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Mild renal dysfunction and long-term adverse outcomes in women with chest pain: results from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE)

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Abstract

Background—Chronic kidney disease (CKD) is associated with accelerated atherosclerosis and adverse cardiovascular outcomes, but mechanisms are unclear. We hypothesized that mild CKD independently predicts adverse outcomes in women with symptoms and signs of ischemia.

Methods—We categorized 876 women from the Women's Ischemia Syndrome Evaluation (WISE) cohort according to estimated glomerular filtration rate (eGFR) [eGFR ≥90, normal; 60–89, mild; <60, severe CKD]. Time to death from all-cause and cardiovascular causes and major adverse outcomes were assessed by multivariate regression adjusted for baseline covariates.

Results—Obstructive coronary artery disease (CAD) was present only in a minority of patients (39%). Even after adjusting for CAD severity, renal function remained a strong, independent predictor of all-cause and cardiac mortality ($p < 0.001$). Every 10 unit decrease in eGFR was associated with a 14% increased risk of all-cause mortality [adjusted hazard ratio (AHR) 1.14 (1.08–1.20); $p < 0.0001$], 16% increased risk of cardiovascular mortality [AHR 1.16 (1.09–1.23);

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p<0.0001], and 9% increased risk of adverse cardiovascular events [AHR 1.09 (1.03–1.15); p=0.002].

Conclusions—Even mild CKD is a strong independent predictor of all-cause and cardiac mortality in women with symptoms/signs of ischemia, regardless of underlying obstructive CAD severity, underscoring the need to better understand the interactions between ischemic heart disease and CKD.

Keywords

Chronic kidney disease; Ischemic heart disease; Mortality; Adverse outcomes

Introduction

Kidney disease is associated with increased risk for adverse cardiovascular outcomes.¹ However, risk estimates vary with the presence of other risk factors for atherosclerosis. Moreover, there are sex-specific differences in prevalence and outcomes of chronic kidney disease (CKD)², as well as coronary artery disease (CAD), but women have generally been under-represented in CAD studies. Hence it is important to better understand how the risk of cardiovascular outcomes in patients with renal failure is influenced by sex. Prospective cohort studies of women offer a unique opportunity to examine relationships between renal impairment and cardiovascular risk. Accordingly, we investigated the risk for adverse outcomes among women enrolled in the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE).³

The WISE enrolled women referred for coronary angiography to evaluate symptoms and/or signs of cardiac ischemia.³ We have previously observed in the WISE that mild serum creatinine [Cr] elevation (1.2–1.9 mg/dL) was associated with angiographic CAD severity.⁴ Furthermore, in a cohort of these women undergoing coronary reactivity testing, coronary flow reserve (CFR) was a strong predictor of outcomes independent of the angiographic severity of CAD.⁵ Without obstructive CAD, CFR is a measure of coronary microvascular function. Recent studies have suggested that CKD is associated with reduced CFR⁶, which might be a predictor of adverse outcomes in patients with kidney disease.⁷ Accordingly, we examined the relationship between degree of renal insufficiency and obstructive CAD at baseline and adverse outcomes over long-term follow-up.

Methods

Study population and design

The WISE (clinicaltrials.gov NCT00000554) enrolled 936 women referred for clinically indicated coronary angiography to further evaluate symptoms/signs of myocardial ischemia. The study design has been described in detail previously.³ These studies conform to ethical principles outlined in the 1975 Declaration of Helsinki and were approved by each institution's review board. All study participants gave written informed consent.

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A total of 876 women had data available to calculate eGFR and follow-up information. Key demographic and laboratory variables were collected at baseline. Quantitative and qualitative analyses of coronary angiograms were performed at the WISE Coronary Angiography Core masked to other clinical data. Women with at least one 50% diameter stenosis in a major coronary artery were classified as having "significant" CAD, those with a stenosis 20 to <50% as "minimal" CAD, and those with <20% stenosis in all coronary arteries as "no CAD"; a CAD severity score was also calculated as detailed previously.⁴

Laboratory testing

Serum creatinine was measured using the standard technique in the clinical laboratory at each site. Estimated glomerular filtration rate (eGFR, ml/min/1.73 m²) was estimated with use of the CKD-EPI equation after decreasing creatinine levels by 5% for calibration of the Modification of Diet in Renal Disease (MDRD) study. Lipid and other biochemical analyses were performed from fasting plasma at the WISE core laboratory (Cedars Sinai Medical Center, Los Angeles, California).

