of 2.5% for GFR and 5% for ERPF. GFR was corrected for 1.73 m\textsuperscript{2} of body surface area (GFR\textsubscript{BSA}) for comparison with the Modification of Diet in Renal Disease (MDRD) and sMDRD.

Laboratory Methods

Urinary volume was measured in each collection. Serum creatinine, urea, albumin, and urine creatinine were determined by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY). CrCl\textsubscript{I} was calculated as the mean of two 24-hour urine creatinine excretions divided by plasma creatinine. CrCl\textsubscript{I} was also corrected for 1.73 m\textsuperscript{2} of body surface area (CrCl\textsubscript{BSA}) for comparison with the MDRD and sMDRD. The daily creatinine production was calculated on the basis of CrCl\textsubscript{I} and serum creatinine: (CrCl\textsubscript{I} $ \times $ serum creatinine)/70.\textsuperscript{11} The body surface area (BSA) was determined as follows: 0.007184 $ \times $ weight$^{0.425} \times $ length$^{0.725}$. To obtain body mass index (BMI), weight (kg) was divided by the square of height (m\textsuperscript{2}).

Formulas Estimating GFR

Three formulas were used as creatinine-based estimations of GFR: Cockcroft-Gault, MDRD, and sMDRD. These formulas are the most commonly used formulas for estimating the GFR in CHF patients.

Cockcroft-Gault Formula

The GFR\textsubscript{c} (mL/min) is calculated as follows\textsuperscript{5}:

\[
\text{Male: } [(140 - \text{age}) \times \text{weight}] / 72 \times \text{serum creatinine}
\]

\[
\text{Female: GFR}\textsubscript{c} \times 0.85
\]

BSA corrected: GFR\textsubscript{c} $ \times $ (1.73/BSA) ($\equiv$ mL/min per 1.73 m\textsuperscript{2})

MDRD Formula

The MDRD (mL/min per 1.73 m\textsuperscript{2}) is calculated as follows\textsuperscript{5}:

\[
\text{Male: } 170 \times (\text{serum creatinine})^{-0.99} \times (\text{age})^{0.167} \times (\text{serum urea})^{0.318}
\]

\[
\text{Black male: MDRD} \times 1.180
\]

\[
\text{Female: MDRD} \times 1.76
\]

\[
\text{Black female: MDRD} \times 0.762 \times 1.180
\]

SMDRD Formula

The sMDRD (mL/min per 1.73 m\textsuperscript{2}) is calculated as follows\textsuperscript{5}:

\[
\text{Male: } 186.3 \times (\text{serum creatinine})^{1.154} \times (\text{age})^{-0.203}
\]

\[
\text{Black male: sMDRD} \times 1.212
\]

\[
\text{Female: sMDRD} \times 0.742
\]

\[
\text{Black female: sMDRD} \times 1.212 \times 0.742
\]

Follow-Up

To compare the prognostic value of the creatinine-based formulas with the true renal function, we performed a follow-up of all our patients. A 12-month follow-up period was available for all patients. A combined clinical outcome parameter was defined consisting of death, heart transplantation, cardiovascular event (myocardial infarction or primary PTCA), and first hospitalization for heart failure.

Statistical Analyses

Correlations between GFR\textsubscript{BSA} and the different formulas or CrCl\textsubscript{BSA} were performed with the use of Pearson correlation coefficients. Comparisons between GFR\textsubscript{BSA} and the different formulas or CrCl\textsubscript{BSA} were performed with a paired sample t test. A probability value $ < $0.05 was considered significant. The creatinine-based formulas and CrCl\textsubscript{BSA} were evaluated by a set of criteria to assess their predictive performance. These criteria included precision, accuracy, and bias.

Precision was evaluated by the degree of spread of series of observations and is reflected by the amount of expected variation in the estimates. The $ r^2 $ statistics were used to measure this and give an indication of the overall fit of the model.\textsuperscript{4}
The accuracy of each equation, or how well it represents the true GFR$_{BSA}$, was assessed by comparing its result with that of the gold standard (iothalamate clearance). We used the following equation: \[(\text{predicted value} - \text{true value (iothalamate clearance)}) \times 100/\text{iothalamate clearance}].^14\] For each equation, the number of subjects with predicted GFR$_{BSA}$ values within the 15% or 30% of the iothalamate clearance was counted.

