Effect of Pravastatin in People with Diabetes and Chronic Kidney Disease

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Although diabetes is a major cause of chronic kidney disease (CKD), limited data describe the cardiovascular benefit of hydroxymethyl glutaryl CoA reductase inhibitors (statins) in people with both of these conditions. This study sought to determine whether pravastatin reduced the incidence of first or recurrent cardiovascular events in people with non–dialysis-dependent CKD and concomitant diabetes, using data from three randomized trials of pravastatin 40 mg daily *versus* placebo. CKD was defined by estimated GFR <60 or 60 to 89.9 ml/min per 1.73 m² with proteinuria. Of 19,737 patients, 4099 (20.8%) had CKD but not diabetes at baseline, 873 (4.4%) had diabetes but not CKD, and 571 (2.9%) had both conditions. The primary composite outcome was time to myocardial infarction, coronary death, or percutaneous/surgical coronary revascularization. Median follow-up was 64 mo. After adjustment for trial and random treatment assignment, the incidence of the primary outcome was lowest in individuals with neither CKD nor diabetes (15.2%), intermediate in individuals with only CKD (18.6%) or only diabetes (21.3%), and highest in individuals with both characteristics (27.0%). Pravastatin reduced the relative likelihood of the primary outcome to a similar extent in subgroups defined by the presence or absence of CKD and diabetes. For example, pravastatin was associated with a significant reduction in the relative risk of the primary outcome by 25% in patients with CKD and concomitant diabetes and by 24% in individuals with neither characteristic. However, the absolute reduction in the risk of the primary outcome as a result of pravastatin use was highest in patients with both CKD and diabetes (6.4%) and lowest in individuals with neither characteristic (3.5%). In conclusion, stage 2 or early stage 3 CKD and diabetes both are associated with higher cardiovascular risk, and pravastatin reduces cardiovascular event rates in people with neither, one, or both characteristics. Given the high absolute benefit of pravastatin in patient with diabetes and stage 2 or early stage 3 CKD, this population in particular should be targeted for widespread use of statins. Additional studies are needed to determine whether these benefits apply to patients with more severe CKD, and recruitment to such studies should be given high priority.

C hronic kidney disease (CKD) is a potent risk factor for cardiovascular disease. Recent data show that even mild CKD is associated with increased rates of cardiovascular events, and death from cardiovascular disease is substantially more common than progression to ESRD among people with CKD (1–3). Despite this burden of disease, medications that prevent cardiovascular events in the general population are underprescribed to people with CKD (4–6).

Hydroxymethyl glutaryl CoA reductase inhibitors ("statins") prevent cardiovascular events in a wide variety of populations, including people with and without a history of coronary heart disease (7,8), and across a wide range of serum cholesterol levels (9). Statins improve cardiovascular outcomes in people with diabetes (10,11) and also in those with moderate (non–dialysis-dependent) CKD (12). However, the recently completed 4D randomized study in 1255 hemodialysis patients with diabetes found no significant cardiovascular benefit of atorvastatin 20 mg daily compared with placebo (13).

No published data describe the effect of statins in patients with diabetes and kidney disease. Because there are at least 1.3 million such individuals in the United States alone (14), these data would be of potential public health importance. The purpose of our analysis was to determine the effect of pravastatin on cardiovascular events in patients who had kidney disease and diabetes and had concomitant coronary disease or who were at high cardiovascular risk.

Materials and Methods
Patients
Design, conduct, and principal results of the West of Scotland Coronary Prevention Study (WOSCOPS), Cholesterol and Recurrent Events (CARE), and Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) studies have been described in detail (7,15,16). All three studies were randomized, double-blinded studies that compared pravastatin 40 mg daily with placebo for approximately 5 yr. Briefly, WOSCOPS studied high-risk individuals who had not previously experienced a myocardial infarction (MI). CARE and LIPID were secondary prevention trials of patients with previous acute coronary syndromes and average cholesterol levels. Outcomes in all three trials were assessed by blinded observers using prespecified criteria and common definitions. The maximum baseline serum creatinine values for patient in WOSCOPS, CARE, and LIPID were 1.7, 2.5, and 4.5 mg/dl, respectively; patients with creatinine values above these levels were ineligible.

