

Renal Function and Risk of Myocardial Infarction in an Elderly Population

The Rotterdam Study

Jasper J. Brugts, MSc; Annemarieke M. Knetsch, MD; Francesco U. S. Mattace-Raso, MD, PhD; Albert Hofman, MD, PhD; Jacqueline C. M. Witteman, PhD

Background: Renal insufficiency is a risk factor for cardiovascular disease in patients with renal disease or coronary heart disease; however, it is unknown whether renal function is an independent predictor of cardiovascular disease in the general population.

Methods: We investigated whether the level of renal function, estimated by glomerular filtration rate, was associated with the risk of incident myocardial infarction among 4484 apparently healthy subjects in the Rotterdam Study (mean age, 69.6 years). We estimated the glomerular filtration rate by Cockcroft-Gault and abbreviated modification of diet in renal disease equations and used Cox regression analysis to estimate hazard ratios adjusted for cardiovascular risk factors, atherosclerosis, and medication use.

Results: During the follow-up period (mean, 8.6 years), 218 subjects (4.9%) had a myocardial infarction. A 10 mL/min per 1.73 m² decrease in glomerular filtration rate was

associated with a 32% increased risk of myocardial infarction ($P < .001$). Compared with subjects in the fourth quartile, the multivariate-adjusted hazard ratios for the risk of myocardial infarction increased from 1.64 (95% confidence interval [CI], 1.03-2.59) in the third quartile to 1.94 (95% CI, 1.21-3.10) in the second quartile and 3.06 (95% CI, 1.80-5.19) in the quartile with the lowest glomerular filtration rate estimated by the Cockcroft-Gault equation. Using the abbreviated modification of diet in renal disease equation, the risk estimates for the third to first quartiles were 1.34 (95% CI, 0.89-2.01), 1.66 (95% CI, 1.14-2.49), and 1.90 (95% CI, 1.25-2.90), respectively.

Conclusions: The present study shows that renal function is a graded and independent predictor of the development of myocardial infarction in an elderly population. Early detection of decreased renal function may identify subjects who are at heightened risk of coronary heart disease.

Arch Intern Med. 2005;165:2659-2665

Author Affiliations: Departments of Epidemiology and Biostatistics (Mr Brugts and Drs Knetsch, Mattace-Raso, Hofman, and Witteman) and Internal Medicine (Dr Mattace-Raso), Erasmus Medical Center, Rotterdam, the Netherlands.

RECENT STUDIES¹⁻⁷ HAVE shown that renal failure is an independent risk factor for cardiovascular mortality and morbidity in high-risk populations such as patients with chronic kidney or cardiovascular disease and patients with cardiovascular risk factors. It remains uncertain whether the level of renal function within asymptomatic ranges predicts the risk of cardiovascular disease in the general population. Until now, population-based studies⁸⁻¹² on renal insufficiency and cardiovascular disease gave conflicting results. Most prospective studies have been conducted with middle-aged populations. In some of these studies,^{8,9} renal insufficiency has been associated with increased risk of cardiovascular disease. In others,^{10,11} renal insufficiency was not an independent predictor after adjustment for cardiovascular risk factors. The Cardiovascular Health Study^{12,13}

(CHS), a prospective population-based study of subjects 65 years or older, is the only study that has investigated the association between renal insufficiency and cardiovascular disease in elderly individuals. In this study, an increased risk of cardiovascular disease was found in subjects with elevated serum cystatin C, whereas a much weaker association

See also page 2666

was found between serum creatinine level and risk of cardiovascular disease. No significant association between glomerular filtration rate (GFR) and risk of myocardial infarction was found.^{12,13}

The elderly population is growing and, because renal function decreases with age, renal insufficiency will become an increasingly important problem. Therefore, we examined the association between renal function, estimated by glomerular filtration rate (eGFR), and risk of myocardial infarc-

tion in the Rotterdam Study, a large population-based study in men and women 55 years and older.

METHODS

STUDY POPULATION

The Rotterdam Study¹⁴ is an on-going prospective population-based cohort study aimed at assessing the incidence and determinants of chronic diseases in the elderly population. In short, all inhabitants 55 years or older of Ommoord, a suburb of Rotterdam, the Netherlands, were invited to participate in the study. A total of 7983 men and women (response rate, 78%) agreed to participate, and 6950 participants visited the research center for the required physical examination. The main reason for not visiting the research center was that an individual lived in a nursing home. Baseline data were collected from March 1990 to July 1993. The medical ethics committee of the Erasmus Medical Center, Rotterdam, approved the study, and written informed consent was obtained from all participants.

