Cardiovascular Disease Risk Factors in Chronic Kidney Disease

Overall Burden and Rates of Treatment and Control

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Background: Mild to moderate chronic kidney disease (CKD) is associated with increased risk for cardiovascular disease. The burden of cardiovascular disease risk factors in this setting is not well described.

Methods: We compared the age- and sex-adjusted prevalence of cardiovascular disease risk factors and their treatment and control among persons with and without CKD in 3258 Framingham offspring cohort members who attended the seventh examination cycle (1998-2001). Glomerular filtration rate (GFR) was estimated using the simplified Modification of Diet in Renal Disease Study equation. We defined CKD as a GFR of less than 59 mL/min per 1.73 m^2 in women and less than 64 mL/min per 1.73 m^2 in men.

Results: Those with CKD were older, more likely to be obese (33.5% vs 29.3%; *P*=.02), and more likely to have low levels of high-density lipoprotein cholesterol (45.2% vs 29.4%; *P*<.001) and high triglyceride levels (39.9% vs 29.8%; *P*<.001). Those with CKD had a higher prevalence of hypertension (71.2% vs 42.7%; *P*<.001) and hypertension treatment (86.0% vs 72.5%; *P*<.001), but were less likely to achieve optimal blood pressure control (27.0% vs 45.5%; *P*<.001). Participants with CKD had a higher prevalence of elevated low-density lipoprotein cholesterol levels (60.5% vs 44.7%; *P*=.06) and lipid-lowering therapy (57.1% vs 42.6%; *P*=.09), although this was not statistically significant. A greater proportion of individuals with CKD than those without had diabetes (23.5% vs 11.9%; *P*=.02) and were receiving diabetes treatment (63.6% vs 46.9%; *P*=.05), but were less likely to achieve a hemoglobin A_{1c} level of less than 7% (43.8% vs 59.4%; *P*=.03).

Conclusions: Chronic kidney disease is associated with a significant burden of cardiovascular disease risk factors in the community. The diagnosis of CKD should alert the practitioner to look for potentially modifiable cardiovascular risk factors.

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CHRONIC KIDNEY DISEASE (CKD) is a risk factor for cardiovascular disease (CVD) and is associated with an increase in all-cause mortality.[1-4] Nineteen million US adults are affected by CKD, including more than 25% of the population 70 years and older.[5] Among those with end-stage renal disease, 50% of all deaths are due to CVD,[6] and the risk of CVD is 10 to 20 times higher than in the general population.[7]

The etiology of the increased risk of CVD in CKD is unknown, but may in part be due to shared CVD risk factors, including diabetes, hypertension, obesity, lipid abnormalities, and smoking.[8-12] The burden of CVD risk factors among patients who have not undergone dialysis and and those who have is extremely high. Data from nephrology clinics demonstrate prevalence rates of hypertension as high as 60% to 95%,[13-16] of lipid abnormalities ranging from 30% to 60%,[14,16] of diabetes as high as 40%,[13-16] of left ventricular hypertrophy of 20%,[14,16] and of cigarette smoking of 30% to 60%.[13-16] Patients with CKD are generally undertreated with respect to cardioprotective medications (including β-blockers, aspirin, angiotensin-converting enzyme inhibitors, and lipid-lowering medications),[15,17] even in settings of congestive heart failure, prior myocardial infarction, and coronary artery bypass graft surgery.[18-20]

Less is known regarding the CVD risk factor burden among individuals with earlier stages of CKD, many of whom are not necessarily treated for CKD or do not manifest clinical CVD. Moderate CKD is an independent risk factor for CVD,[3,4] suggesting a need to better understand CVD risk factor burden and rates of risk factor treatment and control in this group. Thus, the aim of this study was to evaluate the burden of CVD risk factors among those with CKD in an unselected, community-based setting. We also sought

to determine rates of treatment and control of CVD risk factors among those with and without CKD.

METHODS

STUDY SAMPLE

The Framingham Heart Study is a community-based prospective cohort study that began in 1948, consisting of 5209 men and women in the original cohort.[21] In 1971, 5124 men and women enrolled in the Framingham Heart Study offspring cohort, which included the children and spouses of the children of the original cohort. Participant examinations for the offspring cohort occurred approximately every 4 years; the design and methodology have been described elsewhere.[22] The present investigation includes the participants in the offspring cohort who attended the seventh examination cycle (1998-2001).

Of 3537 members of the offspring cohort who attended the seventh examination, 229 were excluded for missing creatinine values and 50 for missing covariate data, resulting in a final study sample of 3258 participants.

MEASUREMENTS AND DEFINITIONS

Kidney function was estimated by glomerular filtration rate (GFR), calculated using the simplified Modification of Diet in Renal Disease (MDRD) Study equation.[23,24] Our definition of CKD was based on the National Kidney Foundation Disease Outcome Quality Initiative Working Group definition of kidney disease, which defines CKD as a GFR of less than 60 mL/min per 1.73 m^2.[23] However, we have found that the use of this cut point classifies approximately 50% more women as having kidney disease than men; therefore, we modified the definition of CKD as a GFR of less than 59 mL/min per 1.73 m^2 in women or less than 64 mL/min per 1.73 m^2 in men.[9]