Follow up procedures

The initial follow-up was conducted by experienced site nurses or physicians through direct, telephone, and/or mail contact at 6 weeks, 1 year, and annually thereafter using a standardized scripted interview. Women were queried about symptoms, medication use, cardiovascular outcomes, hospitalizations, and diagnostic or revascularization procedures since last contact. For cases cared for at a WISE clinical center, patients' medical records were also reviewed. We did a validation study which examined hospital and clinic records from 113 WISE women who had reported 505 total events by telephone follow-up. Only 9 events (1.8%) required reclassification compared with those reported from telephone contact only. In the event of death, a death certificate was obtained. During this period, follow-up information was collected for a median of 6.0 years. For this analysis a major event was defined as a death, nonfatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure.

Subsequently, we conducted a National Death Index search for all women who were thought to be alive, and obtained additional death certificates. This extended the follow-up for mortality to a median 9.3 years (interquartile range 8.5–10.3 years). A team of WISE investigators masked to clinical information classified all deaths as cardiovascular or non-cardiovascular.

Statistical analysis

Continuous variables were summarized as means $\pm$ SD when normally distributed and otherwise as medians and inter-quartile ranges. Dichotomous variables were reported as percentages. Renal function was categorized as normal when eGFR was ≥ 90 ml/min/1.73 m², mild renal failure when eGFR was between 60 and 89 ml/min/1.73 m², and severe renal failure when eGFR was ≤ 59 ml/min/1.73 m². Since mean age differed comparing these renal function categories, we included age as a covariate when assessing other associations. Differences in baseline variables across eGFR groups were evaluated using analysis of variance. Variables that were not distributed normally were log-transformed. Time to adverse event was analyzed using the Kaplan-Meier method. Cox proportional hazards regression was used to analyze independent contributions of relevant covariates to adverse outcomes and to adjust for the effects of possible confounders. To derive the final models, univariate analysis of possible clinical and laboratory parameters was performed to identify predictors of adverse outcomes. Variables with a $p < 0.20$ and covariates were then entered into forward stepwise regression to obtain a preliminary model. This was followed by forcing into the model, one at a time, confounders previously associated with adverse outcomes in the WISE cohort^{5, 8} and retaining those with a $p < 0.05$ or if they modulated the major effects in the model. The final model was compared to the preliminary [nested] models by using the likelihood ratio test. All analyses were performed using the SAS 9.3 software. Statistical significance was set at $p < 0.05$.

RESULTS

Baseline characteristics

The mean age was 58 ± 12 (SD). The majority were Caucasian (82%) and post-menopausal (76%), 52% had used hormone replacement therapy (HRT), and 39% were using HRT at baseline. Most had risk factors for CAD: 66% with a family history, 60% with hypertension, 55% with dyslipidemia, 45% with metabolic syndrome, 25% with diabetes, and 20% current smoking. The majority (71%) had two or more of these risk factors, while 41% had three or more. However, although they were all symptomatic with chest pain and had signs of ischemia and risk factors, only 39% had obstructive CAD.

Pertinent baseline characteristics, by category of renal function, are summarized in Table 1. The mean age was 64 ± 12 years in those with severe CKD, 63 ± 11 years in those with mild CKD, and 53 ± 10 years in those with normal renal function. There were significantly more women with obstructive CAD in those with severe (63%) or moderate (45%) CKD compared with those with normal renal function (29%, $p = 0.002$). There was also a graded increase in severity of CAD with declining renal function, as evidenced by the severity scores. Renal failure was also associated with lower hemoglobin and high interleukin-6

levels while there were no statistically significant differences in c-reactive protein (CRP) values or serum amyloid A.

Adverse outcomes and renal function: univariate analyses

Among the 876 women, 177 (22.2%) died, 110 (82.3%) of cardiovascular-related causes. A total of 245 (28%) had a major adverse event during follow-up. We observed a graded increase in all-cause mortality (Figure 1), and cardiovascular mortality (Figure 2) associated with mild and severe renal failure vs. those with normal renal function. Age, diabetes, systolic blood pressure, CAD severity, resting heart rate, and smoking were significant univariate predictors of all-cause mortality. Interestingly, BMI, history of HRT, low-density lipoprotein, and total cholesterol were not.

