Chronic Kidney Disease and the Risk of Heart Failure in Men

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Background—The relations between chronic kidney disease (CKD) and incident heart failure remain unclear.

Methods and Results—We related CKD to incident nonfatal heart failure and cardiovascular (CVD) death (as separate and combined end points) in 10,181 male participants (mean age, 67 years). Kidney function was assessed by estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease equation in clinically relevant categories of <60 and ≥60 mL·min⁻¹·1.73 m⁻² (referent) and <45, 45 to 60, 60 to 90, and ≥90 mL·min⁻¹·1.73 m⁻² (referent). During follow-up (mean, 10.1 years; range, 0.03 to 12.2), 4,396 developed heart failure and 832 had CVD death/heart failure. In multivariable models, men with eGFR <60 mL·min⁻¹·1.73 m⁻² had a 2-fold risk of heart failure (95% confidence interval, 1.62 to 2.56, P<0.0001) compared with referent category. The hazard ratio (with corresponding 95% confidence interval) for development of heart failure according to eGFR categories of 60 to 90, 45 to 60, and <45 mL·min⁻¹·1.73 m⁻² compared with referent category were 1.24 (0.98 to 1.56), 2.58 (1.91 to 3.49), and 1.52 (0.92 to 2.76), respectively. In the analyses restricted to subgroup of nondiabetic individuals and normotensive individuals at baseline (n=7,545), men with eGFR <60 mL·min⁻¹·1.73 m⁻² had a 2.2-fold risk of heart failure (95% confidence interval, 1.66 to 2.95, P<0.0001) compared with referent category. The hazard ratio (with corresponding 95% confidence interval) for development of heart failure according to eGFR categories of 60 to 90, 45 to 60, and <45 mL·min⁻¹·1.73 m⁻², respectively, was 2.58 (1.91 to 3.49), 2.2-fold higher among individuals with eGFR 45 to 60 and <45 mL·min⁻¹·1.73 m⁻², compared with referent category.

Conclusions—Moderate level of CKD, even in absence of diabetes and hypertension at baseline, is associated with a higher risk of development of heart failure and CVD death/heart failure in men. (Circ Heart Fail. 2011;4:138-144.)

Key Words: heart failure, congestive ■ epidemiology ■ renal disease

Compared with those who have end-stage renal failure, individuals with mild-to-moderate kidney disease have a higher risk of cardiovascular disease (CVD).¹ Epidemiological definition of CVD² includes “heart failure,” though the mechanisms of development of heart failure are not well established.³ Heart failure is increasing in prevalence and incidence, with an average middle-aged individual having 1 in 5 chances of having heart failure in his or her lifetime.⁴

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Cross-sectionally, individuals with mild-to-moderate kidney disease have a higher prevalence of left ventricular hypertrophy (LVH)—a precursor for heart failure.⁵ In fact, data from US National Kidney Foundation estimated that 75% of individuals have LVH at the time of dialysis initiation.⁶ In longitudinal studies, few investigators have separately evaluated the risk of heart failure according to different markers of renal function in selected individuals (ie, older individuals).⁷–¹¹ In addition, prior epidemiological studies evaluating the association between chronic kidney disease (CKD) and CVD (including heart failure) have shown conflicting results, with most reporting a significantly increased risk of CVD in CKD patients,¹²,¹³ whereas some observed no association of CKD to incident CVD in the community.¹⁴,¹⁵ Moreover, data from NHANES shows a lack of association between proteinuria (a marker of early renal disease) and incident heart failure.¹⁶ Overall, it remains unanswered whether there is any increased risk of heart failure in those with mild-to-moderate renal dysfunction.¹

Therefore, in the present investigation, we evaluated the relations of estimated glomerular filtration rate (eGFR) to the incidence of heart failure in the Physicians’ Health Study (PHS) participants who were free of heart failure and myocardial infarction (MI) at baseline. As a secondary aim, we analyzed if the association of CKD to incident heart failure is influenced by prevalent diabetes and hypertension by excluding participants with diabetes and hypertension at baseline. Additionally, we also evaluated the relations of
CKD to CVD death or incident heart failure as a combined end point.

