

Pravastatin for Secondary Prevention of Cardiovascular Events in Persons with Mild Chronic Renal Insufficiency

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Background: Cardiovascular disease is a common cause of morbidity and death in persons with renal insufficiency. Although 3-hydroxy-3methylglutaryl coenzyme A reductase inhibitors (statins) are effective for secondary prevention of cardiovascular events in the general population, they have not been specifically studied in chronic renal insufficiency.

Objective: To determine whether pravastatin is effective and safe for secondary prevention of cardiovascular events in persons with chronic renal insufficiency.

Design: Post hoc subgroup analysis of a randomized, double-blind, placebo-controlled trial.

Setting: The Cholesterol and Recurrent Events (CARE) study, a randomized trial of pravastatin versus placebo in 4159 participants with previous myocardial infarction and total plasma cholesterol levels less than 6.21 mmol/L (<240 mg/dL).

Participants: 1711 participants with chronic renal insufficiency defined by creatinine clearance less than or equal to 75 mL/min, using the Cockcroft–Gault equation.

Measurements: The primary outcome was death from coronary disease or symptomatic nonfatal myocardial infarction.

Results: After a median follow-up of 58.9 months, the incidence of the primary end point was lower in participants receiving pravastatin than in those receiving placebo (adjusted hazard ratio, 0.72 [95% CI, 0.55 to 0.95]; $P = 0.02$). Pravastatin was associated with lower adjusted hazard ratios for major coronary events (0.72 [CI, 0.59 to 0.88]; $P = 0.001$) and coronary revascularization (0.65 [CI, 0.50 to 0.83]; $P = 0.001$), but not total mortality (0.81 [CI, 0.61 to 1.08]; $P = 0.14$) or stroke (0.62 [CI, 0.39 to 1.00]; $P = 0.051$). Tests for interaction suggested that the observed benefit was independent of the presence and severity of renal insufficiency. Incidence of side effects was similar in persons receiving pravastatin and those receiving placebo.

Conclusions: These data suggest that pravastatin is effective and appears safe for secondary prevention of cardiovascular events in persons with mild chronic renal insufficiency. Since statins may be underused in this setting, physicians should consider prescribing them for patients with chronic renal insufficiency and known coronary disease.

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Chronic renal insufficiency is a common condition that may affect as many as 6 million Americans (1) and is associated with high rates of cardiovascular disease. Regardless of diabetic status, persons with chronic renal insufficiency have cardiovascular mortality rates at least 10 times higher than the general population (2). This excess burden of illness appears to be due to a higher prevalence of traditional cardiovascular risks (3–5) and possibly also to non-traditional risk factors, such as homocysteinemia, hyperparathyroidism, and chronic inflammation (6, 7).

Chronic renal insufficiency encompasses all levels of renal dysfunction, up to and including dialysis dependence, but an emerging body of literature suggests that even very mild renal disease increases cardiovascular risk (8–10). Although there is no universally accepted definition of chronic renal insufficiency, previous studies on cardiovascular disease have used creatinine clearance less than or equal to 75 mL/min to identify persons with this condition (11, 12).

Drugs that inhibit 3-hydroxy-3methylglutaryl coenzyme A reductase (statins) are known to reduce mortality in hyperlipidemic persons with coronary disease in the general population (13). However, no published information is available about the efficacy of statins in persons who also have chronic renal insufficiency. Surprisingly, the prevalence of statin use in this subgroup is less than 25% (11).

There is no a priori reason to suspect that statins would be less effective in chronic renal insufficiency; however, lack of proven efficacy or concerns about toxicity may contribute to nonprescription in patients with this condition. To evaluate the efficacy and safety of pravastatin in chronic renal insufficiency, we analyzed data from a subset of participants in a previously conducted randomized trial who had a creatinine clearance less than or equal to 75 mL/min.

