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Cardiovascular Risk Among Adults With Chronic Kidney Disease, With or Without Prior Myocardial Infarction

Keattiyoat Wattanakit, MD, MPH,* Josef Coresh, MD, PhD,†
Paul Muntner, PhD,‡ Jane Marsh, PhD,† Aaron R. Folsom, MD, MPH*
Minneapolis, Minnesota; Baltimore, Maryland; and New Orleans, Louisiana

OBJECTIVES This study sought to determine whether chronic kidney disease (CKD) should be considered a coronary heart disease (CHD) risk equivalent for cholesterol treatment.

BACKGROUND It is unclear whether patients with CKD have a risk of CHD events or cardiovascular disease (CVD) mortality equivalent to patients with a prior myocardial infarction (MI).

METHODS Using data from the ARIC (Atherosclerosis Risk in Communities) study, we categorized nondiabetic participants based on their average level of kidney function (estimated glomerular filtration rate ≥60 or 30 to 59 ml/min/1.73 m^2, which defines stage 3 CKD) and on prior MI (yes or no). Rates and relative risks (RR) of CHD (MI or fatal CHD) events (n = 653) and CVD mortality (n = 209) that occurred over 10 years were compared across these populations.

RESULTS Among 12,243 middle-age participants, 271 had stage 3 CKD. After adjustment for age, gender, race, and center, CHD incidence and CVD mortality rates per 1,000 person-years by presence of CKD and MI were 4.1 and 1.0 in the presence of neither condition, 8.0 and 3.4 in CKD only, 18.8 and 7.0 in MI only, and 30.8 and 18.0 in CKD and MI. After further adjustment for CVD risk factors, RR of CHD and CVD mortality were statistically significantly lower in subjects with CKD and no prior MI (RR = 0.44 [95% confidence interval (CI) 0.28 to 0.72] for CHD and RR = 0.46 [95% CI 0.24 to 0.90] for CVD mortality) than for subjects with no CKD and a prior MI.

CONCLUSIONS Stage 3 CKD confers CHD risk that is lower and not equivalent to a prior MI in this middle-aged, general, nondiabetic population. (J Am Coll Cardiol 2006;48:1183–9)

It is well established that chronic kidney disease (CKD) increases the risks of cardiovascular morbidity and mortality. These increased risks may be explained by: 1) excess comorbidities or cardiovascular disease (CVD) risk factors in patients with CKD; 2) therapeutic nihilism; 3) lack of benefit or excess toxicities from conventional CKD therapies; and 4) unique pathophysiology in the CKD population (1). As a result, the National Kidney Foundation Task Force on Cardiovascular Disease in Chronic Renal Disease (2) and other groups (3,4) have placed patients with CKD in the highest-risk group and recommended that the thresholds for risk factor intervention (e.g., drug therapy to lower low-density lipoprotein [LDL] cholesterol) in CKD patients be lower than in the general population. The National Cholesterol Education Program Adult Treatment Panel-III (NCEP ATP-III) guidelines (5) recommend that diabetes be considered a "risk equivalent" to coronary heart disease (CHD) and that patients with diabetes be treated with lipid-lowering therapies in a similar fashion as their counterparts with a prior myocardial infarction (MI). Chronic kidney disease might also be a CHD risk equivalent, but no study has directly assessed whether the risk of CHD, defined as MI or fatal CHD, and CVD mortality in patients with CKD is as high as in those with clinical CHD. Determining the equivalency in risk for CKD and CHD of future CVD events will assist in the future modification of treatment guidelines.

Therefore, we investigated in a nonreferral, community-derived population whether the rates of CHD and CVD mortality are equivalent in nondiabetic patients with: 1) stage 3 CKD (estimated glomerular filtration rate [eGFR] between 30 and 59 ml/min/1.73 m^2) and no history of prior MI; and 2) no CKD (eGFR ≥60 ml/min/1.73 m^2) and a history of prior MI.

METHODS

Study population. The ARIC (Atherosclerosis Risk in Communities) study (6) is a prospective investigation of the etiology and natural history of atherosclerosis. The study cohort comprised 15,792 white and black men and women ages 45 to 64 years at baseline in 1987 to 1989, recruited from four U.S. communities. The cohort underwent re-examination visits at roughly 3-year intervals.

From the *Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota; †Welch Center for Prevention, Epidemiology, and Clinical Research and the Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; and the ‡Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana. The Atherosclerosis Risk in Communities study was supported by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022. Dr. Wattanakit was supported by National Heart, Lung, and Blood Institute training grant T32-HL07779.