Methods

Study Participants

The design and selection criteria for the PHS have been described previously.21 Briefly, 22,071 apparently healthy male physicians without a history of cardiovascular disease, cancer, or liver or kidney disease were enrolled in this study. Between 1995 and 2000, all current participants (n=14,642) were asked to provide a blood sample by mail. For the present investigation, we selected individuals with available information on measured levels of serum creatinine (n=11,105). A simplified version of the Modification of Diet in Renal Disease equation was used to calculate the eGFR.18 We excluded participants who reported heart failure at baseline or did not report any information about heart failure at the time of blood collection on their annual questionnaire (n=224), participants with a history of MI (n=375), and those with missing covariates (n=325); therefore, for the present study, our final sample included 10,181 participants. There were no significant differences between participants who provided a blood sample from those who did not. Additionally, participants with missing covariates were similar in characteristics to those with all information available (data not shown). All participants signed informed consent, and the protocol for study was approved by Institutional Review Board of Brigham and Women’s Hospital.

Measurement of Risk Factors

All information on demographics, medical history including history of diabetes mellitus, hypertension, heart failure, and other lifestyle variables were obtained annually. Therefore, information on body weight, presence or absence of diabetes mellitus, blood pressure, smoking habits, alcohol consumption, exercise routine, any use of anticholesterol medications, and intermit MI were obtained by questionnaires. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. Alcohol consumption was ascertained by calculating the average number of drinks consumed in categories of rarely or never, 1 to 3/mo, ≥1/ wk, and ≥1/d. Smoking history was reported in categories of never-smokers, former smokers, and current smokers.

Medical records from >95% of participants were obtained after each self-reported nonfatal MI and on receipt of their consent or consent from their next of kin (in case of death) after a fatal MI. Thereafter, an end point committee (by using World Health Organization criteria)19 confirmed all MI diagnoses by inspection of medical records and other available information. Participants reported physical activity to a point of breaking into sweat and were categorized into <1 d/wk (referent), 1 to 3 d/wk, 3 to 4 d/wk, and 5 to 7 d/wk. In the present study, hypertension was present on the basis of self-reported blood pressure of ≥140 mm Hg systolic or ≥90 mm Hg diastolic or history of hypertension or if on antihypertensive medications.

Blood Collection and Measurement of Serum Creatinine

On receipt of all EDTA blood specimens in the mail, samples were centrifuged, divided into aliquots, and frozen. Measurement of serum creatinine was performed in Oxford, England, using the Jaffé technique by a Synchron LX20 autoanalyzer (Beckman Coulter, Fullerton, CA) as previously described.20 Coefficient of variation for blinded duplicate samples was 7.1%, and intrabatch variations ranged from 1.4% to 2.3%.

Ascertainment of Heart Failure and CVD Death

Information on heart failure was collected through self-reports from participants on the annual PHS questionnaire. We examined the validity of these self-reported heart failure events in a subset of 88 alive, randomly selected cases who had reported recent new episodes of heart failure. These selected individuals were mailed a questionnaire to obtain additional information on their symptoms, signs, and laboratory investigations performed at the time of presentation with heart failure. After 2 mailings and further follow-ups by telephone, all collected information was reviewed to verify a diagnosis of heart failure based on Framingham heart failure criteria.21 Of the 88 self-reported heart failure cases, 76 (86%) returned their completed questionnaires. Overall, we successfully confirmed heart failure in 68 (99%) individuals, which suggested reasonably high validity for an epidemiological study as described earlier.22 Additionally, a separate validation using information on invasive and other noninvasive imaging modalities to ascertain the diagnosis of heart failure for this sample of individuals showing 91% accuracy has also been published elsewhere.23

All deaths attributed to CVD were confirmed by an end point committee using information from death certificates, next of kin, and medical records and have been published in detail previously.24 Statistical Analyses

Baseline characteristics of the participants were assessed according to eGFR of <60 and ≥60 mL·min⁻¹·1.73 m⁻². We estimated the cumulative incidence of heart failure per 1000 person-years in each category of eGFR. We also constructed cumulative incidence curves using the Kaplan-Meier method according to eGFR categories. Assumptions for proportional hazard models were tested by fitting a product term eGFR×log (person-time of follow-up), and we found no evidence of violation (P=0.18). Then, after confirming that the assumption of proportionality of hazard was met, we used Cox regression models to relate eGFR levels to the incidence of heart failure. eGFR was analyzed in categories of <60 and ≥60 mL·min⁻¹·1.73 m⁻² (referent) and <45, 45 to 60, 60 to 90, and ≥90 mL·min⁻¹·1.73 m⁻² (referent). All multivariable models were adjusted for age (as part of eGFR calculation), BMI, systolic and diastolic blood pressure, diabetes mellitus, smoking history, alcohol intake, and physical activity (exercise per week). We chose not to adjust for serum cholesterol or treatment of cholesterol because in the PHS data set, serum cholesterol levels have not been associated with incident heart failure.22

We assessed for any effect modification by hypertension, diabetes, and BMI using interaction terms in multivariable models adjusting for all covariates (as above) to assess the risk of heart failure according to eGFR categories of <60 and ≥60 mL·min⁻¹·1.73 m⁻².

Subgroup Analyses

In subgroup analyses, we excluded all participants with diabetes mellitus (n=599) and hypertension at baseline (n=2037) and additionally adjusted for diabetes mellitus, hypertension, and MI as time-dependent covariates (in addition to other covariates as described above for primary analyses). These subgroup analyses were performed because individuals with hypertension and diabetes are highly predisposed to have CKD and heart failure. We did not have enough events for separate analysis in subjects with diabetes or hypertension.

Additional Analyses

Because a fatal heart failure end point was not available in our data set, we examined the combined risk of heart failure and CVD death (whichever came first), according to renal function categories. We estimated the cumulative incidence of CVD death or heart failure per 1000 person-years, constructed cumulative incidence curves, and examined the relations of CKD to CVD death or heart failure using Cox regression models, adjusting for all variables as in our primary analyses (see above) according to each category of eGFR.

All analyses were performed using SAS 9.2 (Cary, NC) software. A 2-sided probability value of <0.05 was considered statistically significant.

Results

Baseline characteristics of the participants according to eGFR levels of <60 and ≥60 mL·min⁻¹·1.73 m⁻² are displayed.
As expected, individuals with eGFR <60 mL·min⁻¹·1.73 m⁻² were older, had higher systolic and diastolic blood pressures, and had higher prevalence of cholesterol-lowering medications use.

In Table 1, as expected, individuals with eGFR <60 mL·min⁻¹·1.73 m⁻² were older, had higher systolic and diastolic blood pressures, and had higher prevalence of cholesterol-lowering medications use.