Multivariable analyses

The final model confirmed eGFR as a strong and independent predictor of major adverse outcomes and all-cause and cardiovascular mortality even after adjustment for age, diabetes, hypertension, smoking, CAD severity, prior MI and resting heart rate (Table 2). Every 10 unit decrease in eGFR was associated with a 14% increased risk of all-cause mortality [AHR 1.14 (1.08–1.20) $p < 0.0001$], 16% increased risk of cardiovascular mortality [AHR 1.16 (1.09–1.23) $p < 0.0001$], and 9% increased risk of adverse cardiovascular events [AHR 1.09 (1.03–1.15) $p = 0.002$]. The strength of these relationships remained robust to changes in the total N or in the number of outcomes and different equations (MDRD and Cockcroft-Gault equations) used to calculate eGFR (data not shown).

CAD Severity Score, CKD, Mortality and Cardiovascular mortality

There was a graded increase in all cause (Figure-3A) as well as cardiovascular mortality (Figure-3B) with each stage of CKD and CAD severity score. This is consistent with the multivariate analysis which showed that the contribution of eGFR to total and cardiovascular mortality was independent of prior myocardial infarction and CAD severity score.

Discussion

Risk of adverse outcomes in women with CKD

Previous studies examining associations of mild renal failure with cardiovascular outcomes and mortality in women have yielded conflicting results. In the Framingham cohort, elevated serum creatinine was not associated with increased mortality in women. The Women's Health Initiative followed 27,939 health professionals aged ≥ 45 and found no associations between renal function and either all-cause mortality or cardiovascular mortality.⁹ However, this was a relatively younger and healthier population at low risk for cardiovascular outcomes vs the women in the WISE. Some small studies involving asymptomatic elderly post-menopausal women suggest that renal function was an independent predictor of mortality and that addition of renal function to the traditional Framingham risk score improved survival predictions.^{9–12} The role of renal function in modulating outcomes in a high-risk population of women with ischemic heart disease remains unknown. In the present study, we found that in symptomatic women with ischemia and risk factors for CAD, renal

failure was independently and significantly associated with higher risk of adverse cardiovascular outcomes and both cardiovascular and all-cause mortality.

Renal function, Obstructive CAD and Outcomes

The mechanism underlying the increased mortality in women with CKD remains unclear. We have previously found a strong independent relationship between mild renal insufficiency and angiographic severity of CAD in the WISE cohort.⁴ Autopsy studies, as well as prospective registries, have linked the extent and severity of coronary stenosis to increasing risk of myocardial infarction and death.¹³ However, these studies have predominantly enrolled men. Surprisingly, in the present study, renal function was a predictor of both coronary and all-cause mortality, independent of the severity of obstructive CAD. Cardiovascular mortality included heart failure and arrhythmic deaths which might be more proximate causes of death in patients with CKD than atherosclerosis.¹⁴ CKD is associated with structural and functional changes in the myocardium, as a consequence of pressure and volume overload as well as direct effects of aldosterone and uremic toxins.¹⁵ However, the WISE women had mild renal disease and little or no left ventricular hypertrophy. In these women, we think it is unlikely that myocardial disease contributed significantly to mortality. Interestingly, in individuals without obstructive CAD, others have suggested that renal function correlates with CFR even when adjusted for age, sex, and hypertension.¹⁶ Two recent studies in small Japanese cohorts of mostly men have suggested that in patients with CKD, CFR is an independent predictor of adverse cardiovascular outcomes.^{7, 17} However, whether or not this applies to women and other race/ethnic populations needs to be validated. Further mechanistic studies are essential to determine whether a generalized microvascular disorder might account for both renal dysfunction and coronary microvascular dysfunction or whether renal dysfunction predisposes to coronary microvascular dysfunction or vice versa.

