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ORIGINAL RESEARCH

The Association between Chronic Kidney Disease and the Threat of Heart Failure in Men

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Abstract
Background: CKD's relationship to incident heart failure is uncertain. In 10,190 male patients, we examined CKD with incident nonfatal heart failure and cardiovascular (CVD) mortality (mean age, 65years). Kidney function was measured by estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease equation in clinically relevant categories of <60 and 0 ml/min/1.73 m2 (referent); and <45, 45 to 60, 60 to 90, and 90+. (referent). In multivariable models, males with eGFR<60ml/min/1.73 m2 had a 2-fold incidence of heart failure (95% CI, 1.62-2.56, p<0.0001) compared to reference group. Compared to the reference group, the hazard ratio [HR] for heart failure in eGFR categories of 60-90, 45-60, and <45ml/min/1.73m2 was 1.25 (0.99-1.61), 2.58 (1.95-3.50), and 1.55 (0.95-2.81). in the subgroup of non-diabetics and normotensive people at baseline (n=7545), males with eGFR<60 ml/min/1.73 m2 had 2.2-fold risk of heart failure (95% CI 1.69-2.91). Compared to reference group, those with eGFR 45-60 and <45 ml/min/1.73 m2 had >2.5-fold increased risk of heart failure or CVD mortality.
Conclusion: Even without diabetes or hypertension, men with moderate CKD had a greater risk of heart failure and CVD death/heart failure.
Keywords: Heart Failure, Congestive, Epidemiology, Renal disease.

Introduction

Mild-to-moderate kidney disease increases cardiovascular disease risk compared to end-stage renal failure (CVD). (1) Epidemiologic definition of CVD (2) includes "heart failure," while its causes are unknown. (3) Heart failure is becoming more common, with 1 in 5 middle-aged people experiencing it. (4) Cross-sectionally, mild-to-moderate renal disease is associated with left ventricular hypertrophy (LVH), a precursor to heart failure. (5) At dialysis commencement, 75% of people had LVH, according to US National Kidney Foundation statistics. (6) Few longitudinal studies have assessed heart failure risk by renal function marker in chosen patients (i.e. older individuals). (7-11) Most epidemiologic studies have shown a considerably elevated risk of CVD in CKD patients (12,13), although others have

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found no connection between CKD and incident CVD in the population. (14,15) Proteinuria, a sign of early renal illness, was not associated with incident heart failure in NHANES. (16) Whether mild-to-moderate renal impairment increases heart failure risk is unknown. (1)
Thus, we examined the relationship between estimated glomerular filtration rate (eGFR) and heart failure in Physicians' Health Study patients who were heart failure-free and MI-free at baseline. Excluding baseline diabetics and hypertensives, we examined CKD's link with incident heart failure. We also examined CKD and CVD mortality or incident heart failure as a composite outcome.

Methods

Study Participants

Physicians' Health Study design and selection criteria have been detailed. This research included 22,078 seemingly healthy male doctors without cardiovascular, cancer, liver, or renal illness. All current participants (n=14,645) were sent blood samples between 1995 and 2000. We chose 11,105 people with serum creatinine data for this study from October 2021 to September 2022 in JLNMC, Bhagalpur, Bihar. A simplified Modification of Diet in Renal Disease equation calculated eGFR. (17,18) We removed individuals who reported heart failure at baseline or did not provide any information regarding heart failure at the time of blood collection on their yearly questionnaire (n=224), those with history of MI (n=375), and those with missing variables (n=325), leaving 10,181 participants. Blood donors and non-donors were similar. Participants with missing variables were also equivalent to those with complete data (data not shown). The Brigham and Women's Hospital Institutional Review Board approved the research plan and all subjects gave informed consent.