Indices of Renal Function and Definition of Diabetes
The primary index of kidney function used the Modified Diet and Renal Disease Trial formula for estimated GFR (MDRD-GFR):

$$186 \times \mathrm{SCr}^{-1.154} \times \mathrm{Age}^{-0.203} \times 1.210^{\delta(\text{black})} \times 1.742^{\delta(\text{female})}$$

where age is in years, SCr is serum creatinine in mg/dl (17), and $\delta()$ is the indicator function (equal to 1 if the condition is true, 0 otherwise). In our previous work, we considered GFR <60 ml/min per 1.73 m² to constitute CKD (12). However, published guidelines indicate that individuals with mildly reduced GFR (60 to 89.9 ml/min per 1.73 m²) and concomitant proteinuria should also be considered to have CKD (17). In this analysis, we defined CKD by the presence of GFR <60 ml/min per 1.73 m² or the coexistence of GFR 60 to 89.9 ml/min per 1.73 m² with trace or greater proteinuria on dipstick urinalysis. Proteinuria was not measured in WOSCOPS, so CKD was defined solely by GFR <60 ml/min per 1.73 m² in WOSCOPS participants. Participants in all three trials were considered to have diabetes when they had known diabetes or were using insulin at baseline. Patients were classified into four mutually exclusive groups: (1) Both CKD and diabetes, (2) CKD without diabetes, (3) diabetes without CKD, and (4) neither CKD nor diabetes. In sensitivity analysis, we used GFR alone (MDRD-GFR <60 ml/min per 1.73 m², without considering proteinuria) to define CKD. A second sensitivity analysis used creatinine clearance (estimated using the Cockcroft-Gault equation [18]) rather than MDRD-GFR to classify participants with respect to CKD status.

Statistical Analyses
Analyses were undertaken on an intention-to-treat basis. The relation among CKD, diabetes, and cardiovascular risk was assessed in categorical analyses using the four groups described above. To avoid confounding by baseline cardiovascular risk and other factors that might be unique to the individual trials, we used generalized log-linear models (19) that included adjustment for trial (CARE, LIPID, or WOSCOPS) for all such analyses. Additional analyses determined the relation among CKD, diabetes, and cardiovascular risk after adjustment for other cardiovascular risk factors (1).

Efficacy of pravastatin for preventing cardiovascular events was assessed in the same four categories. The primary outcome was time to first occurrence of coronary heart disease death, nonfatal MI, or coronary revascularization (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty). In addition, the time to an expanded composite cardiovascular outcome (first occurrence of coronary heart disease death, nonfatal MI, coronary revascularization, or nonfatal stroke) and time to all-cause mortality were examined as secondary outcomes. Influence of pravastatin on outcomes was assessed using proportional hazards regression models. The following covariates were also included in all models: Treatment assignment; age; systolic BP; HDL cholesterol; LDL cholesterol; triglycerides; an indicator for trial (CARE, LIPID, or WOSCOPS); current smoking status; history of stroke; history of coronary heart disease; history of diabetes; insulin dependence; and baseline use of aspirin, β-blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers.

Appropriateness of the proportional hazards assumption was assessed for each outcome by examination of log($-$log[survival]) plots for the four categories of patients defined by diabetic status and CKD status. These figures revealed no important departures from proportionality. Possible two-way interactions between treatment and the presence or absence of diabetes and CKD were tested by including cross-product terms for these characteristics in the model. Analyses were performed using SAS statistical software, version 8.2 (Cary, NC).

Results
Baseline Characteristics
Of 19,737 patients, 4099 (20.8%) had CKD but not diabetes at baseline, 873 (4.4%) had diabetes but not CKD, and 571 (2.9%) had both conditions. The remaining 14,194 (71.9%) had neither CKD nor diabetes. Participants with kidney disease tended to be in stage 2 or early stage 3 CKD. For example, the median GFR among patients with CKD was 56.2 ml/min per 1.73 m² (range 29.5 to 89.8) and 56.3 ml/min per 1.73 m² (range 10.8 to 89.7) with and without diabetes, respectively. The proportion of patients who were assigned to pravastatin was similar for all four subgroups (Table 1). Patients with both diabetes and CKD tended to be older, were more likely to be female, and had a higher prevalence of coronary heart disease at baseline than patients with one or neither of these conditions (Table 1). Patients with diabetes and CKD also tended to have higher baseline systolic BP, lower LDL and HDL cholesterol, and higher serum triglycerides (Table 1). Characteristics were well balanced between pravastatin and placebo groups for each of the four subgroups defined by diabetic and CKD status (data not shown).