BASELINE EXAMINATION

At baseline, a trained research assistant obtained information on smoking habits and medication use from each subject during a home interview. Individuals were classified as never having smoked, a past smoker, or a current smoker. Clinical measurements were obtained during the visit to the research center. Height and weight were measured, and body mass index was calculated as weight in kilograms divided by the square of height in meters.² Blood pressure was calculated as the average of 2 consecutive measurements at the right brachial artery with a random-zero sphygmomanometer. Serum total cholesterol was measured by an automated enzymatic procedure in a nonfasting blood sample. Serum high-density lipoprotein cholesterol was measured similarly after precipitation of the non-high-density lipoprotein fraction. Diabetes mellitus was defined as the use of antidiabetic medication and/or a random or postload serum glucose level above 198.2 mg/dL (11.0 mmol/L). C-reactive protein levels were measured by enzyme-linked high-sensitivity immunoassays. Carotid intima media thickness, as a measurement of generalized atherosclerosis, was assessed by ultrasonography. We computed values of intima media thickness by averaging the anterior and posterior walls of the left and right common carotid arteries (distal).¹⁵ Prevalent myocardial infarction at baseline was considered present in the case of a self-report, verified by a general practitioner or hospital discharge data, or confirmed by electrocardiogram measurements.¹⁶

ASSESSMENT OF RENAL FUNCTION

Serum creatinine was assessed by a nonkinetic alkaline picrate (Jaffe) method.¹⁷ Creatinine clearance was computed with the Cockcroft-Gault¹⁸ equation and standardized for body surface area using the Dubois formula.¹⁹ Creatinine clearance generally exceeds GFR by 10% to 15% due to urinary creatinine derived from tubular secretion.²⁰ The eGFR was therefore calculated using a correction factor of 0.90. In an additional analysis we used the abbreviated modification of diet in renal disease (MDRD) equation.²¹

ASSESSMENT OF INCIDENT MYOCARDIAL INFARCTION

After all baseline examinations were performed, general practitioners in the research area (Ommoord) reported incident cardiovascular events to the study center. An incident

myocardial infarction was considered to have occurred when the event led to hospitalization and the hospital discharge records indicated a diagnosis of myocardial infarction based on symptoms, electrocardiographic recordings, and repeated laboratory investigations during the patient's hospital stay. Research assistants collected all information by checking medical records at the general practitioners' offices, including discharge reports from medical specialists. Subsequently, 2 research physicians independently coded all reported events according to the *International Classification of Diseases, 10th Revision*. If research physicians disagreed on diagnoses, these were discussed to reach consensus. Finally, an expert in the field of cardiology reviewed all events. In case of disagreement between the medical expert and the research physicians, the expert's judgment was considered final. Information on the vital status of the participants was obtained at regular intervals from the municipal authorities in Rotterdam.

POPULATION FOR ANALYSIS

Of the 6950 subjects who visited the research center, 808 (12%) were excluded because of prevalent myocardial infarction. Blood samples for measurement of serum creatinine level were available for 4568 (74.4%) of the remaining 6142 subjects. Data were available on eGFRs for 4484 (73.0%) of 6142 subjects. Baseline data on cardiovascular risk factors were missing for 212 subjects (<5%). For missing data on cardiovascular risk factors, the mean of the study population was imputed. Of the study population, 8 individuals (0.1%) were lost to follow-up. For these subjects, the follow-up time was computed until the last date of contact. Follow-up data on incident myocardial infarction were completed until January 1, 2002.