Bias is any systematic nonrandom deviation causing a prediction error and was calculated as the difference of the logarithmic-transformed GFR$_{BSA}$ and the creatinine-based formulas or CrCl$_{BSA}$. We used the antilogs to obtain the mean percent deviation of the creatinine-based formulas and CrCl$_{BSA}$.^15

The agreements between measured GFR$_{BSA}$ and the different creatinine-based formulas or CrCl$_{BSA}$ were tested, as described by Bland and Altman.\(^15\) The difference between measured GFR$_{BSA}$ and creatinine-based formulas or CrCl$_{BSA}$ of each individual subject was graphed as a scatterplot with the mean of the measured GFR$_{BSA}$ and the creatinine-based formula or CrCl$_{BSA}$ of the same individual subject. The magnitude of the differences increased in the higher ranges of GFR$_{BSA}$, and therefore we conducted a logarithmic transformation of GFR$_{BSA}$, the creatinine-based formulas, and the CrCl$_{BSA}$.\(^15\) Scatterplots include 2 dotted lines representing limits of agreement (mean±2×SD). The antilog of the mean±2 SD is the mean percentage ±2 SD. Ninety-five percent of the differences are situated between the lines of agreement.

To identify confounding factors that could explain the observed difference between the true GFR and creatinine-based formulas, we performed secondary analyses in which we determined the bias of the formulas divided within subgroups of the several parameters. Continuous variables were divided into tertiles, and the bias was calculated per tertile.

To compare the accuracy of the different formulas as predictors of an event within 12 months, the area under the receiver operating characteristic (ROC) curve was calculated. This statistic may vary from 0 to 1, with 1 indicating perfect discrimination and 0.5 indicating what is expected by chance alone. For this additional analysis, a combined endpoint—occurrence of death, heart transplantation, myocardial infarction, or primary PTCA or an admission because of CHF within 12 months—has been defined. The results were displayed graphically, with the optimal cutoff chosen as the shoulder of the ROC curve, at the point of maximum sensitivity and specificity. The statistical analysis was performed with the use of SPSS (Chicago, Ill), version 11, and STATA Statistical Software, release 8.2 (StataCorp LP, College Station, Tex).

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Baseline characteristics are presented in Table 1. Mean age was 58 years, and 76% of patients were male. The full range of severity of CHF from NYHA classes I to IV was present, with a mean NYHA class of 2.5±0.9. All patients received renin-angiotensin system inhibition (85% ACE inhibitor), and a large proportion also received β-blockers and diuretics. Only 7% of the patients had a GFR$_{BSA}$ <30 mL/min per 1.73 m², 27% had a GFR$_{BSA}$ between 30 and 60 mL/min per 1.73 m², 36% had a GFR$_{BSA}$ between 60 and 90 mL/min per 1.73 m², 28% had a GFR$_{BSA}$ between 90 and 120 mL/min per 1.73 m², and 2% had a GFR$_{BSA}$ >120 mL/min per 1.73 m².

Individual values of the true GFR$_{BSA}$, the creatinine-based formulas, and CrCl$_{BSA}$ are presented in Figure 1A. Cumulative distributions of the true GFR$_{BSA}$, CrCl$_{BSA}$, and creatinine-based formulas are shown in Figure 1B. GFR$_{BSA}$ >65 mL/min per 1.73 m² led to underestimation of the true value, whereas GFR$_{BSA}$ <35 mL/min per 1.73 m² led to overestimation.

In Table 2, the predictive performances of the creatinine-based formulas and CrCl$_{BSA}$ are presented. All creatinine-based formulas and CrCl$_{BSA}$ significantly underestimated GFR$_{BSA}$ as measured by iothalamate clearance. MDRD had the highest precision (r²=0.72) but also the highest bias (13%). The validity of the creatinine-based formulas according to Bland-Altman analyses is shown in Table 2 and is depicted graphically in Figure 2, which shows the mean differences between GFR$_{BSA}$ and the creatinine-based formulas with the lines of agreement (mean±2 SD). The agreement with true GFR$_{BSA}$ was best for the MDRD. Furthermore, these figures illustrate an underestimation in the higher range of renal function, as for a GFR$_{BSA}$ of ∼65 mL/min per 1.73 m², and an overestimation in the lower range of renal function, below a GFR$_{BSA}$ of ∼35 mL/min per 1.73 m².

To analyze determinants of the systematic error, we evaluated the predictive performance of the creatinine-based formulas by formula-based subgroups divided into tertiles when measured continuously (Table 3). Especially in the low and high ranges of serum creatinine and urea, the creatinine-based formulas are biased on estimating GFR$_{BSA}$. In patients with low serum creatinine or urea, the bias was larger. Furthermore, weight appeared to be a moderate confounder in the MDRD formulas.