Serum creatinine was measured using the modified Jaffe method. Because the measurement of creatinine level can vary, creatinine level was calibrated using a 2-step process. First, creatinine values from the Third National Health and Nutritional Examination Survey were calibrated to The Cleveland Clinic laboratory values, requiring a correction factor of 0.23 mg/dL (20.3 µmol/L).[25] Then, age- (20-39, 40-59, 60-69, and ≥70 years) and sex-specific creatinine values were aligned with the corresponding corrected Third National Health and Nutrition Examination Survey age- and sex-specific mean values, as previously described.[9]

CVD AND RISK FACTOR ASSESSMENT

Each examination included a CVD assessment and blood testing. Participants with a fasting blood glucose level of at least 126 mg/dL (≥7.0 mmol/L) or who were receiving insulin and/or oral hypoglycemic treatment for diabetes were defined as having diabetes. Participants with a systolic blood pressure of at least 140 mm Hg or a diastolic blood pressure of at least 90 mm Hg (the mean of 2 readings taken by an examining physician) or who were receiving medication for treatment of hypertension were defined as having hypertension. Cholesterol levels were measured after an overnight fast. Low levels of high-density lipoprotein cholesterol (HDL-C) were defined as less than 40 mg/dL (<1.0 mmol/L) in men and less than 50 mg/dL (<1.3 mmol/L) in women. High triglyceride levels were defined as at least 150 mg/dL (>1.7 mmol/L). Hemoglobin A_{1c} level was measured by means of high-performance liquid chromatography; assay coefficient variances were less than 2.5%. Our hemoglobin A_{1c} assay is calibrated against the Diabetes Control and Complications Trial standard hemoglobin A_{1c} assay. Smoking status was defined as smoking 1 or more cigarettes a day in the year preceding the examination. Body mass index was defined as weight in kilograms divided by the square of height in meters. Central obesity was defined as a waist circumference of more than 88 cm in women and more than 102 cm in men. Left ventricular hypertrophy with strain was determined by a physician-interpreted electrocardiogram finding. Framingham risk score values were calculated to predict 10-year CVD risk in participants free of CVD.[26] Prevalent coronary heart disease included recognized or unrecognized myocardial infarction, coronary insufficiency, and angina pectoris. Prevalent CVD was defined as coronary heart disease, stroke, transient ischemic attack, or intermittent claudication. The criteria for diagnosis of these cardiovascular events have been described elsewhere.[27]

TREATMENT AND CONTROL OF CVD RISK FACTORS

Rates of treatment of hypertension were calculated by taking the proportion of those receiving antihypertensive medications among all participants with hypertension. Rates of hypertension control among participants with CKD were calculated by taking the proportion of individuals with a blood pressure of greater than 130/80 mm Hg among all participants with CKD and hypertension, and by taking the proportion of participants with a blood pressure of greater than 140/90 mm Hg among all participants with hypertension but without CKD. Hypertension control cut points were defined according to the guidelines defined in the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[28] Rates of elevated low-density lipoprotein cholesterol (LDL-C) levels were calculated by taking the proportion of those with elevated LDL-C levels according to LDL-C treatment goals set by the National Cholesterol Education Program Adult Treatment Panel III[29] or those receiving lipid-lowering agents. Lipid control was assessed using the the National Cholesterol Education Program Adult Treatment Panel III guidelines for cholesterol level management[29] and was calculated by taking the proportion of individuals with LDL-C levels above their specified goal among all individuals with elevated LDL-C levels. The guidelines of the National Cholesterol Education Program Adult Treatment Panel III recommend a target LDL-C level of less than 160 mg/dL (<4.1 mmol/L) for persons with no or 1 cardiac risk factor, less than 130 mg/dL (<3.4 mmol/L) for persons with 2 or more cardiac risk factors, and less than 100 mg/dL (<2.6 mmol/L) for those with CVD, diabetes mellitus, or other cardiac risk factor equivalents.[29] Rates of control of diabetes were calculated by taking the proportion of individuals with a hemoglobin A_{1c} level of less than 7% of all individuals with diabetes.[30]

STATISTICAL ANALYSIS

Prevalence of CVD risk factors and rates of treatment and control were compared among individuals with and without CKD. In descriptive analyses, we looked at the rates of those participants with each risk factor (hypertension, elevated LDL-C level, and diabetes) and assessed whether risk factors in these individuals were untreated, treated but not controlled, or treated and controlled using the criteria described in the previous sections. These rates were adjusted via multivariable logistic regression.[31] Because prevalence rates and the treatment and control of CVD risk factors can differ by age and clinical CVD status, secondary analyses were performed with stratification of participants into groups younger than 65 years or 65 years or older and by excluding participants with clinically recognized CVD (recognized myocardial infarction, coronary insufficiency, congestive heart failure, or stroke; n = 60 among participants with

Table 1. Cardiovascular Risk Factor Burden Among Study Participants With and Without CKD*