METHODS

Study Group and Design

The design of the Cholesterol and Recurrent Events (CARE) trial has been described in detail elsewhere (14). Briefly, this was a randomized, double-blind, placebo-controlled trial in men and postmenopausal women who had had acute myocardial infarction between 3 and 20 months before randomization and had total plasma cholesterol levels less than 6.21 mmol/L (<240 mg/dL). Participants with 2+ proteinuria or greater on routine dipstick testing or serum creatinine values more than 1.5 times the upper limit of normal (as defined by the central study laboratory) were specifically excluded from the CARE study.

After stratification according to clinical center, eligible persons were assigned by computer-generated random or-

Context

Are statins effective and safe in patients with renal insufficiency?

Contribution

This subgroup analysis of a large randomized, double-blind, placebo-controlled trial shows that pravastatin reduces risk for future cardiovascular events in men and women with recent myocardial infarction, total cholesterol level less than 6.21 mmol/L (240 mg/dL), and mild renal insufficiency. Adverse events were few and were similar in nature and frequency to those that have been reported in patients without renal insufficiency.

Implications

Pravastatin appears to be safe and effective for secondary prevention of cardiovascular events in patients with mild chronic renal insufficiency.

—The Editors

der to receive 40 mg of pravastatin (Pravachol, Bristol-Myers Squibb, Princeton, New Jersey) once daily, or placebo. Treatment allocation was concealed by a centrally maintained code. Participants continued to take all prescribed medication that they were receiving at baseline. All study-specific laboratory measurements were performed at a central facility.

Our analysis used the same cardiovascular end points specified by the original CARE trial. The primary end point was death from coronary disease (including fatal myocardial infarction, sudden death, death during a coronary intervention, and death from other coronary causes) or a symptomatic nonfatal myocardial infarction confirmed by serum creatine kinase measurements. Secondary end points included major coronary events (fatal coronary disease, nonfatal myocardial infarction, coronary artery bypass surgery, or coronary angioplasty), all-cause mortality, stroke, and coronary revascularization. A committee that was blinded to serum lipid levels and treatment assignment determined outcomes. The adequacy of blinding was not formally assessed.

Definitions of Renal Insufficiency

The Cockcroft–Gault equation for creatinine clearance is widely used and is known to correlate well with glomerular filtration rate (15). We initially selected a creatinine clearance less than or equal to 75 mL/min as our primary definition of mild chronic renal insufficiency. Recently published guidelines suggest defining renal function in terms of an equation derived from the Modification of Diet in Renal Disease (MDRD) Study (16). This equation expresses glomerular filtration rate in mL/min per 1.73 m² of body surface area and is defined by $186 \times \text{PCr}^{-1.154} \times \text{age in years}^{-0.203} \times 1.210$ (if black) $\times 0.742$ (if female), where PCr is plasma creatinine

concentration in mg/dL. Mildly decreased glomerular filtration rate is defined as 60 to 89 mL/min per 1.73 m². Although the MDRD equation has not been used as extensively as the Cockcroft–Gault equation, its use is becoming more common. We performed additional analyses by defining mild chronic renal insufficiency as a glomerular filtration rate less than 75 mL/min per 1.73 m².