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Abbreviations and Acronyms

ARIC	= Atherosclerosis Risk in Communities study
CHD	= coronary heart disease
CI	= confidence interval
CKD	= chronic kidney disease
CVD	= cardiovascular disease
eGFR	= estimated glomerular filtration rate
IMT	= intima-media thickness
LDL	= low-density lipoprotein
MI	= myocardial infarction
NCEP ATP-III	= National Cholesterol Education Program Adult Treatment Panel-III
RR	= relative risk

Measurement of baseline risk factors. After informed consent, the ARIC participants underwent a standardized medical history and examination that included interviews, a fasting venipuncture, and carotid intima-media thickness (IMT). Participants were classified as never, former, or current smokers. Physical activity in sports was assessed using the Baecke physical activity questionnaire, with scores ranging from 1 (low) to 5 (high), and participants were categorized as low (<2) moderate (2 to 4), or high (≥4) (7). Participants were asked to bring all current medications to their ARIC study visit. Medication use was recorded, including cholesterol-lowering medications, beta-blockers, and angiotensin-converting enzyme inhibitors. Body mass index was calculated as weight in kilograms divided by the square of height in meters.

All participants had a standard 12-lead electrocardiogram at baseline. A prior MI was defined as a self-reported history of physician-diagnosed MI or a history of MI identified on the baseline electrocardiogram, which was characterized by the presence of a major Q-wave or a minor Q-wave with ischemic ST-T changes. Prevalent hypertension was defined as seated diastolic blood pressure ≥90 mm Hg, systolic blood pressure ≥140 mm Hg, or use of antihypertensive medications within the past 2 weeks. Prevalent diabetes mellitus was defined as a fasting serum glucose level ≥7.0 mmol/l (126 mg/dl), nonfasting glucose level ≥11.1 mmol/l (200 mg/l), participant report of a physician diagnosis of diabetes, or current use of any diabetes medication.

Fasting blood samples were drawn from an antecubital vein for measurement of total cholesterol, triglycerides, high-density lipoprotein cholesterol, and fibrinogen (8). The LDL cholesterol was calculated using the Freidewald equation. B-mode carotid ultrasound (Biosound 2000 II SA; Biosound Inc., Indianapolis, Indiana) evaluations were completed on bilateral segments of the extracranial carotid arteries using a standardized protocol (9,10). Mean far wall IMT was used for this analysis.

Ascertainment of the level of kidney function. To ensure that CKD was chronic and to decrease the effect of day-to-day variation in serum creatinine, we included only participants who had both visit 1 and visit 2 serum creatinine measured and calculated the average GFR estimate of the 2 visits. The coefficient of variation of serum creatinine on repeated measurement in a reliability substudy was 4.3%, and the reliability coefficient was 0.68 (11). Serum creatinine was measured using the modified kinetic Jaffe method. The level of kidney function was ascertained by eGFR calculated using the formula developed and validated in the MDRD (Modification of Diet in Renal Disease) study (12,13):

$$\mathrm{GFR} = 186.3 \times (\text{serum creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \times 1.212\ (\text{if black}) \times 0.742\ (\text{if female}).$$

To use this formula, serum creatinine was calibrated by subtraction of 0.24 (14). We assigned participants with a physiologically implausible high eGFR (n = 3) to a maximum of 200 ml/min/1.73 m^2.

Ascertainment of incident events. The ARIC study ascertained CHD events and mortality from CVD after baseline by identifying all hospitalizations and deaths. For patients hospitalized with potential MI, trained abstractors recorded the presenting signs and symptoms, including chest pain, cardiac enzymes, and related clinical information. Out-of-hospital fatal CHD events were investigated by an interview with one or more next of kin and a questionnaire completed by the patient's physician. The CHD events were validated by a committee of physicians using standardized criteria (15).

A CHD event was defined as a definite or probable hospitalized MI or definite fatal CHD. The CVD mortality was based only on the death certificate and included any underlying cause of death using International Classification of Diseases-9th Revision codes 390 to 459.

Statistical analysis. Of the 15,792 ARIC study participants, we included 13,980 participants who had serum creatinine measured at both visit 1 and visit 2 and who did not have CHD events or CVD death during this interval. Of these, we excluded 192 participants with missing information on prior MI, 85 of race other than black or white, 4 with stage 4 CKD (eGFR of 15 to 29 ml/min/1.73 m^2), and 8 with kidney failure (eGFR <15 ml/min/1.73 m^2). Because diabetes is already considered a CHD risk equivalent, we excluded 1,448 participants with prevalent diabetes, leaving a total of 12,243 participants for analysis.

We followed up all participants through the year 2001. For the CHD event analysis, follow-up time was calculated from the visit 2 date to the time of diagnosis of a first CHD event for those with no history of a prior MI and to the time of diagnosis of a recurrent CHD event for those with a history of prior MI. For participants who did not have a CHD event, follow-up ended on the date of last known contact or December 31, 2001. For the CVD mortality analysis, follow-up time was calculated from the visit 2 date to the date of death, date of last known contact, or December 31, 2001.