Characteristic	Participants With CKD (n = 2977)	Participants Without CKD (n = 281)	*P* Value†
Age, mean ± SD, y	60 ± 9	70 ± 8	<.001
Female	1612 (54)	143 (51)	.45
GFR, mean ± SD, mL/min per 1.73 m^2	88 ± 17	51 ± 10	<.001
Systolic blood pressure, mean ± SD, mm Hg	126 ± 18	134 ± 22	.56
Diastolic blood pressure, mean ± SD, mm Hg	74 ± 10	71 ± 10	.02
Fasting blood glucose level, mean ± SD, mg/dL	103 ± 26	111 ± 34	.03
Total cholesterol level, mean ± SD, mg/dL	200 ± 36	195 ± 37	.08
LDL-C level, mean ± SD, mg/dL	120 ± 33	116 ± 33	.29
HDL-C level, mean ± SD, mg/dL	55 ± 17	48 ± 15	<.001
Triglyceride level, mean ± SD, mg/dL	129 ± 68	150 ± 77	<.001
BMI, mean ± SD	28.1 ± 5.4	28.5 ± 4.8	.09
Obesity (BMI ≥30)	871 (29.3)	94 (33.5)	.02
Low HDL-C level‡	874 (29.4)	127 (45.2)	<.001
Triglyceride level ≥150 mg/dL	887 (29.8)	112 (39.9)	<.001
Total cholesterol level ≥240 mg/dL	424 (14.2)	31 (11.0)	.33
Current smoker	402 (13.5)	19 (6.8)	.28
LVH with strain by ECG	16 (0.5)	7 (2.5)	.02
Framingham 10-y risk score ≥10%§	123 (4.4)	35 (15.8)	.004
Cardiovascular disease	318 (10.7)	90 (32.0)	<.001
Coronary heart disease	224 (7.5)	60 (21.4)	<.001
Myocardial infarction	111 (3.7)	38 (13.5)	<.001
Congestive heart failure	22 (0.7)	14 (5.0)	<.001
Cardioprotective medications/diuretics			
Angiotensin-converting enzyme inhibitor	458 (15.4)	103 (36.7)	<.001
Diuretic	147 (4.9)	58 (20.6)	<.001
Aspirin	961 (32.3)	145 (51.6)	.003
β-Blocker	489 (16.4)	87 (31.0)	.004

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CKD, chronic kidney disease; ECG, electrocardiography; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, by 0.0555; and triglyceride to millimoles per liter, by 0.0113.

*Unless otherwise indicated, data are expressed as number (percentage) of participants.

†Adjusted for age and sex, except for age, which is adjusted for sex, and sex, which is adjusted for age.

‡Defined as less than 40 mg/dL in men and less than 50 mg/dL in women.

§Among participants without prevalent cardiovascular disease.

CKD and n=170 among participants without CKD). Statistical analyses were performed using SAS statistical software, version 8.[32] We did not account for multiple hypothesis testing. A 2-tailed $P<.05$ was defined as statistically significant.

RESULTS

PREVALENCE OF CVD RISK FACTORS

The prevalence of CKD in the study sample was 8.6%. Among those with CKD, 96.1% had stage 3 CKD (n=270)

Table 2. Age- and Sex-Adjusted Rates of CVD Risk Factors

CVD Risk Factors	% of Participants (95% CI) Without CKD (n = 2977)	With CKD (n = 281)	*P* Value
Hypertension			
Prevalence	42.7 (39.9-45.5)	71.2 (65.5-76.3)	<.001
Treatment	72.5 (68.2-76.4)	86.0 (80.0-90.4)	<.001
Control*†	45.5 (41.1-50.0)	27.0 (20.9-34.2)	<.001
Elevated LDL-C levels			
Prevalence	44.7 (41.8-47.6)	60.5 (54.4-66.3)	.06
Treatment	42.6 (38.3-46.9)	57.1 (48.9-64.9)	.09
Control‡	31.1 (27.2-35.3)	41.8 (33.9-50.0)	.19
Diabetes			
Prevalence	11.9 (10.1-13.0)	23.5 (18.5-29.3)	.02
Treatment	46.9 (38.6-55.3)	63.6 (50.1-75.4)	.05
Hemoglobin A_{1c} level <7%§	59.4 (50.5-67.8)	43.8 (30.8-57.6)	.03

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

*Indicates blood pressure of less than 130/80 mm Hg in participants with CKD and of less than 140/90 mm Hg in participants without CKD.

†For participants with and without CKD, proportions with blood pressure of less than 140/90 mm Hg are 37.1% vs 45.5% ($P<.001$).

‡Indicates LDL-C level of less than 100 mg/dL (<2.6 mmol/L) if CVD, stroke, peripheral vascular disease, diabetes mellitus, or Framingham 10-year risk estimate of greater than 20% is present; LDL-C level of less than 130 mg/dL (<3.4 mmol/L) if 2 or more CVD risk factors or Framingham 10-year risk estimate of 10% to 20% is present; and LDL-C level of less than 160 mg/dL (<4.1 mmol/L) if no or 1 CVD risk factor is present.

§Among those treated for diabetes, 28.6% of participants with vs 44.6% of participants without CKD ($P=.007$) had a hemoglobin A_{1c} level of less than 7%.

(GFR, ≥30 mL/min per 1.73 m^2 and <59 mL/min per 1.73 m^2 in women or <64 mL/min per 1.73 m^2 in men). The remaining 3.9% of participants with CKD had stage 4 (n=8) (GFR, 15-29 mL/min per 1.73 m^2) or stage 5 (n=3) (GFR, <15 mL/min per 1.73 m^2) CKD. The participants with CKD were older than those without CKD (**Table 1**). The participants with CKD had lower mean diastolic blood pressure, higher mean fasting blood glucose and serum triglyceride values, and lower mean serum HDL-C values than those without CKD. The participants with CKD had higher prevalence of CVD, myocardial infarction, congestive heart failure, and coronary heart disease than those without CKD ($P<.001$).

Those with CKD were more likely to be obese (Table 1) and to have low HDL-C and high triglyceride levels than those without CKD. The percentage of participants without prevalent CVD but with a Framingham 10-year risk of CVD of 10% or greater was 4 times higher in those with CKD compared with those without CKD. Smoking status did not differ according to CKD status. Rates of hypertension were 71.2% among those with CKD, compared with 42.7% among those without CKD ($P<.001$) (**Table 2**). Overall, more participants with CKD had elevated LDL-C levels as defined by the guidelines of the National Cholesterol Education Program Adult Treatment Panel III than those without CKD (60.5% vs 44.7%), although this difference was not statistically significant ($P=.06$). Diabetes was nearly twice as common among participants with CKD compared with those without CKD (23.5% vs 11.9%; $P=.02$). The number of CVD risk factors among partici-

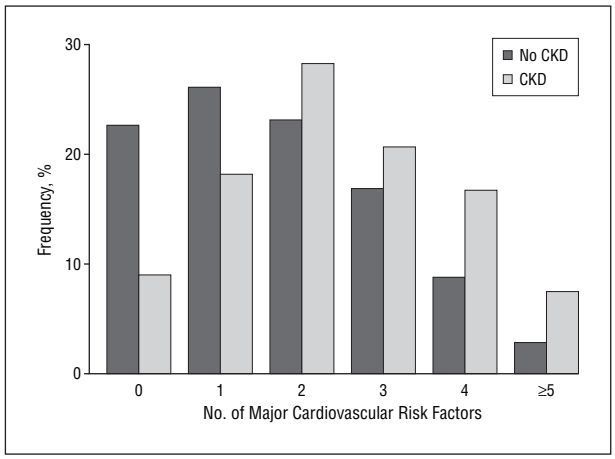

Figure 1. Percentage of subjects with 0 to 5 or more risk factors for cardiovascular disease (CVD) stratified by chronic kidney disease (CKD) status. Risk factors for CVD include hypertension, diabetes, smoking, elevated levels of low-density lipoprotein cholesterol, low levels of high-density lipoprotein cholesterol, and obesity.

pants with and without CKD is displayed in **Figure 1**. Among participants with CKD, 73.0% had 2 or more CVD risk factors, compared with 51.4% of those without CKD.

TREATMENT AND CONTROL OF HYPERTENSION

Most participants were receiving treatment for hypertension, although there was a significantly greater proportion of participants with CKD treated for hypertension than participants without CKD (86.0% vs 72.5%; $P<.001$) (Table 2). Control of hypertension was lower among participants with CKD (27.0%) compared with those without CKD (45.5%; $P<.001$). Nearly twice as many participants with compared with those without CKD were treated for hypertension, but it was not as well-controlled (**Figure 2**A), even though hypertensive participants with CKD received a higher median number of antihypertensive medications compared with participants without CKD (2 vs 1 antihypertensive medication).

TREATMENT AND CONTROL OF ELEVATED LDL-C LEVELS

Participants with CKD were more likely to be treated with lipid-lowering agents than were participants without CKD (57.1% vs 42.6%), although this difference was not statistically significant ($P=.09$). Rates of control of elevated LDL-C levels were poor in both groups (41.8% vs 31.1%; $P=.19$) (Table 2), and nearly half of participants with and without CKD were untreated (Figure 2B).

TREATMENT AND CONTROL OF DIABETES

More participants with diabetes and CKD were receiving hypoglycemic treatment than those without CKD (63.6% vs 46.9%; $P=.05$). Nonetheless, participants with CKD were less likely to have optimal hemoglobin A_{1c} levels (43.8% vs 59.4%; $P=.03$) (Table 2). Among participants treated for diabetes, there was a greater prevalence of suboptimal hemoglobin A_{1c} in those with compared with those without CKD (Figure 2C).

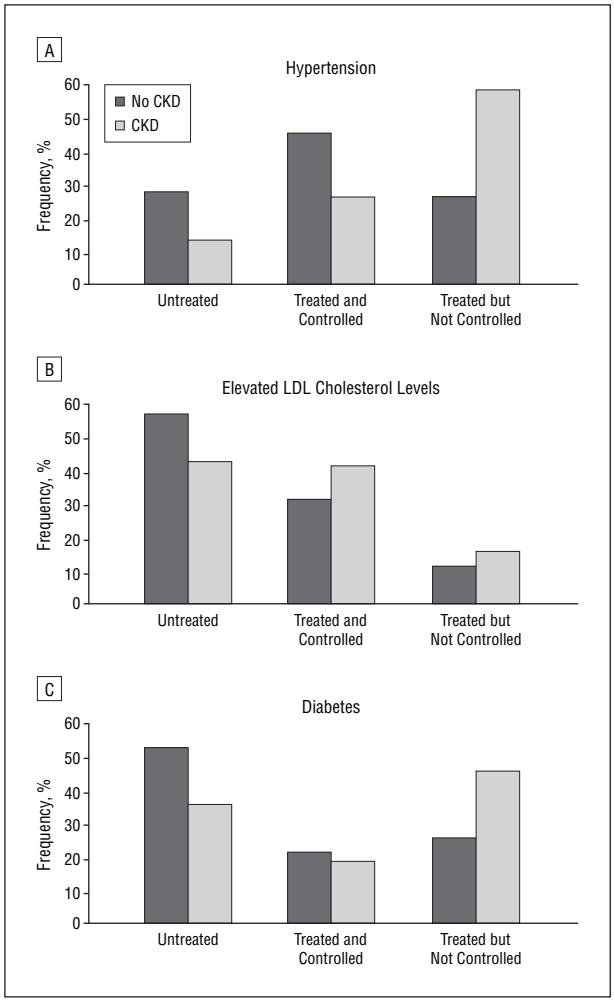

Figure 2. Rates of treatment and control of risk factors for cardiovascular disease (CVD) among participants with and without chronic kidney disease (CKD). Risk factors for CVD include hypertension (A), elevated levels of low-density lipoprotein cholesterol (LDL-C) (B), and diabetes (C).

SECONDARY ANALYSES

In an analysis excluding participants with clinical CVD (recognized myocardial infarction, coronary insufficiency, and stroke), rates of treatment and control for hypertension, elevated LDL-C levels, and diabetes did not materially differ from the overall analysis (data not shown).

In analyses stratified by age (**Table 3**), hypertension was more prevalent in both age groups among participants with CKD. Differences in rates of treatment and control of hypertension among those with and without CKD were more pronounced among those 65 years or older. Higher rates of elevated LDL-C levels among those with CKD were observed among older individuals, but differences in treatment and control of elevated LDL-C levels were not evident in age-stratified analyses. In contrast, differences in the prevalence of diabetes by CKD status were more evident among younger individuals.

Table 3. Age- and Sex-Adjusted Rates of CVD Risk Factors, Stratified by Age

CVD Risk Factors	Participants Aged <65 y, % (95% CI)			Participants Aged ≥65 y, % (95% CI)		
	Without CKD (n = 1982)	With CKD (n = 65)	*P* Value	Without CKD (n = 995)	With CKD (n = 216)	*P* Value
Hypertension						
Prevalence	33.9 (30.6-37.4)	58.5 (46.2-69.8)	.003	60.3 (55.4-66.0)	75.0 (67.9-81.0)	.001
Treatment	70.8 (64.8-76.2)	84.2 (68.5-92.9)	.12	74.3 (68.4-79.5)	86.4 (79.2-91.4)	.001
Control*†	51.4 (45.2-57.8)	31.6 (18.5-48.4)	.03	38.8 (32.9-45.1)	25.9 (18.9-34.5)	.003
Elevated LDL-C levels						
Prevalence	40.7 (37.2-44.2)	43.1 (31.6-55.3)	.71	52.7 (47.7-57.5)	65.7 (58.1-72.7)	.003
Treatment	36.1 (30.8-41.8)	46.4 (28.9-64.9)	.44	52.5 (45.8-59.1)	59.2 (49.3-68.4)	.09
Control‡	26.6 (21.8-32.0)	35.7 (20.1-55.1)	.39	38.2 (31.9-44.9)	43.0 (33.5-53.0)	.28
Diabetes						
Prevalence	8.7 (6.9-11.0)	20.0 (11.7-31.9)	.01	18.2 (14.7-22.2)	24.5 (18.3-32.1)	.08
Treatment	41.6 (30.3-54.1)	61.5 (33.0-83.9)	.21	51.9 (47.0-63.0)	64.2 (47.8-77.8)	.13
Hemoglobin A_{1c} level <7%	59.9 (46.9-71.6)	46.2 (21.2-73.2)	.33	59.0 (47.0-69.9)	43.1 (27.9-59.7)	.06

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

*Indicates blood pressure of less than 130/80 mm Hg in participants with CKD and less than 140/90 mm Hg in participants without CKD.

†Among those younger than 65 years, proportions of participants with and without CKD who also had blood pressure of less than 140/90 mm Hg are 68.4% and 51.4%, respectively (*P*=.03). Among those 65 years or older, proportions of participants with and without CKD who also had blood pressure of less than 140/90 mm Hg are 49.4% and 38.8%, respectively (*P*=.01).

‡Indicates LDL-C level of less than 100 mg/dL (<2.6 mmol/L) if CVD, diabetes mellitus, or Framingham 10-year risk estimate of greater than 20% is present; LDL-C level of less than 130 mg/dL (<3.4 mmol/L) if 2 or more CVD risk factors or Framingham 10-year risk estimate of 10% to 20% is present; and LDL-C level of less than 160 mg/dL (<4.1 mmol/L) if no or 1 CVD risk factor is present.

COMBINATIONS OF RISK FACTOR CONTROL

Among participants without diabetes, dual control of hypertension and elevated LDL-C levels occurred less in participants with (13.1%; 95% confidence interval [CI], 7.1%-22.8%) than in those without (22.5%; 95% CI, 17.3%-28.7%) CKD, although this difference was not statistically significant (*P*=.10). Among participants with diabetes, rates of successful triple control of hypertension and LDL-C and hemoglobin A_{1c} levels were low and did not differ among those with (7.5%; 95% CI, 2.5%-20.9%) and without (8.9%; 95% CI, 4.4%-17.6%) CKD (*P*=.61).

RATES OF CARDIOPROTECTIVE MEDICATION AND DIURETIC USE

Overall use of cardioprotective medications is shown in Table 1. A greater proportion of hypertensive participants with CKD were treated with angiotensin-converting enzyme inhibitors than persons without CKD (57.6% vs 47.0%; *P*=.005) and were more likely to take diuretic medications (28.5% vs 12.8%; *P*<.001). Among participants with prevalent coronary heart disease, there was no difference in aspirin use (83.3% vs 76.8%; *P*=.30) or β-blocker use (60.0% vs 64.7%; *P*=.90) among those with and without CKD.

COMMENT

OVERALL FINDINGS

There is a significant burden of CVD risk factors among participants with CKD in the community. Participants with CKD are more likely to be treated for hypertension, elevated LDL-C levels, and diabetes, but rates of control are uniformly low in those with and without CKD. In general, when we stratified our analysis using an age cutoff of 65 years, older individuals demonstrated more significant differences in hypertension prevalence, treatment, and control.

HYPERTENSION

The prevalence of hypertension was significantly higher among those with compared with those without CKD. These differences were more evident among older individuals, consistent with previously published data demonstrating lower rates of blood pressure control (<130/80 mm Hg) among older individuals with mild to moderate CKD.[33] Participants with CKD had higher rates of hypertension treatment than participants without CKD, leading us to question whether the treatment modalities themselves might increase serum creatinine levels modestly enough to classify these participants with CKD. Indeed, hypertensive participants with CKD were more likely to be treated with angiotensin-converting enzyme inhibitors and diuretics, which can increase serum creatinine levels.[34,35] This increase does not significantly further the progression of renal dysfunction in patients with mild to moderate CKD.[34,36] The CKD participants with hypertension in our study, despite increased use of antihypertensive therapy, were less likely to achieve recommended treatment goals.

Hypertension is a well-established independent risk factor for the development of end-stage renal disease[37,38] and CKD progression.[39] However, it is unclear whether patients with CKD benefit from tighter blood pressure control targets. Three recent studies[40-42] of tight vs usual blood pressure control have reported conflicting results regarding outcomes of end-stage renal disease and GFR

decline. The African-American Study of Kidney Disease and Hypertension[42] and the Ramipril Efficacy in Nephropathy 2 Trial[40] demonstrated no benefit on these outcomes from blood pressure reduction, whereas long-term follow-up of the MDRD Study,[41] which had the longest follow-up period and achieved the largest mean blood pressure difference between treatment groups, showed a benefit in the tight blood pressure control arm among patients with primarily nondiabetic kidney disease. Therefore, lack of definitive data in this area may contribute to the failure to reach lower blood pressure targets among individuals with CKD.

The effect of hypertension and hypertension treatment in CKD on CVD outcomes has not been well studied. A subgroup analysis of the Systolic Hypertension in the Elderly Program demonstrated a 30% to 40% reduction in CVD events via systolic blood pressure reduction among elderly persons with mild renal dysfunction.[36] Additional studies specifically examining effects of hypertension control on CVD outcomes among those with CKD are needed to expand on these findings.

ELEVATED LDL-C LEVELS

Among all participants, levels of elevated LDL-C did not significantly differ according to CKD status, although older individuals with CKD had higher prevalence rates of elevated LDL-C levels. Participants with CKD were more likely to have elevated triglyceride values and lower HDL-C values, consistent with prior analyses of adverse lipid profiles associated with CKD.[11,14] We chose to focus our analysis primarily on management of LDL-C levels because of clear guidelines regarding management.

There is evidence that the treatment of hyperlipidemia may reduce the rate of kidney function decline in individuals with stage 3 CKD.[43,44] In addition, 2 post hoc analyses of clinical trials with gemfibrozil[45] and pravastatin sodium[46] have shown beneficial effects of lipid-lowering medications on CVD outcomes among patients with moderate CKD (GFR, 30-70 mL/min per 1.73 m^2). However, a recent randomized clinical trial in patients with diabetes undergoing hemodialysis demonstrated no protective benefit of lipid-lowering medication on CVD end points,[47] although the generalizability of these findings to patients with CKD who are not undergoing hemodialysis is uncertain. Taken together, these data suggest that lipid-lowering therapy among individuals with moderate CKD has beneficial effects on renal and CVD outcomes. Additional clinical trials are necessary to examine the effects of lipid-lowering agents on both CKD progression and CVD risk reduction.

DIABETES MELLITUS

The rates of diabetes control were significantly lower among participants with CKD. This is surprising in light of evidence from the United Kingdom Prospective Diabetes Study[48] and the Diabetes Control and Complications Trial,[49] which demonstrated that tight glycemic control is associated with reduced progression of nephropathy and doubling of serum creatinine levels. Recent data[50] suggest that tight control of glucose levels among patients with type 1 diabetes reduces long-term CVD risk; however, clinical trial data in those with type 2 diabetes remain inconclusive. Whether subgroups of patients with diabetes and CKD would experience a reduction in CVD outcomes with tight glycemic control requires further research.

STRENGTHS AND LIMITATIONS

There are several strengths to our study design. The Framingham Heart Study is a community-based sample not selected for CKD, reducing the risk of referral or selection bias. We have excellent assessment and documentation of CVD risk factors and treatment. Several limitations exist as well. Our study sample is limited geographically and ethnically because our participants are primarily white individuals. Nevertheless, the relation between CVD risk factor outcomes observed in the Framingham data set has been validated in 6 ethnically and geographically diverse populations, suggesting that our findings are applicable in other populations.[51] We used guidelines for treatment that were not necessarily in place at the time of data collection. Because the MDRD equation that we used to estimate GFR has been validated in subjects with GFR of less than 90 mL/min per 1.73 m^2, values outside of this range are extrapolated.[5] A recent study[52] showed that the MDRD equation underestimates GFR by 29% in healthy persons, but by only 6.2% among patients with CKD. However, given that we did not use GFR as a continuous variable in our analysis, it remains unclear how this would affect the determination of CKD in our sample. Our definition of CKD as a disease trait falls within the range that has been validated for the MDRD equation,[24] improving the robustness of our results for our dichotomous analysis. Our definition of CKD is limited to a single measurement of serum creatinine level on one occasion, not measured during a period of 3 months or longer as has been defined by the National Kidney Foundation.[23] We measured risk factors on a single occasion, which could have led to outcome misclassification, thus biasing our results toward the null value. Furthermore, we used the simplified MDRD study equation to estimate GFR, instead of measuring it directly. To improve the validity and accuracy of the MDRD equation, we indirectly calibrated our creatinine values. We were unable to account for albuminuria, which may have led to an underestimation of CKD in our study. Although cross-sectional study designs are generally considered to be limiting in that they cannot determine the directionality of our reported relations, our primary aim was to characterize CVD risk factor burden, treatment, and control at a given point in time, therefore making the cross-sectional design the most favorable for this analysis.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Individuals with CKD had higher Framingham risk scores and low rates of optimization of all risk factors. Understanding barriers to effective risk factor modification in CKD is essential. Health care practitioners may not be aware of the relatively low creatinine values that corre-

spond to CKD; among non-Hispanic white individuals aged 60 years, the mean creatinine cut point corresponding to a GFR in the CKD range is only 1.0 mg/dL (88.4 µmol/L) in women and 1.3 mg/dL (114.9 µmol/L) in men.[25] Efforts should focus on educating health care providers about the need to manage CVD risk factors in patients with CKD, with the ultimate aim of preventing CKD progression and promoting reductions in cardiovascular morbidity and mortality. Given the high prevalence of CVD risk factors and the relatively low levels of risk factor control, there may be a need to more aggressively manage CKD in this specific subgroup of individuals.

Chronic kidney disease, with its high burden of vascular disease risk factors and associated risk of adverse CVD outcomes, represents an important public health concern. The identification of an individual with CKD should alert the practitioner to a large underlying burden of potentially modifiable CVD risk factors.

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REFERENCES

1. 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.
2. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis*. 1998;32(suppl 3):S112-S119.
3. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004; 351:1296-1305.
4. 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.
5. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis*. 2003;41:1-12.
6. U.S. Renal Data System. *USRDS 2002 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*. Bethesda, Md: National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health; 2002.
7. Baigent C, Burbury K, Wheeler D. Premature cardiovascular disease in chronic renal failure. *Lancet*. 2000;356:147-152.
8. Bleyer AJ, Shemanski LR, Burke GL, Hansen KJ, Appel RG. Tobacco, hypertension, and vascular disease: risk factors for renal functional decline in an older population. *Kidney Int*. 2000;57:2072-2079.
9. Fox CS, Larson MG, Leip EP, et al. Predictors of new-onset kidney disease in a community-based population. *JAMA*. 2004;291:844-850.
10. Manttari M, Tiula E, Alikoski T, Manninen V. Effects of hypertension and dyslipidemia on the decline in renal function. *Hypertension*. 1995;26:670-675.
11. Muntner P, Coresh J, Smith JC, Eckfeldt J, Klag MJ. Plasma lipids and risk of developing renal dysfunction: the atherosclerosis risk in communities study. *Kidney Int*. 2000;58:293-301.
12. Tozawa M, Iseki K, Iseki C, et al. Influence of smoking and obesity on the development of proteinuria. *Kidney Int*. 2002;62:956-962.
13. Cheung AK, Sarnak MJ, Yan G, et al. Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. *Kidney Int*. 2000;58:353-362.
14. Longenecker JC, Coresh J, Powe NR, et al. Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study. *J Am Soc Nephrol*. 2002;13:1918-1927.
15. Tonelli M, Bohm C, Pandeya S, et al. Cardiac risk factors and the use of cardioprotective medications in patients with chronic renal insufficiency. *Am J Kidney Dis*. 2001;37:484-489.
16. Wheeler DC, Townend JN, Landray MJ. Cardiovascular risk factors in predialysis patients: baseline data from the Chronic Renal Impairment in Birmingham (CRIB) study. *Kidney Int Suppl*. May 2003:S201-S203.
17. Fox CS, Longenecker JC, Powe NR, et al; CHOICE Study. Undertreatment of hyperlipidemia in a cohort of United States kidney dialysis patients. *Clin Nephrol*. 2004;61:299-307.
18. Berger AK, Duval S, Krumholz HM. Aspirin, beta-blocker, and angiotensin-converting enzyme inhibitor therapy in patients with end-stage renal disease and an acute myocardial infarction. *J Am Coll Cardiol*. 2003;42:201-208.
19. Ezekowitz J, McAlister FA, Humphries KH, et al; APPROACH Investigators. The association among renal insufficiency, pharmacotherapy, and outcomes in 6427 patients with heart failure and coronary artery disease. *J Am Coll Cardiol*. 2004; 44:1587-1592.
20. Gibney EM, Casebeer AW, Schooley LM, et al. Cardiovascular medication use after coronary bypass surgery in patients with renal dysfunction: a National Veterans Administration study. *Kidney Int*. 2005;68:826-832.
21. Dawber TR, Kannel WB, Lyell LP. An approach to longitudinal studies in a community: the Framingham Study. *Ann N Y Acad Sci*. 1963;107:539-556.
22. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families: the Framingham Offspring Study. *Am J Epidemiol*. 1979;110:281-290.
23. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002; 39(suppl 1):S1-S266.
24. Levey AS, Bosch JP, Lewis JB, et al; Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med*. 1999;130:461-470.
25. Coresh J, Astor BC, McQuillan G, et al. Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. *Am J Kidney Dis*. 2002;39:920-929.
26. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998; 97:1837-1847.
27. Cupples LA, D'Agastino RB. Some risk factors related to the annual incidence of cardiovascular disease and death using pooled repeated biennial measurements: Framingham Study, 30-year follow-up. In: Kannel WB, Wolf PA, Garrison RJ, eds. *The Framingham Heart Study: an Epidemiologic Investigation of Cardiovascular Disease*. Washington, DC: National Institutes os Health; 1987:87-203.
28. Chobanian AV, Bakris GL, Black HR, et al; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report [published correction appears in *JAMA*. 2003;290:197]. *JAMA*. 2003; 289:2560-2572.
29. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001; 285:2486-2497.
30. American Diabetes Association. Standards of medical care in diabetes [published correction appears in *Diabetes Care*. 2005;28:990]. *Diabetes Care*. 2005; 28(suppl 1):S4-S36.
31. Hosmer DW Jr, Lemeshow S. *Applied Logistic Regression*. New York, NY: John Wiley & Sons Inc; 1989.
32. SAS Institute Inc. *SAS/STAT User's Guide: Version 8*. Cary, NC: SAS Institute Inc; 2000.
33. Peralta CA, Hicks LS, Chertow GM, et al. Control of hypertension in adults with chronic kidney disease in the United States. *Hypertension*. 2005;45:1119-1124.
34. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor–associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med*. 2000; 160:685-693.
35. Burkhardt H, Bruckner D, Gladisch R. Risk factors of worsening renal function in hospitalized elderly patients. *J Nephrol*. 2005;18:166-173.
36. Pahor M, Shorr RI, Somes GW, et al. Diuretic-based treatment and cardiovascular events in patients with mild renal dysfunction enrolled in the Systolic Hypertension in the Elderly Program. *Arch Intern Med*. 1998;158:1340-1345.
37. Klag MJ, Whelton PK, Randall BL, et al. Blood pressure and end-stage renal disease in men. *N Engl J Med*. 1996;334:13-18.
38. Perry HM Jr, Miller JP, Fornoff JR, et al. Early predictors of 15-year end-stage renal disease in hypertensive patients. *Hypertension*. 1995;25:587-594.

39. Young JH, Klag MJ, Muntner P, et al. Blood pressure and decline in kidney function: findings from the Systolic Hypertension in the Elderly Program (SHEP). *J Am Soc Nephrol*. 2002;13:2776-2782.
40. Ruggenenti P, Perna A, Loriga G, et al; REIN-2 Study Group. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet*. 2005;365:939-946.
41. Sarnak MJ, Greene T, Wang X, et al. The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the Modification of Diet in Renal Disease Study. *Ann Intern Med*. 2005;142:342-351.
42. Wright JT Jr, Bakris G, Greene T, et al; African American Study of Kidney Disease and Hypertension Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial [published correction appears in *JAMA*. 2006;295:2726]. *JAMA*. 2002;288:2421-2431.
43. Tonelli M, Moye L, Sacks FM, Cole T, Curhan GC; Cholesterol and Recurrent Events Trial Investigators. Effect of pravastatin on loss of renal function in people with moderate chronic renal insufficiency and cardiovascular disease. *J Am Soc Nephrol*. 2003;14:1605-1613.
44. Tonelli M, Isles C, Craven T, et al. Effect of pravastatin on rate of kidney function loss in people with or at risk for coronary disease. *Circulation*. 2005;112:171-178.
45. Tonelli M, Collins D, Robins S, Bloomfield H, Curhan GC; Veterans' Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) Investigators. Gemfibrozil for secondary prevention of cardiovascular events in mild to moderate chronic renal insufficiency. *Kidney Int*. 2004;66:1123-1130.
46. Tonelli M, Isles C, Curhan GC, et al. Effect of pravastatin on cardiovascular events in people with chronic kidney disease. *Circulation*. 2004;110:1557-1563.
47. Wanner C, Krane V, Marz W, et al; German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis [published correction appears in *N Engl J Med*. 2005;353:1640]. *N Engl J Med*. 2005;353:238-248.
48. UK Prospective Diabetes Study (UKPDS) Group. UK Prospective Diabetes Study (UKPDS) Group [published correction appears in *Lancet*. 1999;354:602]. *Lancet*. 1998;352:837-853.
49. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy [published correction appears in *N Engl J Med*. 2000;342:1376]. *N Engl J Med*. 2000; 342:381-389.
50. Nathan DM, Cleary PA, Backlund JY, et al; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005;353:2643-2653.
51. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P; CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA*. 2001;286:180-187.
52. Rule AD, Larson TS, Bergstralh EJ, et al. Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease. *Ann Intern Med*. 2004;141:929-937.