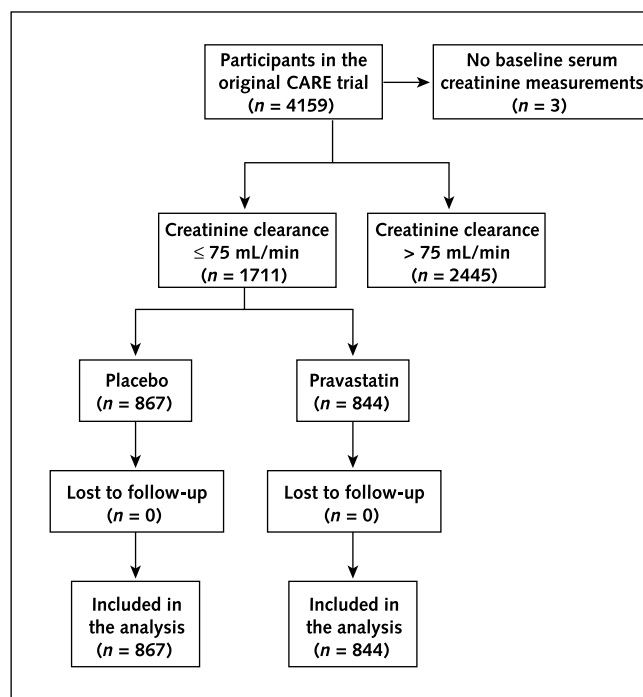
Subgroup Analysis

We performed several additional analyses to evaluate the potential interactions among pravastatin use, chronic renal insufficiency, and certain subgroups. These subgroups were determined according to published recommendations (17) and were defined by diabetic status, serum lipid levels at baseline, different levels of renal function, and proteinuria (defined as detectable protein on routine urine dipstick testing).

Statistical Analysis

All analyses were performed on an intention-to-treat basis; *P* values are two sided. The effect of pravastatin on the rate of the primary end point was assessed by using the log-rank test. All other hazard ratios (HRs) and associated 95% CIs were assessed with Cox proportional hazards

Figure. Flow of participants through the study.



Inclusion criteria were age 21 to 75 years, plasma total cholesterol level < 6.21 mmol/L (<240 mg/dL), low-density lipoprotein cholesterol level 3.0 to 4.5 mmol/L (115 to 174 mg/dL), fasting triglyceride level < 4.0 mmol/L (<350 mg/dL), fasting glucose level ≤ 12.2 mmol/L (≤220 mg/dL), left ventricular ejection fraction ≥ 25%, and no symptomatic congestive heart failure. Serum lipid levels were measured at two or three specified visits to the clinic at least 8 weeks after hospitalization for myocardial infarction and after 4 weeks of treatment with the National Cholesterol Education Program Step 1 diet. These values were averaged to determine eligibility. CARE = Cholesterol and Recurrent Events.

Table 1. Baseline Characteristics in Participants according to Creatinine Clearance and Treatment Status*

Variable	Participants with Creatinine Clearance > 75 mL/min	Participants with Creatinine Clearance ≤ 75 mL/min
Patients, <i>n</i>	2445	1711
Age, <i>y</i>	54.7 ± 8.8	64.3 ± 6.8
Men, <i>n</i> (%)	2239 (91.6)	1342 (78.4)
White ethnicity, <i>n</i> (%)	2276 (93.1)	1573 (91.9)
Body surface area, <i>m</i> ²	2.02 ± 0.18	1.83 ± 0.16
History of hypertension, <i>n</i> (%)	965 (39.5)	807 (47.2)
Current smoker, <i>n</i> (%)	461 (18.9)	210 (12.3)
History of diabetes mellitus, <i>n</i> (%)	348 (14.2)	237 (13.9)
History of congestive heart failure, <i>n</i> (%)	134 (5.5)	165 (9.6)
Left ventricular ejection fraction	0.537 ± 0.119	0.534 ± 0.117
Medication use, <i>n</i> (%)		
Pravastatin	1237 (50.6)	844 (49.3)
ACE inhibitor	307 (12.6)	282 (16.5)
Aspirin	2056 (84.1)	1404 (82.1)
β-Adrenergic antagonist	995 (40.7)	654 (38.2)
Calcium-channel antagonist	928 (38.0)	700 (40.9)
Baseline lipid status		
Total cholesterol level, <i>mmol/L</i> (<i>mg/dL</i>)	5.39 ± 0.44 (208.3 ± 17.0)	5.40 ± 0.45 (209.0 ± 17.3)
LDL cholesterol level, <i>mmol/L</i> (<i>mg/dL</i>)	3.58 ± 0.38 (138.6 ± 14.6)	3.58 ± 0.37 (138.6 ± 14.5)
HDL cholesterol level, <i>mmol/L</i> (<i>mg/dL</i>)	0.97 ± 0.21 (37.6 ± 8.3)	1.05 ± 0.26 (40.6 ± 9.9)
Triglyceride level, <i>mmol/L</i> (<i>mg/dL</i>)	1.81 ± 0.70 (160.3 ± 62.4)	1.68 ± 0.66 (148.8 ± 58.3)
Renal function and blood pressure		
Creatinine clearance, <i>mL/min</i>	100.3 ± 21.6	61.3 ± 10.1
Serum creatinine concentration, <i>μmol/L</i> (<i>mg/dL</i>)	91 ± 14 (1.0 ± 0.2)	111 ± 21 (1.2 ± 0.2)
Serum urea level, <i>mmol/L</i> (<i>mg/dL</i>)	5.7 ± 1.4 (16.0 ± 4.1)	6.7 ± 2.0 (18.7 ± 5.3)
Proteinuria (dipstick positive), <i>n</i> (%)	642 (26.3)	523 (31.0)
Systolic blood pressure, <i>mm Hg</i>	127.4 ± 17.0	131.0 ± 19.4
Diastolic blood pressure, <i>mm Hg</i>	79.5 ± 10.0	77.3 ± 10.3
Mean arterial pressure, <i>mm Hg</i>	103.4 ± 12.2	104.2 ± 13.4