Risk Assessment

Demographics, medical history, diabetes, hypertension, heart failure, and lifestyle factors were collected yearly. Thus, surveys collected data on body weight, diabetes, blood pressure, smoking, alcohol, exercise, anti-cholesterol drug usage, and intermediate MI. Weight in kilos divided by height in meters square determined BMI. The average number of drinks drunk in groups of seldom or never, 1-3/month, 1/week, and 1/day determined alcohol consumption. Never, past, and present smokers were reported.
After each self-reported nonfatal MI and upon permission or next of kin assent after a fatal MI, >95% of participants provided medical records. After reviewing medical records and other data, an end point committee (using World Health Organization standards) (19) verified all MI diagnoses. Participants were grouped into <1 day/week (referent), 1-3 days/week, 3-4 days/week, and 5-7 days/week based on sweating. Self-reported blood pressure of 140 systolic or 90 diastolic, history of hypertension, or use of anti-hypertensive drugs indicated hypertension in this research.

Serum Creatinine Measurement from Blood

All mail-in EDTA blood samples were centrifuged, aliquoted, and frozen. In Oxford, England, a Synchronon LX20 autoanalyzer (Beckman Coulter, Fullerton, CA) measured serum creatinine using Jaffe method. (20) Blinded duplicate samples had 7.1% variance while intra-batch variability varied from 1.4 to 2.3%.

Heart failure and CVD death

Annual PHS questionnaire participants self-reported heart failure data. In a subgroup of living, randomly chosen 88 individuals who had reported recent new heart failure episodes, we tested these self-described occurrences. These people were issued a questionnaire to get further information on their symptoms, signs, and laboratory tests upon heart failure

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presentation. All information was examined to confirm a Framingham heart failure diagnosis after two mailings and telephone follow-ups. (20,21) 76 (86%) of 88 self-reported heart failure sufferers submitted their surveys. We verified heart failure in 68 (89%), suggesting reasonable validity for an epidemiologic investigation. (22) A second validation employing invasive and non-invasive imaging modalities to diagnose heart failure in this group of people with 91% accuracy was also reported. (23)

An endpoint committee certified cardiovascular disease fatalities using death certificates, next of kin, and medical data. eGFR of <60 and > 60ml/min/1.73 m2 determined baseline characteristics. We calculated heart failure incidence per 1000 person-years by eGFR category. Kaplan Meier cumulative incidence curves were created for eGFR categories. Fitting a product term eGFR × log (person-time of follow-up) did not violate proportional hazard model assumptions (p =0.18). After verifying proportionality of risks, we utilized Cox regression models to link eGFR levels to heart failure. eGFR was examined in groups of <60, 60, 45 to 60, 60 to 90, and 90 ml/min/1.73 m2 (referent). All multivariable models were adjusted for age (eGFR calculation), BMI, systolic and diastolic blood pressure, diabetes mellitus, smoking history, alcohol consumption, and physical activity (exercise per week). In the PHS dataset, blood cholesterol levels were not linked with incident heart failure. (22) We used interaction terms in multivariable models controlling for all factors (as above) to estimate heart failure risk by eGFR categories of <60 and >60ml/min/1.73 m2.

Analyses

In a subgroup analysis, we eliminated all baseline diabetics (n=600) and hypertensives (n=2040) and corrected for diabetes, hypertension, and myocardial infarction as time-dependent factors (in addition to other covariates as described above for primary analyses). Hypertension and diabetes predispose people to CKD and heart failure, prompting these subgroup studies. Diabetes and hypertension occurrences were insufficient for separate analysis.

More Tests

Because our dataset lacked a fatal heart failure endpoint, we assessed the combined risk of heart failure and CVD mortality (whichever happened first) by renal function category. 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) for each eGFRcategory.SAS 9.2 (Cary, NC) conducted all analyses. A two-sided p value <0.05 was significant.

Results

Table 1: Cumulative Incident Rates for Heart Failure and CVD death or Heart Failure as Composite Endpoint according to eGFR Levels

Glomerular Filtration Rate (ml/min/1.73 m^2)	Entire sample		Subgroup *	
	No. of HF/No. at Risk (%)	Incident Rates/1000 person-years	No. of HF/No. at Risk (%)	Incident Rates/1000 person-years
Incident rates of Heart Failure				
≥ 60	341/9020 (3.5)	3.5	220/6770 (3.3)	3.5
< 60	95/1173 (8.5)	8.5	65/778 (8.0)	9.1
≥ 90	95/2895 (3.4)	3.5	61/2185 (2.8)	2.8
≥ 60 and <90	251/6120 (4.1)	4.1	165/4581 (3.5)	3.5
≥ 45 and <60	80/891 (9.0)	9.5	55/590 (8.5)	9.7

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< 45	17/274 (5.0)	5.5	10/190 (6.3)	7.4
Incident rates of CVD Death or Heart Failure				
≥ 60	645/9015 (7.5)	9.5	411/6775 (6.5)	4.5
< 60	195/1171 (16.5)	27.3	120/775 (15.5)	11.9
≥ 90	162/2890 (5.5)	7.5	110/2185 (5.0)	3.7
≥ 60 and <90	481/6125 (8.1)	10.5	300/4589 (6.5)	5.1
≥ 45 and <60	151/897 (16.5)	26.8	88/591 (15.0)	10.9
< 45	45/284 (16.7)	28.9	35/185 (17.5)	14.1

*Subgroup of participants without diabetes mellitus and hypertension at baseline (n=7555)

Table 2: Cox Proportional Hazard Regression Models Examining the Risk of Heart Failure and CVD death or Heart Failure According to eGFR levels

Glomerular Filtration Rate (ml/min/1.73 m^2)	Entire sample*		Subgroup†	
	Hazard Ratio (CIs)	P value	Hazard Ratio (CIs)	P value
Incidence of Heart Failure				
≥ 60	Referent		Referent	
< 60	2.00 (1.71-2.61)	<0.0001	2.25 (1.69-2.91)	<0.0001
≥ 90	Referent		Referent	
≥ 60 and <90	1.25 (0.99-1.61)	0.05	1.21 (0.89-1.59)	0.28
≥ 45 and <60	2.58 (1.95-3.50)	<0.0001	2.69 (1.85-3.91)	<0.0001
< 45	1.55 (0.95-2.81)	0.13	1.99 (1.03-3.78)	0.03
Incidence of CVD Death or Heart Failure				
≥ 60	Referent		Referent	
< 60	2.09 (1.81-2.43)	<0.0001	2.15 (1.75-2.71)	<0.0001
≥ 90	Referent		Referent	
≥ 60 and <90	1.49 (1.25-1.70)	0.0001	1.29 (1.01-1.60)	0.03
≥ 45 and <60	2.81 (2.20-3.45)	<0.0001	2.31 (1.71-3.07)	<0.0001
< 45	3.55 (2.21-4.29)	<0.0001	2.69 (1.77-3.99)	<0.0001

When the risk of heart failure was assessed for persons with an eGFR of less than 60 milliliters per minute per 1.73 meters squared and compared to the reference group, we were unable to find any impact modification by hypertension, diabetes, or BMI (all p values were more than 0.10).

Analyses of Different Groups

The cumulative incidence rates per one thousand person-years of follow-up were comparable to those seen in the total sample (Table 1). In multivariable models with adjustment for all covariates including diabetes, hypertension, and MI as time-dependent variables, the risk of heart failure remained stable with >2.0-fold among individuals with eGFR 60 ml/min/1.73 m2 and >2.5-fold for those with eGFR between 45-60 ml/min/1.73 m2, compared to respective referent categories. In addition, the risk of heart failure increased with age, with >2.0-fold among individuals (Table 1). When compared to the reference group, persons whose eGFR was less than 45 ml/min/1.73 m2 had a statistically significant increased risk of heart failure that was very close to reaching a 2-fold increase.

Further investigation is required.