Inflammation, functional status and cardiovascular outcomes

Chronic kidney disease has been associated with elevated levels of inflammatory markers such as CRP¹⁸, serum amyloid A (SAA)¹⁹, and interleukin-6 (IL-6). Systemic inflammation, manifested by high SAA, IL-6, or high sensitivity-CRP levels, may promote plaque destabilization as well as CKD. Although the ability of elevated inflammatory markers to predict coronary outcomes and mortality have yielded conflicting results in other populations²⁰, in the WISE women we have found a strong independent relationship between inflammation and future cardiovascular outcomes.²¹ In the present study, we did not find significant differences in inflammatory markers between different eGFR groups, when controlled for age. Also, these inflammatory markers did not contribute significantly to our model. This could be due, in part, to the fact that most of our women had only mild renal failure and there were only four subjects with eGFR<30 ml/min/1.73 m². If cardiovascular mortality was influenced by heart failure and arrhythmias, then novel biomarkers which reflect myocardial pathology such as galectin-3 or ST-2 might have been more predictive of adverse outcomes.¹⁵

Functional status, as reflected by the Duke Activity Status Index (DASI), was lower in women with severe CKD but not in those with mild CKD, compared with those with eGFR

90 ml/min/1.73 m². Although we have previously shown that DASI score is an independent predictor of mortality⁸, this self-reported functional status score did not appear to contribute significantly to the multivariate model, possibly due to collinearity with other risk factors.

Study limitations

Six percent of women had missing baseline Cr or demographic data needed to calculate eGFR and were not included in the study. However, these women did not differ from the rest of the WISE cohort in available clinical or laboratory parameters. Creatinine was measured by assays standard at the recruiting institution and prior to the Isotope Dilution Mass Spectrometry (IDMS) standards being established. However, we used a validated method to calibrate non-standardized serum creatinine measures and to ensure comparability.²² We only included baseline renal function and have no information about renal function over time. This is particularly relevant since women might be at increased risk of contrast induced nephropathy²³ and consideration must be given to minimizing the use of contrast and instituting preventive measures for contrast nephropathy. Moreover, progression of CKD might be predictive of coronary and/or all-cause mortality.²⁴ Proteinuria was not estimated, which could be important in light of recent suggestions that presence of proteinuria and CKD portends adverse impacts on vascular health.²⁵ Finally, these data were obtained in women referred for angiography to evaluate signs and symptoms of myocardial ischemia and may not be generalizable to the normal or other populations of women.

Conclusion

In a cohort of women with ischemia and no severe obstructive CAD, we found that even mild renal failure is a strong and independent predictor of all-cause and cardiac mortality even after controlling for all traditional risk factors for atherosclerosis. Interestingly, this mortality risk is not explained by severity of underlying obstructive CAD. This has important prognostic implications and underscores the need for better understanding the mechanistic basis of chest pain in women, including the contribution of coronary microvascular dysfunction to the increased cardiovascular morbidity/mortality documented in CKD patients.

Abbreviations and Acronyms

BMI	body mass index
CAD	coronary artery disease
CKD	chronic kidney disease
DASI	Duke Activity Status Index
eGFR	estimated glomerular filtration rate
HR	hazard ratio
HRT	hormone replacement therapy

WISE Women's Ischemia Syndrome Evaluation

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Figure 1. Kaplan-Meier Survival Analysis: Freedom from all-cause mortality
All-cause mortality in women with mild and severe renal failure increased compared with those with normal renal function. eGFR=estimated glomerular filtration rate

Figure 2. Kaplan-Meier Survival Analysis: Freedom from cardiovascular mortality
Cardiovascular mortality in women with mild and severe renal failure increased compared with those with normal renal function. eGFR=estimated glomerular filtration rate

A

B

Figure 3. Mortality, eGFR and Severity of CAD

(A) All-cause mortality stratified by eGFR and CAD Severity Score (B) Cardiovascular mortality stratified by eGFR and CAD Severity Score. eGFR=estimated glomerular filtration rate in ml/min/1.73 m²

Table I

Baseline characteristics of the women (stratified by eGFR)