Table 1. Baseline Characteristics of Participants According to eGFR Levels

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GFR, mL·min⁻¹·1.73 m⁻²</th>
<th>No. of participants, n</th>
<th>eGFR, mL·min⁻¹·1.73 m⁻²</th>
<th>Age, y</th>
<th>BMI, kg/m²</th>
<th>Diabetes mellitus, %</th>
<th>Systolic blood pressure, mm Hg</th>
<th>Diastolic blood pressure, mm Hg</th>
<th>Total cholesterol, mg/dL</th>
<th>Treatment for cholesterol, %</th>
<th>Exercise days per week, %</th>
<th>Alcohol drinks, %</th>
<th>Cigarette smoking, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥60</td>
<td>&lt;60</td>
<td>84.8±16.5</td>
<td>66.5±8.2</td>
<td>25.5±3.1</td>
<td>5.7</td>
<td>126±12</td>
<td>78±7</td>
<td>204±34</td>
<td>18.9</td>
<td>&lt;1 d/wk</td>
<td>≥1/d</td>
<td>Past</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>49.9±9.1</td>
<td>72.2±9.1</td>
<td>25.6±3.2</td>
<td>7.3</td>
<td>131±14</td>
<td>80±7</td>
<td>205±37</td>
<td>22.2</td>
<td>1–2 d/wk</td>
<td>≥1/wk</td>
<td>46.8</td>
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<td></td>
<td></td>
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<td>60</td>
<td>60</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>3–4 d/wk</td>
<td>12.8</td>
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<td></td>
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<td></td>
<td>1.73 m⁻²</td>
<td>1.73 m⁻²</td>
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<td></td>
<td></td>
<td></td>
<td>5–7 d/wk</td>
<td>23.9</td>
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<td>2</td>
<td>1.73 m⁻²</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>1–7 d/wk</td>
<td>19.8</td>
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<td></td>
<td></td>
<td></td>
<td>Rarely or never</td>
<td>19.6</td>
</tr>
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<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Current</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation or otherwise indicated.

Table 2. Cumulative Incident Rates for Heart Failure and CVD Death or Heart Failure as Composite End Point According to eGFR Levels

<table>
<thead>
<tr>
<th>GFR, mL·min⁻¹·1.73 m⁻²</th>
<th>Entire Sample</th>
<th>Subgroup*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of HF/No.</td>
<td>Incident Rates/1000 Person-Years</td>
</tr>
<tr>
<td>Incident rates of heart failure</td>
<td>≥60</td>
<td>345/9012 (3.8)</td>
</tr>
<tr>
<td></td>
<td>&lt;60</td>
<td>94/1169 (8.0)</td>
</tr>
<tr>
<td></td>
<td>≥90</td>
<td>97/2891 (3.4)</td>
</tr>
<tr>
<td></td>
<td>≥60 and &lt;90</td>
<td>248/6121 (4.0)</td>
</tr>
<tr>
<td></td>
<td>≥45 and &lt;60</td>
<td>80/890 (9.0)</td>
</tr>
<tr>
<td></td>
<td>&lt;45</td>
<td>14/279 (5.0)</td>
</tr>
<tr>
<td>Incident rates of CVD death or heart failure</td>
<td>≥60</td>
<td>641/9012 (7.1)</td>
</tr>
<tr>
<td></td>
<td>&lt;60</td>
<td>191/1169 (16.3)</td>
</tr>
<tr>
<td></td>
<td>≥90</td>
<td>162/2891 (5.6)</td>
</tr>
<tr>
<td></td>
<td>≥60 and &lt;90</td>
<td>479/6121 (7.8)</td>
</tr>
<tr>
<td></td>
<td>≥45 and &lt;60</td>
<td>146/890 (16.4)</td>
</tr>
<tr>
<td></td>
<td>&lt;45</td>
<td>45/279 (16.1)</td>
</tr>
</tbody>
</table>

*Subgroup of participants without diabetes mellitus and hypertension at baseline (n=7545).
when compared with referent categories. Further, when age was included as a variable (in addition to using age in calculation of eGFR) in multivariable models, the risk of heart failure was attenuated; however, it remained statistically significant for individuals with eGFR between 45 to 60 mL \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2} (HR, 1.45; 95% CI, 1.07 to 1.97). The risk of heart failure was attenuated and was not statistically significant in individuals with eGFR <45 mL \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}, perhaps because there were fewer individuals in that category compared with referent category (Table 3). Additionally, when we excluded men with eGFR <30 mL \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2} (n=44; 3 heart failure events), the risk of heart failure was further attenuated among those with eGFR <45 mL \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2} (HR, 1.49; 95% CI, 0.80 to 2.78; P=0.21).

We could not detect any effect modification by hypertension, diabetes, or BMI when heart failure risk was evaluated for individuals with eGFR <60 mL \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2} compared with the referent category (all probability values >0.10).