STATISTICAL ANALYSIS

Cox proportional hazard regression analysis was used to estimate hazard ratios for incident myocardial infarction with corresponding 95% confidence intervals (CIs). Analyses were conducted with eGFRs divided into sex-specific quartiles. The quartile with the highest eGFR was used as the reference quartile. Analyses were conducted for crude values (model 1), adjusted for age, sex, body mass index, systolic and diastolic blood pressure, smoking habits, total and high-density lipoprotein cholesterol, and diabetes mellitus (model 2) and further adjusted for use of cardiac medication (angiotensin-converting enzyme inhibitors, diuretics, and β -blocking agents) and nonsteroidal anti-inflammatory drugs, C-reactive protein, and carotid intima media thickness (full model). The association between the eGFR and the risk of myocardial infarction was also assessed with the eGFR as a continuous variable. Tests for trend were performed, using the quartiles of the eGFR as a categorical measurement. In an additional analysis, the eGFR was estimated using the abbreviated MDRD equation rather than the Cockcroft-Gault equation. Kaplan-Meier survival plots of quartiles of the eGFR in relation to the risk of myocardial infarction were examined with log-rank test. The attributable risk and population-attributable risk percentage of renal insufficiency associated with myocardial infarction were calculated using an eGFR below 60 mL/min per 1.73 m² as the cutoff point.²² For purposes of comparison, we calculated the attributable risk and population-attributable risk of the 4 major, classical cardiovascular risk factors. All measurements of association are presented with 95% CIs. A *P* value of less than .05 was considered statistically significant. All analyses were performed using SPSS statistical software (version 12.0; SPSS Inc, Chicago, Ill) for Windows.

Table 1. Baseline Characteristics of the Study Population*

Characteristic	All Subjects (N = 4484)	Men (n = 1628)	Women (n = 2856)
Age, y	69.6 ± 8.8	68.8 ± 8.1	70.1 ± 9.1
Body mass index†	26.2 ± 3.7	25.6 ± 3.0	26.6 ± 4.1
Systolic blood pressure, mm Hg	139.6 ± 22.3	139.4 ± 21.9	139.7 ± 22.5
Diastolic blood pressure, mm Hg	73.8 ± 11.7	74.9 ± 12.1	73.2 ± 11.4
Current smoker	1044 (23.3)	505 (31.0)	539 (18.9)
Former smoker	1738 (38.8)	963 (59.2)	775 (27.1)
Total cholesterol, mg/dL (mmol/L)	254.8 ± 46.3 (6.6 ± 1.2)	243.2 ± 46.3 (6.3 ± 1.2)	262.5 ± 46.3 (6.8 ± 1.2)
HDL cholesterol, mg/dL (mmol/L)	50.2 ± 15.4 (1.3 ± 0.4)	46.3 ± 11.6 (1.2 ± 0.3)	54.1 ± 15.4 (1.4 ± 0.4)
Diabetes mellitus	447 (10.0)	152 (9.3)	295 (10.3)
C-reactive protein, mg/L	3.1 ± 5.7	3.4 ± 5.5	2.9 ± 5.8
Cardiac medication	1335 (29.8)	387 (23.8)	948 (33.2)
ACE inhibitors	202 (4.5)	88 (5.4)	114 (4.0)
Diuretics use	661 (14.7)	137 (8.4)	524 (18.3)
β-Blockers use	597 (13.3)	196 (12.0)	401 (14.0)
NSAID use	366 (8.2)	91 (5.6)	275 (9.6)
Body surface area, m ² ‡	1.8 ± 0.2	1.9 ± 0.1	1.7 ± 0.1
Carotid intima media thickness, mm	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1

Abbreviations: ACE, angiotensin-converting enzyme; HDL, high-density lipoprotein; NSAID, nonsteroidal anti-inflammatory drug.

*Data are given as numbers (percentages) for dichotomous variables and mean ± SD for continuous variables.

†Calculated as weight in kilograms divided by the square of height in meters.

‡Body surface area is computed by $0.007184 \times \text{weight}^{0.425}$ (in kilograms) $\times \text{height}^{0.725}$ (in meters).

Table 2. Hazard Ratios (HRs) for Incident Myocardial Infarction Associated With eGFR Levels Based on the Cockcroft-Gault Equation

Quartile	eGFR*	Total/Events	HR (95% CI)		
			Unadjusted HRs	Traditional CVD Risk Factors†	Full Model‡
Men					
Fourth	81.42	407/19	1.00	1.00	1.00
Third	68.19	407/29	1.56 (0.88-2.78)	1.60 (0.87-2.89)	1.60 (0.89-2.89)
Second	59.43	407/35	1.97 (1.13-3.45)	2.10 (1.14-3.85)	2.06 (1.12-3.79)
First	45.93	407/42	3.04 (1.77-5.24)	3.17 (1.58-6.34)	2.96 (1.48-5.95)
Women					
Fourth	79.79	714/13	1.00	1.00	1.00
Third	65.24	714/19	1.51 (0.74-3.05)	1.71 (0.82-3.54)	1.64 (0.78-3.42)
Second	55.92	714/23	1.88 (0.95-3.71)	1.87 (0.88-3.96)	1.74 (0.81-3.70)
First	42.18	714/38	4.02 (2.14-7.56)	3.43 (1.50-7.87)	3.34 (1.45-7.66)
Overall					
Fourth	80.38	1121/32	1.00	1.00	1.00
Third	66.36	1121/48	1.54 (0.98-2.41)	1.64 (1.04-2.60)	1.64 (1.03-2.59)
Second	57.19	1121/58	1.92 (1.25-2.96)	1.98 (1.24-3.17)	1.94 (1.21-3.10)
First	43.05	1121/80	3.42 (2.27-5.16)	3.22 (1.90-5.47)	3.06 (1.80-5.19)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate.

*The mean of eGFR for descending quartiles of eGFR. The risk estimates for using eGFR as continuous variable are 1.30 (1.11-1.50) for men, 1.37 (1.16-1.59) for women, and 1.32 (1.18-1.47) for the total group for every 10 mL/min per 1.73 m².

†Adjusted for age, sex, BMI, systolic and diastolic blood pressure, smoking habits, total and high-density lipoprotein cholesterol levels, and diabetes mellitus.

‡Adjusted for age, sex, BMI, systolic and diastolic blood pressure, smoking habits, total and high-density lipoprotein cholesterol levels, diabetes mellitus, use of cardiac medication (angiotensin-converting enzyme inhibitors, diuretics, and β-blocking agents) and nonsteroidal anti-inflammatory drugs, C-reactive protein level, and carotid intima media thickness.

RESULTS

Baseline characteristics of the study population are shown in **Table 1**. The mean ± SD age was 69.6 ± 8.8 years, and 63.7% of the population were women. The eGFRs (mean ± SD, 61.9 ± 14.7) ranged from 6.1 to 142.6 mL/min per 1.73 m². A mild degree of renal insufficiency, with an eGFR between 60 and 89, was

present in 2317 subjects (51.7%). The mean ± SD follow-up time was 8.6 ± 2.8 years. During follow-up, 38 479 person-years were collected. Incident myocardial infarction occurred in 218 subjects (4.9%; 125 men and 93 women). The risk of myocardial infarction is significantly increased in the lower 3 quartiles compared with the highest quartile of eGFR (*P* value for trend, <.001) (**Table 2**). Risk estimates using

Table 3. Hazard Ratios (HRs) for Incident Myocardial Infarction Associated With eGFR Levels Based on the Abbreviated MDRD Formula

Quartile	eGFR*	Total/Events	HR (95% CI)		
			Unadjusted	Traditional CVD Risk Factors†	Full Model‡
Fourth	94.21	1121/44	1.00	1.00	1.00
Third	78.41	1121/50	1.12 (0.74-1.67)	1.35 (0.90-2.03)	1.34 (0.89-2.01)
Second	69.46	1121/58	1.34 (0.90-1.98)	1.70 (1.14-2.55)	1.66 (1.14-2.49)
First	55.87	1121/66	1.68 (1.15-2.46)	1.99 (1.31-3.03)	1.90 (1.25-2.90)
Total	74.49				

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease.

*The mean of eGFR for the descending quartiles of eGFR.

†Adjusted for age, sex, BMI, systolic and diastolic blood pressure, smoking habits, total and high-density lipoprotein cholesterol levels, and diabetes mellitus.

‡Adjusted for age, sex, BMI, systolic and diastolic blood pressure, smoking habits, total and high-density lipoprotein cholesterol levels, diabetes mellitus, use of cardiac medication (angiotensin-converting enzyme inhibitors, diuretics, and β -blocking agents) and nonsteroidal anti-inflammatory drugs, C-reactive protein level, and carotid intima media thickness.

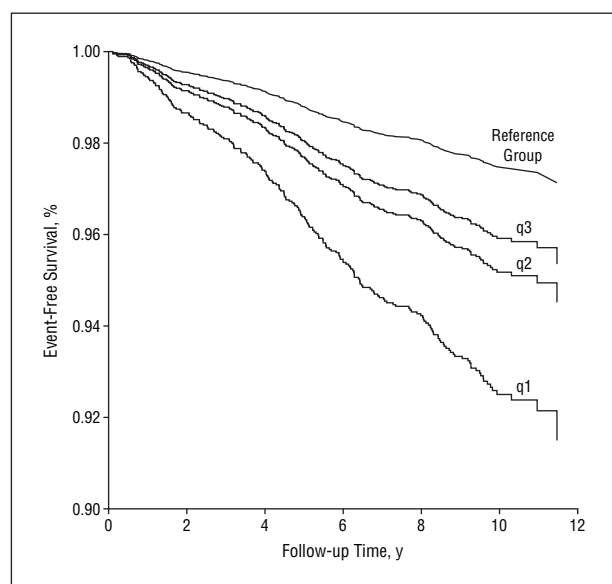


Figure. Event-free survival curves for quartiles of estimated glomerular filtration rate (eGFR) (Cockcroft-Gault equation). Kaplan-Meier survival curves were used to calculate the event-free survival curves in the descending quartiles of eGFR. The lines correspond to the survival curves of the fourth quartile as reference group, third quartile (q3), second quartile (q2), and the lowest quartile of the eGFR (q1), respectively.

quartiles of eGFRs based on the abbreviated MDRD equation were somewhat smaller, but a similar trend was seen (Table 3). In the following analyses, the eGFR is based on the Cockcroft-Gault equation. The survival curves for quartiles of eGFRs are shown in the Figure. The log-rank test gave P values of .056, .002, and less than .001, respectively, corresponding to descending quartiles of eGFRs. The attributable and population-attributable risks of renal insufficiency associated with myocardial infarction were 32.8% and 14.7%, respectively (Table 4). If renal insufficiency is assumed to be causally related to myocardial infarction, our findings suggest that it contributed to 32.8% of the cases affected by renal insufficiency and that it was involved in the pathogenesis of 14.7% of all myocardial infarctions in the study sample.

COMMENT

In this population-based cohort study of adults 55 years or older, we found that impaired renal function was common and associated with an increased risk of myocardial infarction. Even the earlier stages of renal function loss, before there are any symptoms of renal disease, are associated with an increased risk of myocardial infarction. This association is independent of cardiovascular risk factors and atherosclerosis. The population-attributable risk is substantial and within range of traditional cardiovascular risk factors.

A previous study⁷ demonstrated the association between renal insufficiency and adverse outcomes in patients after a myocardial infarction. Relatively few studies⁸⁻¹² have evaluated the relationship between renal function and risk of incident coronary heart disease in the general population. The results of these studies were inconsistent. Most studies⁸⁻¹¹ reported on the association between renal function and cardiovascular disease in middle-aged subjects. The Framingham Heart Study¹⁰ and the National Health and Nutrition Examination Survey¹¹ (NHANES I) found no association between elevated serum creatinine level and cardiovascular events after adjustment for cardiovascular risk factors. The Atherosclerotic Risk in Communities study⁹ in subjects aged 45 to 64 years (mean age, 54.2 years) showed an association between renal insufficiency and atherosclerotic cardiovascular disease as a composite outcome. Although the investigators in that study found an increased risk of 1.38 (95% CI, 1.02-1.87) for subjects with an eGFR below 60 mL/min per 1.73 m² and a risk of 1.16 (95% CI, 1.00-1.34) for subjects with an eGFR above 60 mL/min per 1.73 m² compared with subjects with an eGFR above 90 mL/min per 1.73 m², these risks are relatively small compared with those found in the present study and were not adjusted for C-reactive protein and a measurement of atherosclerosis. No separate analysis of myocardial infarction was performed. A recent study⁸ in a middle-aged population of 1 120 295 insured adults 20 years or older (mean age, 52 years) reported an in-

Table 4. Attributable Risk and Population-Attributable Risk Percentages Associated With Incident Myocardial Infarction, Based on Cockcroft-Gault Equation

Risk Factor	Prevalence, %	Age-Adjusted Hazard Ratio*	Attributable Risk, %	Population-Attributable Risk, %
Diabetes mellitus	10.0	1.6	38.1	3.8
Hypertension	25.6	1.5	34.5	8.8
Smoking†	23.3/38.8	1.9/1.6	48.2/38.8	11.2/15.0
Hypercholesterolemia‡	60.9	1.4	26.8	16.3
Renal insufficiency§	44.9	1.5	32.8	14.7

*Determined by Cox proportional hazards regression analysis. Hypertension defined as systolic blood pressure of at least 160 mm Hg and/or diastolic blood pressure of at least 100 mm Hg, and/or use of blood pressure-lowering medication.

†Current smoker compared with those who never smoked or past smoker compared with those who have never smoked.

‡Hypercholesterolemia, defined as total cholesterol level of 239.4 mg/dL (6.2 mmol/L) or higher.

§Renal insufficiency with an estimated glomerular filtration rate of 60 mL/min per 1.73 m² as the cutoff point.

creased risk of cardiovascular events (heart failure, stroke, coronary heart disease, and peripheral artery disease) in subjects with chronic kidney disease, defined as an eGFR below 60 mL/min per 1.73 m². This risk⁸ increased substantially at an eGFR below 45 mL/min per 1.73 m². Although we support their results, our study differs in several important aspects. First, we found an increased risk at higher levels of renal function, namely, in asymptomatic subjects with an eGFR well above the level of patients with chronic kidney disease. Second, the authors of the California study⁹ were not able to adjust for smoking, cholesterol and C-reactive protein levels, blood pressure, use of cardiac medication, and measurements of atherosclerosis. In addition, we excluded subjects with a history of myocardial infarction at baseline.

Our study is the first to show a graded and independent association between renal function and the risk of myocardial infarction in an elderly population. The only previous study that evaluated the association between renal function and cardiovascular disease in an elderly population was the CHS. The CHS (mean age of subjects, 72.9 years) found an association between elevated serum creatinine level and total cardiovascular disease as a combined outcome. In that study,¹² a 1.5 times increased risk was found for subjects with elevated serum creatinine level, defined as 1.5 mg/dL (132.6 μmol/L) or higher in men or 1.3 mg/dL (114.9 μmol/L) or higher in women, compared with subjects with creatinine levels in the reference range. In contrast with our study, however, no association of elevated serum creatinine level with incident myocardial infarction was found after adjusting for cardiovascular risk factors.¹² A recent report¹³ of the CHS concluded that serum cystatin C level is a stronger predictor of the risk of cardiovascular outcomes than serum creatinine level and eGFR. The study showed a relationship between serum cystatin C level and the risk of death from cardiovascular disease; the association of cystatin C level with incident myocardial infarction was less strong than was the case for association with mortality outcomes. In multivariate analysis, only a subgroup of the highest quintile (quintile subgroup 5c) was at significantly increased risk of myocardial infarction. Creatinine level and eGFR estimated by MDRD equation had no significant association with myocardial infarction in either unadjusted or adjusted analyses. Risk

estimates were not adjusted for measurements of atherosclerosis, low-density lipoprotein cholesterol, or history of smoking.¹³ We have no explanation for the discrepancy with our findings. However, there are important differences between the 2 studies in population (the CHS population is somewhat older), ascertainment methods, and analysis.

The reason why mild renal insufficiency is associated with an increased risk of cardiovascular disease in our study is not clear. It has been suggested the increased risk can be explained by co-occurrence of a high prevalence of cardiovascular risk factors at baseline.^{5,10} In that case, renal insufficiency would be a marker for cardiovascular risk factors and their severity rather than an independent risk factor. However, we still observed an independent association after adjusting for cardiovascular risk factors. Another possible explanation is the presence of atherosclerosis, commonly thought to preexist in individuals with mild renal insufficiency. However, after adjustment for carotid intima media thickness, as a measurement of generalized atherosclerosis, an increased risk remained associated with lower levels of renal function. Therefore, preexisting atherosclerotic vascular disease cannot fully explain the relationship, although the possibility exists that it is mediated by small vessel disease rather than large vessel disease. Finally, renal insufficiency itself might initiate and accelerate cardiovascular disease.

The US National Kidney Foundation has provided guidelines for the assessment of renal function. Definitions of stages 1 to 5 of renal function correspond to eGFR levels of 90 or higher (reference range), 60 to 89, 30 to 59, 15 to 29, and less than 15 mL/min per 1.73 m². Stage 3 is the first stage at which a patient shows symptoms of renal insufficiency, and it is considered the cutoff point for chronic kidney disease.² The results of our study show an increased risk of myocardial infarction starting at earlier stages of renal function loss than commonly thought, namely, well above the levels of chronic kidney disease. Using the Cockcroft-Gault equation, the third quartile with a mean eGFR of 66.3 mL/min per 1.73 m² was associated with a 64% increased risk of myocardial infarction. An additional analysis with the MDRD equation showed a 66% increased risk of myocardial infarction for subjects in the second quartile with a mean eGFR of 69.5 mL/min per 1.73 m². Both equations show a significantly in-

creased risk at these mildly decreased eGFR levels, with the difference in size of risk estimates related to the difference in mean eGFR levels of the quartiles. These mildly decreased eGFR levels, corresponding to stage 2, represent subjects at an early stage of renal insufficiency, without symptoms or signs of renal function loss. With descending quartiles of eGFR, the risk of myocardial infarction increased gradually to a 2-fold (MDRD equation; mean eGFR, 54) to a 3-fold (Cockcroft-Gault equation; mean eGFR, 44 mL/min per 1.73 m²) increased risk.

A mild degree of renal insufficiency with an eGFR of 60 to 89 mL/min per 1.73 m² (based on the Cockcroft-Gault equation) was present in 51% of the study population. In aging populations, such as that of Western Europe, mild degrees of renal insufficiency will be progressively more important because renal function declines rapidly with age but life expectancy is increasing. Early detection of decreased renal function, using eGFR measurements as a relatively simple screening method, may identify subjects at high risk of coronary heart disease. Because renal insufficiency is associated with a high prevalence of traditional risk factors, early risk factor reduction measures may be of benefit in these subjects. Therefore, the early stages of renal insufficiency may be a key target to prevent worsening renal function as well as to reduce the risk of cardiovascular disease. Some of the factors detrimental to kidney function, such as smoking, dyslipidemia, and elevated blood pressure, can be modified. Recent studies^{3,23} report that angiotensin-converting enzyme inhibitors may have renoprotective effects and delay the progression of renal insufficiency.

Because the subjects in our study were predominantly white, the generalizability of the study to other racial groups is limited. Moreover, data on proteinuria were unavailable in this database because urinalyses were not performed in the Rotterdam Study.¹⁴ Microalbuminuria is an early marker of diabetic nephropathy and cardiovascular disease; however, a recent study²⁴ showed that the GFR is a predictor of cardiovascular events independent of the presence of microalbuminuria in patients with asymptomatic diabetes mellitus. The CHS study found that cystatin C was a stronger predictor of cardiovascular events than serum creatinine level and eGFR. Cystatin C levels were not available in our study, but the use of an eGFR in our study provided risk estimates for myocardial infarction stronger than those based on cystatin C levels in the CHS study.¹³ A study on the diagnostic accuracy of eGFR formulas and cystatin C concluded that cystatin C is superior to serum creatinine in estimating renal function but similar to estimates of GFR by Cockcroft-Gault or MDRD equations.²⁵ Whether serum cystatin C has potential clinical value and could be a useful prognostic tool in the evaluation of elderly patients needs to be confirmed in future studies.^{13,25} The use of serum creatinine alone may lead to some underrecognition of renal insufficiency, particularly in elderly subjects, because muscle mass tends to decline with age.^{26,27} We used the Cockcroft-Gault equation corrected for body surface area and tubular secretion to estimate eGFR more accurately in elderly individuals.^{18,20,26,27} The new MDRD equation has not yet been validated in elderly individuals and in healthy subjects, and the accuracy of this for-

mula in these populations is still being discussed.^{21,28,29} Using the MDRD equation in our study yielded similar results.

In this prospective, population-based study of older individuals, we found that renal insufficiency was highly prevalent and predicted the onset of myocardial infarction even in subjects without symptoms or signs of renal disease. The population-attributable risk was substantial and within the range of that of traditional cardiovascular risk factors. Therefore, the impact of renal insufficiency on the development of coronary heart disease may be larger than commonly thought. This suggests that assessment and treatment of decreased renal function at an early stage may help in the prevention of coronary heart disease.

Accepted for Publication: July 1, 2005.

Correspondence: Jacqueline C. M. Witteman, PhD, Department of Epidemiology and Biostatistics, Erasmus Medical Center, PO Box 1738, 3000 DR Rotterdam, the Netherlands (j.witteman@erasmusmc.nl).

Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosure: None.

Funding/Support: The Rotterdam Study is supported in part by the NESTOR program for geriatric research in the Netherlands (Ministry of Health and Ministry of Education), the Municipality of Rotterdam, the Netherlands Heart Foundation, the Netherlands Organization for Scientific Research, and the Rotterdam Medical Research Foundation.

Acknowledgment: We gratefully acknowledge the contribution to the data collection by field workers, ultrasonography and laboratory technicians, and computer assistants. We are indebted to the general practitioners of the Ommoord area in Rotterdam for providing information on incident cardiovascular disease.

REFERENCES

1. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: statement from the American Heart Association councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. *Circulation*. 2003; 108:2154-2169.
2. Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med*. 2003;139:137-147.
3. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. *Ann Intern Med*. 2001;134:629-636.
4. Beddhu S, Allen-Brady K, Cheung AK, et al. Impact of renal failure on the risk of myocardial infarction and death. *Kidney Int*. 2002;62:1776-1783.
5. Shlipak MG, Fried LF, Crump C, et al. Cardiovascular disease risk status in elderly persons with renal insufficiency. *Kidney Int*. 2002;62:997-1004.
6. Edwards MS, Craven TE, Burke GL, Dean RH, Hansen KJ. Renovascular disease and the risk of adverse coronary events in the elderly: a prospective population-based study. *Arch Intern Med*. 2005;165:207-213.
7. Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med*. 2004; 351:1285-1295.
8. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004; 351:1296-1305.

9. Manjunath G, Tighiouart H, Ibrahim H, et al. Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. *J Am Coll Cardiol*. 2003;41:47-55.
10. Culeton BF, Larson MG, Wilson PW, Evans JC, Parfrey PS, Levy D. Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. *Kidney Int*. 1999;56:2214-2219.
11. Garg AX, Clark WF, Haynes RB, House AA. Moderate renal insufficiency and the risk of cardiovascular mortality: results from the NHANES I. *Kidney Int*. 2002; 61:1486-1494.
12. Fried LF, Shlipak MG, Crump C, et al. Renal insufficiency as a predictor of cardiovascular outcomes and mortality in elderly individuals. *J Am Coll Cardiol*. 2003; 41:1364-1372.
13. Shlipak MG, Sarnak MJ, Katz R, et al. Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med*. 2005;352:2049-2060.
14. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol*. 1991;7:403-422.
15. Iglesias del Sol A, Bots ML, Grobbee DE, Hofman A, Witteman JC. Carotid intima-media thickness at different sites: relation to incident myocardial infarction. *Eur Heart J*. 2002;23:934-940.
16. de Bruyne MC, Mosterd A, Hoes AW, et al. Prevalence, determinants, and misclassification of myocardial infarction in the elderly. *Epidemiology*. 1997;8:495-500.
17. Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: new insights in old concepts. *Clin Chem*. 1992;38:1933-1953.
18. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31-41.
19. Wang Y, Moss J, Thisted R. Predictors of body surface area. *J Clin Anesth*. 1992; 4:4-10.
20. Vervoort G, Willems HL, Wetzels JF. Assessment of glomerular filtration rate in healthy subjects and normoalbuminuric diabetic patients: validity of a new (MDRD) prediction equation. *Nephrol Dial Transplant*. 2002;17:1909-1913.
21. Levey A, Bosch J, Lewis J, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med*. 1999;130:461-470.
22. Hennekens C, Buring J. *Epidemiology in Medicine*. Boston, Mass: Little, Brown; 1987.
23. Barnett A, Bain S, Bouter P, et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med*. 2004; 351:1952-1961.
24. Knobler H, Zornitzki T, Vered S, et al. Reduced glomerular filtration rate in asymptomatic diabetic patients: predictor of increased risk for cardiac events independent of albuminuria. *J Am Coll Cardiol*. 2004;44:2142-2148.
25. Harmoinen A, Lehtimäki T, Korpela M, Turjanmaa V, Saha H. Diagnostic accuracies of plasma creatinine, cystatin C, and glomerular filtration rate calculated by the Cockcroft-Gault and Levey (MDRD) formulas. *Clin Chem*. 2003;49:1223-1225.
26. Swedko PJ, Clark HD, Paramsothy K, Akbari A. Serum creatinine is an inadequate screening test for renal failure in elderly patients. *Arch Intern Med*. 2003; 163:356-360.
27. Corsonello A, Pedone C, Corica F, Mussi C, Carbonin P, Incalzi R. Concealed renal insufficiency and adverse drug reactions in elderly hospitalized patients. *Arch Intern Med*. 2005;165:790-795.
28. Nicoll SR, Sainsbury R, Bailey RR, et al. Assessment of creatinine clearance in healthy subjects over 65 years of age. *Nephron*. 1991;59:621-625.
29. Lamb EJ, Webb MC, Simpson DE, et al. Estimation of glomerular filtration rate in older patients with chronic renal insufficiency: is the modification of diet in renal disease formula an improvement? *J Am Geriatr Soc*. 2003;51: 1012-1017.