Baseline Characteristic	eGFR Category (ml/min/1.73 m2)			Age-Adjusted P*
	59 (N=94)	60–89 (N=371)	90 (N=411)	
Demographics:				
Age (mean ± SD) yrs	64 ± 12	63 ± 11	53 ± 10	<0.0001
Post-menopausal	85%	89%	63%	<0.0001
Non-white	24%	13%	23%	0.005
Systolic blood pressure	146 ± 23	137 ± 20	134 ± 21	0.004
Pulse pressure	68 ± 18	62 ± 18	57 ± 16	0.022
Resting heart rate	74 ± 13	73 ± 12	74 ± 12	0.54
History of Hypertension	82%	61%	53%	0.0004
Total cholesterol	192 ± 48	197 ± 43	194 ± 46	0.49
Triglycerides [median (IQR)]	175 (95, 232)	134 (89, 190)	116 (76, 180)	0.041
LDL-C	106 ± 42	114 ± 37	110 ± 38	0.19
History of dyslipidemia	69%	56%	51%	0.15
Body mass index	29.6 ± 6.1	29.1 ± 6.4	30.2 ± 6.8	0.66
Waist/hip ratio	0.86 ± 0.10	0.85 ± 0.11	0.85 ± 0.10	0.59
Diabetes	44%	22%	23%	0.0003
Current smoker	13%	16%	26%	0.78
Ever smoker	56%	49%	58%	0.32
Family history of CAD	61%	64%	70%	0.38
Metabolic syndrome	59%	44%	43%	0.06
Functional capacity (DASI)	12.8 ± 9.2	20.7 ± 15.2	20.6 ± 14.9	<0.0001
Other blood markers:				
Hemoglobin	12.0 ± 1.4	13.0 ± 1.3	13.0 ± 1.3	<0.0001
Creatinine	1.69 ± 1.20	0.88 ± 0.11	0.69 ± 0.11	<0.0001
Fasting glucose (means)	131 ± 70	118 ± 60	115 ± 52	0.09
Inflammatory Markers:				
Hs-CRP [median (IQR)]	4.8 (2.0, 8.7)	3.6 (1.5, 8.9)	4.0 (1.8, 8.8)	0.75
IL6 [median (IQR)]	4.3 (2.4, 8.0)	3.0 (1.8, 5.8)	2.8 (1.7, 4.6)	0.007
SAA [median (IQR)]	0.82 (0.39, 1.34)	0.55 (0.33, 1.09)	0.53 (0.30, 0.91)	0.60
Angiographic findings:				
CAD (50% stenosis)	63%	45%	29%	0.002
CAD severity score [median (IQR)]	13.8 (8.0, 28.5)	9.2 (5.0, 20.2)	6.2 (5.0, 13.8)	0.004

CAD, coronary artery disease; DASI, Duke Activity Status Index; eGFR, estimated glomerular filtration rate; Hs-CRP, high-sensitivity c-reactive protein; IL6, interleukin 6; IQR, inter-quartile range; LDL-C, low-density lipoprotein cholesterol; SAA, serum amyloid A; SD, standard deviation.

* All *P*-values except age and menopausal status are age-adjusted. *P*-values for continuous variables estimated by one-way analysis of variance; for highly skewed variables (triglycerides, inflammatory markers, CAD severity score), *P*-values were obtained using their logarithmic transformations. *P*-values for frequencies estimated by logistic regression.

Table 2
Independent Predictors of All-Cause Mortality, Cardiovascular (CV) Mortality, and Major Adverse Outcomes

N=854	All-Cause Mortality (– 170 deaths)		CV Mortality (– 107 CV deaths)		Major Adverse Outcomes (– 236 Major Outcomes)	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
eGFR (per 10 units)	1.14 (1.08–1.20)	<0.0001	1.16 (1.09–1.23)	<0.0001	1.09 (1.03–1.15)	0.002
CAD severity (log)	1.55 (1.28–1.88)	<0.0001	1.60 (1.25–2.05)	0.0002	1.56 (1.32–1.84)	<0.0001
Diabetes	1.81 (1.31–2.51)	0.0003	2.41 (1.61–3.62)	<0.0001	1.66 (1.25–2.20)	0.0004
Ever smoked	1.73 (1.26–2.38)	0.0008	1.76 (1.18–2.34)	0.001	1.79 (1.36–2.36)	<0.0001
Hypertension	1.47 (1.02–2.11)	0.037	1.71 (1.05–2.78)	0.031	1.21 (0.90–1.62)	0.20
Resting heart rate (bpm)	1.02 (1.00–1.03)	0.010	1.02 (1.01–1.04)	0.004	1.02 (1.00–1.03)	<0.0001
Age	1.02 (1.00–1.04)	0.008	1.03 (1.00–1.04)	0.010	1.01 (1.00–1.03)	0.030
Prior MI	1.33 (1.01–1.74)	0.040	1.13 (0.80–1.61)	0.49	1.31 (1.04–1.66)	0.020

bpm, beats per minute; CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio.