Mild renal dysfunction and long-term adverse outcomes in women with chest pain: Results from the National Heart, Lung, and Blood Institute–sponsored Women's Ischemia Syndrome Evaluation (WISE)

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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 cohort according to estimated glomerular filtration rate (eGFR) (eGFR ≥90 mL/min per 1.73 m^2 [normal], 60-89 mL/min per 1.73 m^2 [mild CKD], ≤59 mL/min per 1.73 m^2 [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 few patients (39%). Even after adjusting for CAD severity, renal function remained a strong independent predictor of all-cause and cardiac mortality ($P < .001$). 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], $P < .0001$), 16% increased risk of cardiovascular mortality (AHR 1.16 [1.09-1.23], $P < .0001$), and 9% increased risk of adverse cardiovascular events (AHR 1.09 [1.03-1.15], $P = .002$).

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. (Am Heart J 2015;169:412-8.)

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 underrepresented 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 National Heart, Lung, and Blood Institute–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 WISE that mild serum creatinine 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

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suggested that CKD is associated with reduced CFR,[6] 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 no. 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.

A total of 876 women had data available to calculate estimated glomerular filtration rate (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 1 ≥50%-diameter stenosis in a major coronary artery were classified as having "significant" CAD, those with 20% to <50% stenosis 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, milliliters per minute per 1.73 m^2) was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation after decreasing creatinine levels by 5% for calibration of the Modification of Diet in Renal Disease study. Lipid and other biochemical analyses were performed from fasting plasma at the WISE core laboratory (Cedars-Sinai Medical Center, Los Angeles, CA).

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 that 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 (MI), nonfatal 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 of 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 noncardiovascular.

Statistical analysis

Continuous variables were summarized as means ± SD when normally distributed and otherwise as medians and interquartile ranges. Dichotomous variables were reported as percentages. Renal function was categorized as normal when eGFR was ≥90 mL/min per 1.73 m^2, mild renal failure when eGFR was between 60 and 89 mL/min per 1.73 m^2, and severe renal failure when eGFR was ≤59 mL/min per 1.73 m^2. Because 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 $P < .20$ and covariates were then entered into forward stepwise regression to obtain a preliminary model. This was followed by forcing into the model, 1 at a time, confounders previously associated with adverse outcomes in the WISE cohort[5,8] and retaining those with a $P < .05$ or if they modulated the major effects in the model. The final model was compared with the preliminary (nested) models by using the likelihood ratio test. All analyses were performed using the SAS 9.3 software (SAS, Cary, NC). Statistical significance was set at $P < .05$.

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