In Table 4, the bias is shown for subgroups divided into tertiles for other clinical parameters. Several variables reflect...
with severe CHF, precision and accuracy were improved (data not shown).

During the follow-up of 12 months, 17 patients had an event, of whom 6 patients died, 1 patient had a heart transplantation, and 10 patients were admitted for worsening heart failure. None of the patients had an ischemic cardiovascular event. The predictive value of GFR\textsubscript{BSA} for an event was high, which was shown in an area under the ROC curve of 0.83. The areas under the ROC curve were comparable for MDRD (0.81; \( P = 0.432 \)), CrCl\textsubscript{BSA} (0.81; \( P = 0.583 \)), and sMDRD (0.78; \( P = 0.176 \)), but the Cockcroft-Gault formula corrected for BSA (GFR\textsubscript{cg-BSA}) was significantly worse (0.72; \( P = 0.015 \)). The sensitivity and 1 - specificity of GFR\textsubscript{BSA}, sMDRD, and GFR\textsubscript{cg-BSA} are presented in Figure 3. The shoulder of the ROC curves allows the point of best overall discrimination to be identified. From these data, this corresponded to 63 mL/min per 1.73 m\(^2\) for GFR\textsubscript{BSA} (sensitivity 81%, specificity 81%), 45 mL/min per 1.73 m\(^2\) for the MDRD (sensitivity 63%, specificity 93%), 49 mL/min per 1.73 m\(^2\) for sMDRD (sensitivity 63%, specificity 89%), and 59 mL/min per 1.73 m\(^2\) for GFR\textsubscript{cg-BSA} (sensitivity 70%, specificity 76%).

**Discussion**

This is the first study that validated, in a wide range of CHF patients, the commonly and widely used creatinine-based formulas and CrCl with true renal function measurements. The formulas were significantly biased and especially underestimated GFR at near-normal values. The most accurate renal function estimates were derived with the MDRD formulas in patients with severe CHF.

For exact quantitative assessment of GFR, determination of the renal clearance of an exogenous marker, such as inulin, \(^{125}\text{I}-\text{iothalamate}, \text{or} \(^{51}\text{Cr-EDTA, is required. Our center has}\)

20 years of experience with \(^{125}\text{I}-\text{iothalamate clearance, and this method has been validated extensively.}\) Furthermore, we also measured urine concentration of \(^{125}\text{I}-\text{iothalamate and} \(^{131}\text{I-hippuran to adjust for possible measurement errors, resulting in a very low day-to-day variance.}\)

We used precision, accuracy, and bias to validate the formulas and CrCl. High precision is important because it informs us whether the distribution of estimated renal function is parallel to exact measured renal function. High accuracy implies that the values of the formulas and CrCl are in close range with the exact measured renal function. This means that the variance is low. Bias informs us about the degree of systematic error present. Bias is preferably

### Table 2. Predictive Performances of Creatinine-Based Formulas and CrCl in CHF

<table>
<thead>
<tr>
<th></th>
<th>Precision</th>
<th></th>
<th></th>
<th>Accuracy*</th>
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<tr>
<td></td>
<td>Mean</td>
<td>Minimum/Maximum</td>
<td>( r^2 )</td>
<td>( 15% )</td>
<td>( 30% )</td>
<td>Mean %</td>
</tr>
<tr>
<td>GFR\textsubscript{BSA}</td>
<td>73±27</td>
<td>13-133</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>CrCl\textsubscript{BSA}</td>
<td>68±26†</td>
<td>11-125</td>
<td>0.56</td>
<td>45</td>
<td>76</td>
<td>-7</td>
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<tr>
<td>GFR\textsubscript{cg-BSA}</td>
<td>67±21†</td>
<td>19-123</td>
<td>0.63</td>
<td>48</td>
<td>76</td>
<td>-6</td>
</tr>
<tr>
<td>MDRD</td>
<td>62±19†</td>
<td>17-107</td>
<td>0.72</td>
<td>44</td>
<td>83</td>
<td>-13</td>
</tr>
<tr>
<td>sMDRD</td>
<td>62±18†</td>
<td>19-101</td>
<td>0.68</td>
<td>43</td>
<td>80</td>
<td>-12</td>
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</tbody>
</table>

*Percentage within specified range of GFR\textsubscript{BSA}.

† \( P < 0.001 \) with GFR\textsubscript{BSA}.
low but can be corrected by multiplying with a correction factor, given that the precision and accuracy are high. When these methods are considered, the MDRD is probably the best method to use. However, most studies do not use the MDRD but instead use the sMDRD, which does not require information about serum urea and serum albumin. In our patients with CHF, this formula showed a predictive performance similar to that of the MDRD.

Creatinine-based formulas have been validated in a variety of patient populations, primarily community-based populations or populations with chronic renal disease. Recently, a smaller retrospective study has validated these formulas in patients with advanced CHF. Similar to our findings, the formulas overestimated renal function in the lower values. In patients with mild to moderate CHF, no information was available until now. The present study emphasizes that these formulas cannot be easily extrapolated to other conditions in which they were developed and validated and that caution is required when these formulas are used for a different condition, eg, CHF.

All parameters included in the formulas were more or less confounders, especially serum creatinine. The difference in gender can be explained by the differences in renal function (78 mL/min per 1.73 m² for male versus 60 mL/min per 1.73 m² for female subjects), and the formulas performed more precisely and accurately in the lower ranges of renal function. We showed that the impact of age was only moderate, probably because the formulas perform better at higher serum creatinine levels and serum creatinine increases with age.

The performance of the formulas varied within the subgroups of our CHF population. For this reason it could be argued that the selected formula should be tailored to the study population of interest. For example, in an obese population the use of the Cockcroft-Gault formula might be advocated instead of the MDRD formula. However, this should be studied in more detail.

**Implications**

The value and usefulness of renal function formulas in clinical practice are dependent on the precision and bias of the calculated value. The degree of variation that is acceptable will depend on the particular clinical situation in which the formula is used. The main implications of this study for daily practice are clear; the interpretation of estimations of renal function with the use of creatinine-based formulas.
based formulas and CrCl$_{BSA}$ on an individual level suggests cautious interpretation. The variance is wide, at ±30 mL/min per 1.73 m$^2$, meaning that the accuracy is low. In particular, the CrCl has a low accuracy, and therefore we do not recommend using this method, in accordance with the Kidney Disease Outcome Quality Initiative guidelines, for renal function measurement.$^{18}$ Four other clinically important findings have been encountered. First, in the near-normal values of renal function, all formulas underestimate the true GFR$_{BSA}$. This is in agreement with several other studies in different study populations.$^{14,19}$ When the estimated renal function is >65 mL/min per 1.73 m$^2$, the true renal function is in fact higher.

Second, in the lower ranges the estimated renal function overestimates the exact measured renal function. Interestingly, this has only been reported in populations with primary renal disease in predialysis ranges of GFR$_{BSA}$. The overestimation in less severe ranges might be typical for CHF and needs further study. The primarily hemodynamically driven nature of the impaired renal function in CHF might be relevant here. CHF is characterized by low blood pressure and reduced renal perfusion pressure, leading to reduced filtration rate in viable nephrons with intact tubuli still capable of secreting creatinine actively.$^{21}$ Primary renal diseases are characterized by loss of glomeruli and loss of corresponding tubuli as well. For physicians, it is important to recognize that at a renal function <35 mL/min per 1.73 m$^2$, the estimated renal function starts to be overestimated. This might endanger the patient if one is not aware of this systematic deviation. This is
TABLE 4. Bias of the Formulas Stratified to Clinical Parameters

<table>
<thead>
<tr>
<th>NYHA class</th>
<th>GFR_{\text{ck}-\text{BSA}} Bias</th>
<th>MDRD Bias</th>
<th>sMDRD Bias</th>
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<tr>
<td></td>
<td>n</td>
<td>Mean %</td>
<td>95% CI</td>
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<tr>
<td>I + II</td>
<td>61</td>
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<td>-42/21</td>
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<tr>
<td>III + IV</td>
<td>49</td>
<td>8*</td>
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<td>&lt;0.23</td>
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<td>-50/81</td>
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<tr>
<td>Yes</td>
<td>92</td>
<td>-6</td>
<td>-42/51</td>
</tr>
<tr>
<td>Diuretic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>31</td>
<td>-18</td>
<td>-42/15</td>
</tr>
<tr>
<td>Yes</td>
<td>79</td>
<td>-1*</td>
<td>-42/67</td>
</tr>
<tr>
<td>Spironolactone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>66</td>
<td>-14</td>
<td>-43/28</td>
</tr>
<tr>
<td>Yes</td>
<td>44</td>
<td>7*</td>
<td>-37/83</td>
</tr>
</tbody>
</table>

BP indicates blood pressure.

*P < 0.05 compared to the first tertile.
†P < 0.05 compared to the third tertile.

particularly important in elderly patients in whom age-related physiological change results in reduced renal function and, for example, changes in drug pharmacokinetics and pharmacodynamics. We therefore recommend measuring the exact renal function periodically in these patients, especially if heart transplantation or renal replacement therapy is considered. These 2 factors could also be of importance in long-term monitoring of renal function. Although we did not study the predictive performance of the formulas longitudinally,
physicians should be aware of the possible change in predictive performance across the spectrum from mild to severe CHF, from underestimation to overestimation. This could mean that, although estimated renal function suggests a stable condition during worsening of CHF, it may in fact be declining.

Third, in CHF patients these formulas can be used very well for pharmacokinetic purposes. Adjustments in dosage of drugs is often recommended when GFR is <60 mL/min per 1.73 m² or when GFR is <30 mL/min per 1.73 m². This study has shown that the formulas perform very well within this range, and therefore dose adjustment can be safely executed with the use of these formulas.

Finally, our study is the first to compare the prognostic value of the estimated renal function for cardiovascular outcome with the true renal function. The true renal function is the best parameter to predict an event. The MDRD and the CrClBSA were both accurate parameters to predict events. In contrast, the Cockcroft-Gault formula was a significantly worse prognostic parameter. We therefore recommend that the latter formula not be used for prognostic purposes.

Limitations
In this study all patients were using renin-angiotensin system inhibitors (angiotensin II converting-enzyme inhibitors or angiotensin II receptor type 2 antagonists). In the past, the effect of ACE inhibitors on renal function has been studied in CHF patients. Some studies found an increase in GFR,23 others found a decrease, and others did not find any significant effect.23,24 The net effect of renin-angiotensin system inhibitors on renal function in CHF patients remains to be elucidated. However, to the best of our knowledge, no available data suggest that renin-angiotensin system blockade could alter the relationship between true renal function and equation-derived estimates of renal function. Therefore, we do not consider it likely that the use of renin-angiotensin system inhibitors affected our results. Renin-angiotensin system inhibitors are considered essential therapies in patients with CHF, and therefore it would be difficult to obtain renal function measurements before and after the initiation of these medications. The population studied consisted of only patients with systolic dysfunction. The performance and prognostic value of the formulas should also be studied in patients with preserved systolic function.

Our CHF patients were of white ethnicity and formed a representative sample of the Dutch population, but whether the predictive performance MDRD formulas are the same for CHF patients with black or other ethnicities remains to be elucidated.

Conclusion
All formulas underestimated GFRBSA in the near-normal and normal ranges of renal function and tended to overestimate GFRBSA in the low and very low ranges, although the predictive performance improved in patients with severe CHF. The MDRD formula is the most precise, especially in the lower ranges of GFRBSA, which makes this formula the most reliable in clinical practice. True renal function provided the best prognostic index for cardiovascular outcome, whereas the CrClBSA and the MDRD had a good prognostic value for cardiovascular outcome as well, and the sMDRD, which is from a clinical perspective the most practical formula, was slightly less accurate.

Acknowledgments
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Disclosures
None.

References
17. O’meara E, Chong KS, Gardner RS, Jardine AG, Neilly JB, McDonagh TA. The Modification of Diet in Renal Disease (MDRD)
Formulas estimating renal function are widely used in the clinic, especially for patients with chronic heart failure. The estimated renal function is an important prognostic risk marker but is also used when the renal function should be known for pharmacological purposes. The formulas are inexpensive and easy to use and therefore ideal for clinical practice. However, these formulas have not been developed in heart failure patients. Therefore, we validated the most commonly used formulas estimating renal function in patients with chronic heart failure. Furthermore, we studied the prognostic value of these formulas compared with the accurately measured renal function. We found that the formulas estimate the true renal function very well. However, in patients with worse renal function (glomerular filtration rate < 35 mL/min), the formulas tend to overestimate the true renal function. This could potentially harm the patient if the physician is not aware of this. The prognostic value was comparable to the true renal function, except for the Cockcroft-Gault formula, for which prognostic value was significantly worse.
Drawbacks and Prognostic Value of Formulas Estimating Renal Function in Patients With Chronic Heart Failure and Systolic Dysfunction
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