### Subgroup Analyses

In the subgroup of individuals without diabetes and hypertension at baseline, 532 individuals had diabetes, 2424 had hypertension, 398 had interim MI, and 284 participants had heart failure on follow-up. Cumulative incident rates per 1000 person-years of follow-up were similar to that of the entire sample (Table 2). In multivariable models with adjustment for all covariates including diabetes, hypertension, and MI as time-dependent variables, the risk of heart failure remained robust, with >2.0-fold among individuals with eGFR <60 mL \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2} and >2.5-fold for those with eGFR between 45 to 60 mL \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}, compared with the respective referent categories (Table 2). The risk of heart failure in individuals with eGFR <45 mL \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2} was statistically significant and almost reached 2-fold, compared with the referent category.

### Additional Analyses

Because we did not have information on fatal heart failure events, we also examined the relations of eGFR categories to the incidence of heart failure and CVD death as a combined end point. There were 832 combined events on follow-up (mean, 10 years). Cumulative incidence curves showed graded increasing risk (Figure 3), and incident rates increased

<table>
<thead>
<tr>
<th>GFR, mL \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}</th>
<th>Incidence of heart failure</th>
<th>Entire Sample*</th>
<th>Subgroup†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of heart failure</td>
<td></td>
<td>HR (CIs)</td>
<td>P Value</td>
</tr>
<tr>
<td>≥60</td>
<td>Referent</td>
<td>2.05 (1.62–2.59)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt;60</td>
<td>Referent</td>
<td>2.22 (1.66–2.95)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≤60 and &lt;90</td>
<td>Referent</td>
<td>1.24 (0.86–1.56)</td>
<td>0.08</td>
</tr>
<tr>
<td>≥45 and &lt;60</td>
<td>Referent</td>
<td>2.58 (1.91–3.49)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt;45</td>
<td>Referent</td>
<td>1.58 (0.92–2.76)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Incidence of CVD death or heart failure</th>
<th></th>
<th>HR (CIs)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>Referent</td>
<td>2.07 (1.76–2.44)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt;60</td>
<td>Referent</td>
<td>2.18 (1.76–2.69)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≤60 and &lt;90</td>
<td>Referent</td>
<td>1.42 (1.19–1.70)</td>
<td>0.0001</td>
</tr>
<tr>
<td>≥45 and &lt;60</td>
<td>Referent</td>
<td>2.74 (2.19–3.44)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt;45</td>
<td>Referent</td>
<td>3.05 (2.19–2.45)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Adjusted for age (as part of calculated eGFR), BMI, diabetes mellitus, systolic and diastolic blood pressure, smoking, alcohol intake, and exercise days.

†Subgroup analyses of participants with no hypertension or diabetes mellitus at baseline (n=7545) adjusting for all covariates as for the entire sample and with additional adjustment for hypertension, diabetes mellitus, and MI as time-dependent variables.
new-onset heart failure was compared with the referent category (eGFR failure or CVD death, (HR 3.05 95% CI 2.19 to 4.25), tensive individuals at baseline.

It was the referent category.

subgroup of normotensive and nondiabetics, compared with eGFR <45 mL · min⁻¹ · 1.73 m⁻² had a 3-fold higher risk of incident heart failure or CVD death, (HR 3.05 95% CI 2.19 to 4.25), compared with the referent category (eGFR ≥90 mL · min⁻¹, 1.73 m⁻²; Table 3). These associations remained robust and were slightly attenuated after excluding men with diabetes and hypertension at baseline (Table 3). Last, CVD death or new-onset heart failure was >2-fold higher among individu- als with eGFR <60 mL · min⁻¹ · 1.73 m⁻², even in the subgroup of normotensive and nondiabetics, compared with the referent category.

Discussion

Principal Findings

Our primary results were 3-fold. First, in individuals who were free of heart failure at baseline, eGFR between 45 to 60 mL · min⁻¹ · 1.73 m⁻² was associated with higher risk of heart failure on follow-up. Categorical models showed approximately 2- to 2.5-fold higher risk of heart failure in individuals within this category, although in the multivariable models, age was a confounder of the association between CKD and heart failure risk. Second, the subgroup of nondiabetic and normotensive men with eGFR between 45 to 60 mL · min⁻¹ · 1.73 m⁻² had the greatest risk of developing new-onset heart failure. Third, among individuals with eGFR <45 mL · min⁻¹ · 1.73 m⁻² and those with eGFR 45 to 60 mL · min⁻¹ · 1.73 m⁻², the risk of CVD death or heart failure was >2.5-fold compared with the referent category and was attenuated minimally with exclusion of diabetics and normotensive individuals at baseline.

Comparison With Prior Literature

Prior results from 2 large, epidemiological studies did not show any increased risk of heart failure with higher serum creatinine, but others have observed higher risk of heart failure with increasing serum creatinine levels and with lower eGFR. Recently, newer but costlier markers such as cystatin C have been studied to measure kidney function decline in assessment of heart failure risk; researchers have observed differences by race and blood pressure such that blacks were at higher risk compared with white individuals and hypertensive individuals were more prone to have heart failure compared with normotensive individuals.

Mechanisms

There are several possible mechanisms that can increase the risk of heart failure in individuals with CKD. First, as postulated earlier, individuals with CKD have higher prevalence of hypertension, diabetes mellitus, higher BMI, and other coronary risk factors that are also known to increase the risk for heart failure. Moreover, many researchers evaluating the risk of CVD in CKD patients have also postulated that most of the CVD risk probably is due to higher prevalence of traditional coronary risk factors in CKD patients. In the present study, however, the risk of heart failure in participants with eGFR <60 mL · min⁻¹ · 1.73 m⁻² was maintained after adjustment for traditional risk factors. Subgroup analyses also revealed that there was no difference when the risk for heart failure was evaluated among nondiabetic and normotensive individuals with adjustment for MI on follow-up.

Second, damage to nephrons in renal dysfunction leads to high blood pressure through mechanisms such as plasma volume expansion, overactivity of the sympathetic nervous system, and the renin-angiotensin-aldosterone axis, which sets a vicious circle of higher blood pressure thereby leading to left ventricular enlargement, a known precursor for heart failure. A regression of hypertrophy is associated with reduced cardiac failure outcomes. Of note, a tighter control of blood pressure is also known to decrease the progression of kidney disease in some but not all studies. However, in the present study, nondiabetic and normotensive individuals with moderate to severe kidney disease exhibited similar and higher risk of heart failure compared with the entire sample, independent of having hypertension on follow-up.

Third, moderate to advanced kidney disease is associated with higher serum phosphorus, which is further linked to development of LVH in experimental studies and higher incidence of CVD mortality in some but not all epidemiological studies. However, recent data also suggest that a high but “normal” level of serum phosphorus is associated with greater risk of development of CVD (including heart failure) in the community. Therefore, it is plausible that mild to moderate CKD may lead to elevated serum phosphorus, which then can lead to an increased risk for the development of LVH and clinical heart failure.

Last, patients with CKD have decreased erythropoietin formation, which leads to development of anemia. A graded decrease in hemoglobin concentration is significantly associated with increases in left ventricular mass. Conversely, even partial correction of anemia in dialysis patients has been shown to produce regression of LVH.

Strengths and Limitations

The present study has the largest sample size, including a large subgroup of nondiabetic individuals and normotensive individuals, with decreasing eGFR categories (Table 2). In multivariable models, individuals with eGFR between 45 to 60 mL · min⁻¹ · 1.73 m⁻² had a 2.7-fold risk of an event (HR, 2.74; 95% CI, 2.19 to 3.44), whereas those with eGFR <45 mL · min⁻¹ · 1.73 m⁻² had a 3-fold higher risk of incident heart failure compared with normotensive individuals.26
individuals, as compared with previous studies. In the present analyses, we accounted for all traditional coronary risk factors as well as CHD, diabetes, and hypertension on follow-up, which strengthens our study. Some limitations also merit discussion. First, measurement of renal function based on different formulas to measure eGFR has been questioned, and some have found novel markers such as cystatin C to be better predictors of renal dysfunction; however, eGFR remains the least expensive and more precise method of measuring kidney function. CKD is defined by the National Kidney Foundation as eGFR <60 mL \cdot min^{-1} \cdot 1.73 m^{-2} for a period of at least 3 months. In the present study (and perhaps in most other large epidemiological studies), a single measurement is often used. Moreover, any misclassification in the present study probably would underestimate the relations and would bias results toward the null. It is plausible that the risk of heart failure and CVD death may vary with time, especially in individuals with impaired kidney function. Second, in our data set, we did not have information on fatal heart failure events; therefore, we performed additional analyses using CVD death or heart failure as a combined event. Individuals within eGFR categories of 45 to 60 mL \cdot min^{-1} \cdot 1.73 m^{-2} and <45 mL \cdot min^{-1} \cdot 1.73 m^{-2} had a statistically significant higher risk of combined event (heart failure and CVD death). Of note, the hazard ratio for incident CVD death is even higher among men with eGFR <45 mL \cdot min^{-1} \cdot 1.73 m^{-2} compared with those with eGFR between 45 to 60 mL \cdot min^{-1} \cdot 1.73 m^{-2}. Therefore, it is plausible that individuals in the category of eGFR <45 mL \cdot min^{-1} \cdot 1.73 m^{-2} had more first fatal heart failure episodes. However, data from US renal data system indicates that only 13% of CVD deaths are associated with heart failure, which also includes deaths among patients with chronic heart failure. Last, participants in our study were predominantly white men who were physicians; hence, results may have limited generalizability for women and may differ with socioeconomic class.

Conclusion
In this sample of men free of heart failure at baseline, moderate CKD was associated with a higher incidence of heart failure and CVD death or heart failure on follow-up. Additionally, a subgroup of normotensive and non diabetic individuals with moderate CKD also had a similar and higher risk of heart failure as for the whole sample.

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Disclosures
Dr Gaziano reported receiving investigator-initiated research funding from the National Institutes of Health, the Veterans Administration, Veroscience, and Amgen; serving as a consultant or receiving honoraria from Bayer AG and serving as an expert witness for Merck. Dr Djoussé reported that he is currently the recipient of investigator-initiated grants from the National Institutes of Health and that over the past 5 years he has received an investigator-initiated grant from the Biomedical Research Institute, Brigham and Women’s Hospital.

References
Individuals with chronic kidney disease (CKD) have higher prevalence of left ventricular hypertrophy and cardiovascular disease; however, it remains unclear if development of CKD is associated with higher incidence of heart failure, independent from diabetes and hypertension. We analyzed the relations of CKD to incident heart failure and to cardiovascular disease (CVD) death or heart failure (combined end point) in 10,181 Physicians’ Health Study male participants (mean age, 67 years). Kidney function was assessed by estimating the glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease equation in clinically relevant categories of <60 mL·min⁻¹·1.73 m⁻² (referent) and <45 to 60, 60 to 90, and ≥90 mL·min⁻¹·1.73 m⁻² (referred). During follow-up, heart failure developed in 439 participants and 832 had a combined end point of CVD death or heart failure. In multivariable models, men with eGFR 45 to 60 and <45 mL·min⁻¹·1.73 m⁻² had >2.5-fold risk of CVD death or heart failure compared with referent category. Further, these relations remained robust in the analyses restricted to a subgroup of nondiabetic individuals and normotensive individuals at baseline (n=7545). In addition, men with eGFR 45 to 60 and <45 mL·min⁻¹·1.73 m⁻² had >2.5-fold risk of heart failure compared with referent category. In summary, our results show that moderate level of CKD, even in the absence of diabetes and hypertension, is associated with a higher risk of development of heart failure and CVD death/heart failure in men.

CLINICAL PERSPECTIVE
Chronic Kidney Disease and the Risk of Heart Failure in Men
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