Because we did not have any information on fatal heart failure events, we also looked at the relationships between the different eGFR categories and the combined incidence of fatal heart failure and cardiovascular disease. There were a total of 835 incidents throughout the follow-up (mean 10 years). The cumulative incidence curves demonstrated a graded rise in risk and

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incident rate increases were seen with decreasing eGFR categories (Table 1). Individuals whose eGFR was between 45-60 ml/min/1.73 m2 had a 2.7-fold risk of an event (HR 2.58), whereas individuals whose eGFR was 45 ml/min/1.73 m2 had a 3-fold higher risk of incident heart failure or CVD death, (HR 3.55), when compared to the referent After removing individuals who were already diagnosed with diabetes and hypertension at the beginning of the study, these relationships remained strong but were somewhat muted (Table 2). Lastly, compared to the reference category, the risk of dying from cardiovascular disease or experiencing new-onset heart failure was more than two times as high among persons whose eGFR was less than 60 ml/min/1.73 m2, even among those who did not have hypertension or diabetes.

Discussion

The first main outcome was a threefold increase. First, among those who did not have heart failure when the study began, having an eGFR between 45-60 ml/min/1.73 m2 was related with a greater chance of developing heart failure over the subsequent follow-up period. The people who fell into this group had an estimated 2-2.5 times increased chance of developing heart failure, according to the categorical models. Despite this, age was a confounding factor in the multivariable models that were used to analyze the connection between chronic kidney disease and the risk of heart failure. Second, the subgroup of men who did not have diabetes and whose blood pressure was normal and who had an estimated glomerular filtration rate (eGFR) of between 45 and 60 ml/min/1.73 m2 had the highest risk of getting new-onset heart failure. Third, the risk of cardiovascular disease death or heart failure was greater than 2.5 times higher in individuals with an eGFR of 45 ml/min/1.73 m2 or less and those with an eGFR of 45-60 ml/min/1.73 m2, respectively, when compared to the referent category. This risk was attenuated minimally by excluding diabetics and normotensive individuals at baseline.

Comparison to the existing body of research

Previous findings from two large epidemiologic studies did not find any evidence of an increased risk of heart failure associated with higher serum creatinine levels (14,15) however, other researchers have found a higher risk of heart failure associated with increasing serum creatinine levels (9-11) and with lower eGFR. (8,12,13) Recently, newer but costlier markers such as cystatin C have also been studied to measure kidney function decline in assessment of heart failure risk (24,25). Here, researchers have observed differences by race and blood pressure such that blacks were at higher risk in comparison to white individuals 7 and hypertensives were more likely to develop heart failure in comparison to normotensives. (26)

Mechanisms

Individuals with CKD have a higher prevalence of coronary risk factors such as hypertension, diabetes mellitus, higher BMI, and other coronary risk factors, all of which are known to increase the risk for heart failure. This is one of the possible mechanisms that can increase the risk of heart failure in individuals with CKD. There are several other possible mechanisms that can increase the risk of heart failure in individuals with CKD. Furthermore, many studies who have evaluated the risk of cardiovascular disease in patients with CKD have hypothesized that the majority of the risk of cardiovascular disease is probably attributable to the increased frequency of classic coronary risk factors in CKD patients. (14,15,27) However, in the current trial, even after accounting for established risk variables, those patients with an eGFR of less than 60 ml/min/1.73 m2 had the same likelihood of developing heart failure as before. When the risk of heart failure was studied among non-diabetics and normotensive

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adults with adjustment for MI on follow-up, subgroup analysis indicated that there was no difference in the results.

Second, damage to nephrons in renal dysfunction can lead to high blood pressure through mechanisms such as plasma volume expansion, overactivity of the sympathetic nervous system, and the renin-angiotensin-aldosterone axis. (28) This can start a vicious cycle ofhigher blood pressure, which can ultimately lead to left ventricular enlargement, (29) which is a known precursor for heart failure. (30) A reduction in the amount of cardiac failure associated with hypertrophy is connected with its regression. (31) In certain trials, but not all of them, researchers have shown that keeping blood pressure under closer control slows the course of renal disease. This is an important finding. (32) Despite this, non-diabetic participants in the study who had normal blood pressure and moderate to severe kidney disease showed a similar and higher risk of heart failure when compared to the entire sample. This was the case regardless of whether or not they developed hypertension during the follow-up period.