* Values presented with plus/minus signs are means ± SD. ACE = angiotensin-converting enzyme; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

models, adjusting for covariates that might confound the relationship between treatment assignment and outcomes. Review of the log–log survival curves for each model showed no evidence that the proportional hazards assumption was violated. There was no evidence of effect modification by center, and stratifying models by center did not affect the results. Analyses were performed by using SAS software, version 8.2 (SAS Institute, Inc., Cary, North Carolina).

Role of the Funding Source

The CARE trial and this substudy on renal insufficiency are investigator-initiated studies funded by Bristol-Myers Squibb. The data were collected and analyzed by and are now maintained at the coordinating center at the University of Texas School of Public Health, Houston, Texas. The authors had unlimited access to the data used in this analysis. The sponsor is entitled to comment on manuscripts before submission, and the authors may consider these comments, but the rights to publication reside contractually with the investigators. The sponsor maintained information on adverse events and other trial data, as required by federal regulations.

RESULTS

Baseline Characteristics

Of the 4159 persons in the original trial, 1711 had chronic renal insufficiency according to the primary defi-

nition (creatinine clearance ≤ 75 mL/min) (Figure). Participants with renal insufficiency were older, were more likely to be women and to have a history of hypertension or congestive heart failure, and had slightly higher systolic blood pressure than those without renal insufficiency. Dipstick-positive proteinuria was slightly more common in persons with chronic renal insufficiency. Persons with renal insufficiency in the pravastatin and placebo groups were similar at baseline (Table 1).

Adherence to Therapy and Use of Co-Medications

Rates of therapy discontinuation between the pravastatin and placebo groups were similar among participants with renal insufficiency (46 of 844 participants vs. 54 of 867 participants; *P* > 0.2). Rates of use of β-adrenergic blockers, aspirin, and angiotensin-converting enzyme inhibitors were similar between treatment groups at baseline and during annual follow-up visits. Angiotensin-receptor antagonists were not widely available when the CARE study was conducted.

Cardiovascular Event Rates in Participants with Chronic Renal Insufficiency

The cumulative incidence of the primary end point and of major coronary events were similar in persons with and without chronic renal insufficiency. Two hundred fifteen of the 1711 participants with renal insufficiency experienced the primary end point, compared with 271 of the 2448 participants with normal renal function (11.1%) (ad-

Table 1— Continued

Participants in the Placebo Group with Creatinine Clearance \leq 75 mL/min	Participants in the Pravastatin Group with Creatinine Clearance \leq 75 mL/min
867	844
64.2 \pm 6.7	64.4 \pm 6.8
678 (78.2)	661 (78.3)
792 (91.4)	778 (92.2)
1.83 \pm 0.16	1.82 \pm 0.16
414 (47.8)	392 (46.5)
106 (12.2)	104 (12.3)
130 (15.0)	107 (12.7)
82 (9.5)	83 (9.8)
0.525 \pm 0.128	0.520 \pm 0.119
0 (0)	844 (100)
138 (15.9)	144 (17.1)
714 (82.4)	687 (81.4)
317 (36.6)	337 (40.0)
338 (39.0)	362 (42.9)
5.41 \pm 0.44 (209.2 \pm 17.2)	5.40 \pm 0.45 (208.7 \pm 17.5)
3.59 \pm 0.37 (138.8 \pm 14.4)	3.58 \pm 0.38 (138.4 \pm 14.7)
1.05 \pm 0.26 (40.7 \pm 9.9)	1.05 \pm 0.26 (40.5 \pm 9.9)
1.68 \pm 0.64 (148.6 \pm 57.0)	1.68 \pm 0.67 (148.6 \pm 59.5)
61.3 \pm 10.3	61.2 \pm 9.9
111 \pm 21 (1.2 \pm 0.2)	111 \pm 20 (1.2 \pm 0.2)
6.7 \pm 1.9 (18.9 \pm 5.5)	6.6 \pm 1.8 (18.6 \pm 5.0)
267 (30.8)	255 (30.2)
130.9 \pm 19	131.2 \pm 20
77.3 \pm 10.4	77.3 \pm 10.2
104.1 \pm 13.2	104.2 \pm 13.6

justed HR, 1.20 [95% CI, 0.94 to 1.51]). Participants with chronic renal insufficiency had higher rates of all-cause mortality (unadjusted HR, 1.63 [CI, 1.33 to 2.00]) and stroke (unadjusted HR, 1.98 [CI, 1.40 to 2.80]) than those without. However, after adjustment for baseline factors, these differences were no longer statistically significant.

Pravastatin Use in Chronic Renal Insufficiency

Median duration of follow-up was 58.9 months in the participants with chronic renal insufficiency; complete

follow-up data were available for all participants in this subgroup. Persons in the pravastatin group with and without renal insufficiency had similar changes in plasma lipid levels in response to therapy. Among those with renal insufficiency, pravastatin was associated with statistically significant reductions in mean low-density lipoprotein cholesterol level (by 0.96 mmol/L [37.3 mg/dL]), mean total cholesterol level (by 1.03 mmol/L [39.8 mg/dL]), and triglyceride level (by 0.14 mmol/L [12.5 mg/dL]) compared with placebo. Increase in mean high-density lipoprotein cholesterol level was 0.02 mmol/L (0.73 mg/dL) greater in those receiving pravastatin than in those receiving placebo.

Pravastatin use was associated with a lower rate of cardiovascular events in chronic renal insufficiency, even after adjustment for potential confounders (Table 2). Participants with renal insufficiency who received pravastatin had an adjusted HR of 0.72 (CI, 0.55 to 0.95) for the primary end point of fatal coronary disease or myocardial infarction. The rates of major coronary events (adjusted HR, 0.72 [CI, 0.59 to 0.88]) and coronary revascularization (adjusted HR, 0.65 [CI, 0.50 to 0.83]) were significantly lower. However, pravastatin use did not significantly reduce total mortality and incidence of stroke (adjusted HRs, 0.81 [CI, 0.61 to 1.08] and 0.62 [CI, 0.39 to 1.00], respectively). The adjusted and unadjusted HRs were similar for all models.

Pravastatin and Alternate Definitions of Chronic Renal Insufficiency

We repeated our analysis of major coronary events using different diagnostic criteria for chronic renal insufficiency. The glomerular filtration rate was less than or equal to 75 mL/min per 1.73 m² in 2508 participants. The magnitude of benefit associated with pravastatin use was similar in this subgroup and in those who had chronic renal insufficiency according to the primary definition. Among these 2508 persons, the adjusted HR was 0.77 (CI, 0.62 to 0.96) for the primary end point and 0.80 (CI, 0.68 to

Table 2. Effect of Pravastatin Use on Incidence of Cardiovascular Events in Participants with Chronic Renal Insufficiency, as Defined by Creatinine Clearance of 75 mL/min or Less*

Event	Participants in the Placebo Group	Participants in the Pravastatin Group†	Adjusted Hazard Ratio with Pravastatin (95% CI)	P Value‡
	← n (%) →			
Death from CHD or nonfatal MI§	126 (14.5)	89 (10.5)	0.72 (0.55–0.95)	0.02
Major coronary event	234 (27.0)	171 (20.3)	0.72 (0.59–0.88)	0.001
Total mortality	111 (12.8)	86 (10.2)	0.81 (0.61–1.08)	0.14
Fatal MI or confirmed nonfatal MI	90 (10.4)	65 (7.7)	0.73 (0.52–1.01)	0.06
CABG or PTCA	153 (17.6)	105 (12.4)	0.65 (0.50–0.83)	0.001
Unstable angina	142 (16.4)	133 (15.8)	0.93 (0.73–1.18)	>0.2
Stroke	46 (5.3)	29 (3.4)	0.62 (0.39–1.00)	0.051

* All models were based on complete data for 1711 participants (867 in the placebo group and 844 in the pravastatin group). Hazard ratios and P values were derived from Cox proportional hazards models. Patient-specific data were used to compute P values and confidence intervals. CABG = coronary artery bypass grafting; CHD = coronary heart disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

† Percentages are cumulative incidences.

‡ Adjusted for age; sex; history of hypertension; smoking at baseline; diabetes mellitus; previous congestive heart failure; use of angiotensin-converting enzyme inhibitors, calcium-channel blockers, β -adrenergic blockers, and aspirin; proteinuria; systolic and diastolic blood pressure; baseline high-density lipoprotein and low-density lipoprotein cholesterol levels; baseline triglyceride levels; serum albumin levels; body surface area; and pravastatin use.

§ This combined variable was the specified primary end point.

Table 3. Major Coronary Events in Subgroups of Participants with Chronic Renal Insufficiency, Defined by Baseline Variables*

Variable	Participants in the Placebo Group	Participants in the Pravastatin Group	Participants in the Placebo Group with a Coronary Event	Participants in the Pravastatin Group with a Coronary Event	Unadjusted Absolute Reduction in Cumulative Incidence
	<i>n</i>		<i>n</i> (%)		
Diabetes mellitus					
Present	130	107	53 (40.7)	32 (29.9)	10.8
Absent	737	737	181 (24.6)	139 (18.9)	5.7
History of hypertension					
Present	415	392	131 (31.6)	86 (21.9)	9.7
Absent	452	452	103 (22.8)	85 (18.8)	4.0
Total cholesterol level					
≤5.40 mmol/L (≤209 mg/dL)	414	418	104 (25.1)	80 (19.1)	6.0
>5.40 mmol/L (>209 mg/dL)	453	426	130 (28.7)	91 (21.4)	7.3
LDL cholesterol level					
<3.23 mmol/L (≤125 mg/dL)	174	181	33 (19.0)	40 (22.1)	–
3.23–3.88 mmol/L (125–150 mg/dL)	495	470	136 (27.5)	86 (18.3)	9.2
>3.88 mmol/L (>150 mg/dL)	198	193	65 (32.8)	45 (23.3)	9.5
HDL cholesterol level					
≤0.96 mmol/L (≤37 mg/dL)	368	366	103 (28.0)	77 (21.0)	7.0
>0.96 mmol/L (>37 mg/dL)	499	478	131 (26.3)	94 (20.0)	6.3
Triglyceride level					
<1.63 mmol/L (<144 mg/dL)	456	476	134 (29.4)	95 (20.0)	9.4
≥1.63 mmol/L (≥144 mg/dL)	411	368	100 (24.3)	76 (20.7)	3.6
Proteinuria					
Present	268	255	81 (30.2)	65 (25.5)	4.7
Absent	589	575	148 (25.1)	104 (18.1)	7.0
Creatinine clearance					
<75 mL/min per 1.73 m ²	1164	1139	315 (27.1)	244 (21.4)	5.7
≤75 mL/min	867	844	234 (27.0)	171 (20.3)	6.7
60–75 mL/min	518	524	143 (27.6)	103 (19.7)	7.9
50–75 mL/min	736	719	207 (28.1)	140 (19.5)	8.6
≤60 mL/min	349	320	91 (26.1)	68 (21.3)	4.8
≤50 mL/min	131	125	27 (20.6)	31 (24.8)	–

* Definition of renal insufficiency is creatinine clearance ≤ 75 mL/min unless otherwise specified. Major coronary events included fatal ischemic heart disease, nonfatal myocardial infarction, coronary artery bypass surgery, or coronary angioplasty. Although the absolute reductions in cumulative incidence in the categories of variables are descriptive of patients with mild chronic renal insufficiency, the reductions in these subgroups did not significantly differ from each other. HDL = high-density lipoprotein; LDL = low-density lipoprotein.

0.94) for major coronary events. The HRs for myocardial infarction (0.75 [CI, 0.58 to 0.98]) and coronary revascularization (0.76 [CI, 0.62 to 0.92]), but not the HR for total mortality (0.94 [CI, 0.75 to 1.21]), were reduced with pravastatin use.

Pravastatin Use in Subgroups of Participants with Chronic Renal Insufficiency

We analyzed the effect of pravastatin use on cardiovascular events among subgroups of persons with chronic renal insufficiency defined by baseline variables (Table 3). No evidence showed a statistically significant interaction between any of these characteristics and HRs associated with pravastatin use ($P > 0.15$ for interaction in all cases). In particular, no significant interaction between the severity of renal insufficiency and the effect of pravastatin was

found, regardless of whether creatinine clearance or the MDRD equation was used as the defining criterion.

Adverse Events

Adverse events associated with pravastatin use were infrequent among persons with chronic renal insufficiency according to the primary definition. No significant differences were seen in the numbers of participants in the pravastatin and placebo groups who developed elevated serum creatine phosphokinase levels greater than three times the upper limit of normal (6 of 844 vs. 3 of 867; $P > 0.2$), other abnormalities on liver function tests (5 of 844 vs. 5 of 867; $P > 0.2$), or rhabdomyolysis (0 of 844 vs. 3 of 867; $P > 0.2$). The numbers of participants who had depression (10 of 844 vs. 14 of 867; $P > 0.2$), had nondermatologic

malignancy (133 of 844 vs. 146 of 867; $P > 0.2$), or committed suicide (1 of 844 vs. 0 of 867; $P > 0.2$) were also similar between treatment groups. The incidence of skin cancer was marginally higher in pravastatin recipients (57 of 844 vs. 41 of 867; $P = 0.08$). The number of noncardiovascular deaths did not differ significantly between treatment groups (30 of 844 vs. 43 of 867; $P = 0.15$).

DISCUSSION

Chronic renal insufficiency is an established risk factor for cardiovascular disease, which in turn is a major cause of death in affected patients. Our results show that pravastatin reduces cardiovascular events in persons with mild chronic renal insufficiency, as defined by creatinine clearance less than or equal to 75 mL/min. The magnitude of the observed benefit from pravastatin was similar in persons with and those without renal insufficiency. Pravastatin treatment seems to reduce the incidence of cardiovascular events and coronary revascularization in persons with chronic renal insufficiency. Defining renal insufficiency in terms of glomerular filtration rate rather than creatinine clearance did not change these results.

Baseline lipid status was not associated with the magnitude of benefit associated with pravastatin use. As in the original CARE analysis, neither diabetes mellitus nor baseline proteinuria on routine dipstick testing was associated with the reduction in cardiovascular events in participants with renal insufficiency who were receiving pravastatin (18). Although there was no evidence that severity of renal dysfunction affected pravastatin, only a few participants had advanced kidney disease. The effect of statins in this population deserves further investigation.

Although the MDRD equation for glomerular filtration rate has been extensively validated in moderate to severe chronic renal insufficiency (16), its accuracy in patients with better renal function, such as most of the CARE participants, is not as well established. For this reason, we chose a priori to primarily define renal insufficiency in terms of creatinine clearance rather than glomerular filtration rate. The risk reduction associated with pravastatin was qualitatively similar for participants with creatinine clearance less than or equal to 75 mL/min and glomerular filtration rate less than or equal to 75 mL/min per 1.73 m². Despite the well-known limitations of creatinine clearance, all persons with creatinine clearance values in this range almost certainly have impaired renal function, especially since creatinine clearance tends to overestimate glomerular filtration rate. Thus, our results demonstrate that pravastatin seems to reduce the incidence of cardiovascular events in persons with mild renal insufficiency.

We found that the magnitude of the increased mortality rate associated with chronic renal insufficiency was similar to that in a recent reanalysis of the Heart Outcomes and Prevention Evaluation (HOPE) (9). For example, the crude HR of total mortality among participants with

chronic renal insufficiency was 1.60 in our study, compared with 1.83 in HOPE. In the current analysis, adjustment for confounders such as blood pressure and congestive heart failure rendered these differences in outcome statistically nonsignificant. The degree of renal dysfunction in HOPE participants appeared similar to that in our analysis. However, the HOPE authors did not report mean serum creatinine concentration or creatinine clearance, making this observation difficult to confirm.

Like the authors of the Framingham Study (19), we did not find mild renal insufficiency to be an independent risk factor for cardiovascular events. These findings might suggest that the adverse outcomes associated with mild chronic renal insufficiency are predominantly mediated by traditional markers of risk rather than factors unique to renal dysfunction. Interpretation of previous work is complicated by the lack of uniform adjustment for congestive heart failure and proteinuria (which are known to be correlated with cardiovascular outcomes) and by slightly different definitions of renal insufficiency (9, 10). Although we did not find an independent association, persons with renal insufficiency clearly constitute a large, readily identifiable group in whom cardiovascular events are common. These persons may benefit substantially from therapies that reduce cardiovascular risk.

Pravastatin was well tolerated in persons with mild to moderate renal insufficiency. The incidence of rhabdomyolysis, elevated aminotransferase levels, and acute renal failure did not differ in the pravastatin and placebo groups, and no evidence showed that pravastatin use was associated with more frequent noncardiovascular death. In addition, adverse event rates were similar among participants with and without renal insufficiency (18). These findings are reassuring, since concern has been raised that rates of medication-related adverse events may be higher among persons with renal insufficiency, particularly with other classes of hypolipidemic agents (such as fibrates) (20, 21). Perhaps for this reason, statins are infrequently used in patients with renal insufficiency and concomitant cardiovascular disease (11). Our data suggest that pravastatin is safe in persons with mild to moderate renal insufficiency. Pravastatin has theoretical advantages in patients with kidney disease because its clearance is not affected by glomerular filtration rate (22). However, because our study included a limited number of participants with severe renal impairment, it is impossible to draw conclusions about adverse event rates in more advanced disease.

Our study has several limitations. We were unable to determine the cause of renal dysfunction in study participants, and we did not have quantitative information on proteinuria. Because of the select nature of CARE participants, our results may not be generalizable to all patients with renal insufficiency. In addition, since this was a post hoc analysis, we adjusted for potential imbalances in confounding variables between treatment groups. In the case of stroke and nonfatal myocardial infarction, the number

of variables adjusted for may have been high compared with the number of events. However, because the unadjusted HR for these outcomes was very similar to the adjusted value, it is unlikely that this affected our results. Finally, there were no statistically significant differences between treatment groups in the use of potentially confounding co-medications at baseline or during follow-up or in the rates of therapy discontinuation. We believe that the large size and high quality of the CARE study offer a unique opportunity to gain insight into the potential cardiovascular benefits of statins in mild chronic renal insufficiency. We used the term *chronic renal insufficiency* in our study although the duration of low creatinine clearance at baseline in CARE participants was unknown. However, given the very low frequency of acute renal failure in ambulatory, free-living persons such as those who participated in CARE, assumption of chronic insufficiency seems reasonable.

In conclusion, pravastatin seems to be effective for secondary prevention of cardiovascular events in persons with mild chronic renal insufficiency. The low rate of adverse events associated with pravastatin use is reassuring and supports more frequent prescription of statins to persons with this condition. If more widely used, this strategy might safely reduce the burden of cardiovascular disease in this population. Further work should be done to evaluate the benefits of statins in patients with more severe renal disease.

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