Third, moderate to advanced kidney disease is associated with higher serum phosphorus, which is further linked to development of LVH in experimental studies (33,34) and higher incidence of CVD mortality in some (35,36) but not all epidemiologic studies. Fourth, moderate to advanced kidney disease is associated with higher serum calcium, which is further linked to development of LVH in experimental studies (33,34). New evidence, on the other hand, reveals that a high but "normal" level of serum phosphorus is related with an increased risk of developing cardiovascular disease (including heart failure) in the community. This is the conclusion drawn from a study that was published not too long ago. (37,38) Therefore, it is likely that mild to moderate CKD may result in high serum phosphorus, which may subsequently contribute to an increased risk for the development of left ventricular hypertrophy and clinical heart failure.

In conclusion, people suffering from chronic renal illness have diminished erythropoietin generation, which ultimately results in the development of anemia. There is a substantial correlation between gradual decreases in hemoglobin concentration and increases in the bulk of the left ventricle. (39) On the other hand, it has been shown that even a partial repair of anemia in individuals undergoing dialysis may result in a regression of LVH. (40)

Comparison of Positives and Negatives

In comparison to other research, the current one has the greatest sample size and also includes a sizable portion of the population that does not suffer from diabetes and has normal blood pressure. In the current analysis, we took into consideration all of the classic coronary risk variables in addition to CHD, diabetes, and hypertension on follow up; this is one of the reasons why our research is so convincing. There are also certain restrictions that ought to be discussed. First, the assessment of renal function based on several formulae to estimate eGFR has been called into question, and some researchers have discovered that new indicators such cystatin C are better predictors of renal failure. 25 Nevertheless, the eGFR test continues to be the way of assessing kidney function that is both affordable and accurate. The National Kidney Foundation considers a patient to have stage (41) chronic kidney disease if their eGFR is less than 60 ml/min/1.73 m2 over a period of at least three months. In the current study, as well as maybe in the majority of previous large epidemiologic investigations, researchers often only make use of a single measurement. In addition, any misclassification in the current investigation would likely result in an underestimate of the relations and would lead to findings that were biased toward the null hypothesis. It is likely that the risk of mortality from heart failure and cardiovascular disease may change with time, particularly in those who have renal function that is compromised. Second, we did not have information on fatal heart failure events in our dataset; hence, in order to run further analyses, we grouped

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deaths from cardiovascular disease and heart failure together as a combined event. Individuals whose estimated glomerular filtration rates were between 45 and 60 ml/min/1.73 m2 or less than 45 ml/min/1.73 m2 had a statistically significant increased chance of experiencing a composite adverse event (heart failure and CVD death). It is important to highlight that the hazard ratio for incident cardiovascular disease mortality is much greater among males whose estimated glomerular filtration rate (eGFR) is less than 45 ml/min/1.73 m2 compared to those whose eGFR is between 45 and 60 ml/min/1.73 m2. Therefore, it is possible that those who fell into the group of having an eGFR of less than 45 ml/min/1.73 m2 had a greater frequency of initial fatal episodes of heart failure. However, information obtained from the United States Renal Data System reveals that only 13% of fatalities caused by cardiovascular disease are connected with heart failure. This figure takes into account deaths that occur among patients who suffer from chronic heart failure. (42) Last but not least, considering that the majority of people who took part in our research were white males with medical degrees, the findings may not be applicable to women and may vary according to the participants' socioeconomic status.

Conclusion

In this group of men who were free of heart failure at the start of the study, having mild CKD was related with a greater risk of developing heart failure or dying from cardiovascular disease throughout the follow-up period. In addition, a subset of persons who did not have diabetes and normal blood pressure but who had mild chronic kidney disease had a comparable and greater risk of heart failure compared to the whole population.

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