Association among CKD, Diabetes, and Cardiovascular Risk
CKD and diabetes both were independently associated with an increased risk for the primary outcome (adjusted hazards ratio [HR] 1.15, 95% confidence interval [CI] 1.07 to 1.24; and adjusted HR 1.39, 95% CI 1.24 to 1.55, respectively). The association between CKD and the risk for cardiovascular events was nonsignificant when limited to patients with diabetes at baseline, although the hazard ratio was similar. Specifically, the adjusted HR associated with CKD among patient with diabetes was 1.16 (95% CI 0.95 to 1.41) for the primary outcome of

Table 1. Descriptive statistics for baseline parameters by baseline renal function and diabetic status in patients who had or were at high risk for coronary disease[a]

	No CKD Nondiabetic	CKD Nondiabetic	No CKD Diabetic	CKD Diabetic
N	14194	4099	873	571
Female	981 (6.9)	839 (20.5)	115 (13.2)	156 (27.3)
Current smokers	3203 (22.6)	493 (12.0)	118 (13.5)	42 (7.4)
Previous stroke	296 (2.1)	170 (4.1)	40 (4.6)	48 (8.4)
Known coronary disease	6492 (45.7)	3018 (73.6)	660 (75.6)	500 (87.6)
Known hypertension	3914 (27.6)	1905 (46.5)	400 (45.8)	343 (60.1)
Previous angina	6722 (47.4)	2524 (61.6)	601 (68.8)	326 (57.1)
Using antihypertensive medication	6896 (48.6)	3158 (77.0)	661 (75.7)	504 (88.3)
Previous MI	6017 (42.4)	2805 (68.4)	609 (69.8)	464 (81.3)
Previous unstable angina	2159 (15.2)	797 (19.4)	193 (22.1)	102 (17.9)
Pravastatin use	7135 (50.3)	2024 (49.4)	429 (49.1)	290 (50.8)
Age (yr)	56.8 ± 7.9	62.0 ± 8.0	60.0 ± 7.9	64.2 ± 7.0
Systolic BP (mmHg)	132.9 ± 18.0	134.5 ± 19.7	135.0 ± 18.9	137.9 ± 20.1
Diastolic BP (mmHg)	81.6 ± 10.6	80.5 ± 10.9	80.1 ± 10.8	79.1 ± 11.0
Weight (kg)	78.3 ± 12.2	78.4 ± 13.5	84.4 ± 15.7	83.2 ± 15.7
BMI (kg/m^2)	26.4 ± 3.6	26.9 ± 4.0	28.7 ± 5.0	28.9 ± 4.6
Serum creatinine (mg/dl)	1.0 ± 0.1	1.3 ± 0.2	1.0 ± 0.2	1.3 ± 0.2
MDRD-GFR (ml/min per 1.73 m^2)	78.1 ± 12.9	56.5 ± 10.3	79.9 ± 15.7	57.9 ± 12.7
Total cholesterol (mg/dl)	239.5 ± 38.1	223.5 ± 32.9	215.0 ± 33.3	212.5 ± 25.6
HDL cholesterol (mg/dl)	40.5 ± 9.8	38.4 ± 9.4	36.4 ± 9.0	36.3 ± 9.3
LDL cholesterol (mg/dl)	166.1 ± 31.6	152.6 ± 28.7	143.6 ± 29.2	140.2 ± 22.0
Triglycerides (mg/dl)	158.0 ± 75.2	160.9 ± 71.9	175.7 ± 87.7	181.1 ± 82.8

[a]Values are mean (SD) or number (%) where appropriate. *P* for trend across groups all are <0.001 except for pravastatin use (*P* = 0.76). CKD, chronic kidney disease; MI, myocardial infarction; BMI, body mass index; MDRD, Modification of Diet in Renal Disease.

coronary death, nonfatal MI, or the need for coronary revascularization and 1.16 (95% CI 0.96 to 1.39) for the expanded outcome of coronary death, nonfatal MI, coronary revascularization, or stroke, compared with individuals with diabetes but no CKD. Among participants with CKD, the presence of diabetes was independently associated with an adjusted HR of 1.42 (95% CI 1.20 to 1.68) and 1.47 (95% CI 1.25 to 1.72) for primary and expanded outcomes, respectively.

The incidence of the primary outcome was lowest in individuals with neither CKD nor diabetes and highest in patients with both characteristics. This relation remained after adjustment for the presence or absence of symptomatic coronary heart disease at baseline (CARE/LIPID *versus* WOSCOPS; Table 2). For example, the adjusted risk for the primary outcome was 15.2% (neither CKD nor diabetes), 18.6% (CKD alone), 21.3% (diabetes alone), and 27.0% (both CKD and diabetes) in the four subgroups of participants. Results were similar when risk was expressed per 100 patient-years of follow-up (3.1, 4.0, 4.8, and 6.4 events per 100 patient-years, respectively). Similar findings were observed for the expanded outcome and for all-cause mortality. Tests for interaction between diabetic status and CKD status on the risk for these clinical events were nonsignificant (all *P* > 0.6). Additional adjustment for other cardiovascular risk factors did not affect these results (data not shown).

Effect of Pravastatin on Cardiovascular Events

Pravastatin significantly reduced the adjusted incidence of the primary and secondary outcomes in all four subgroups of participants (Table 3). Tests for interaction between diabetic and CKD status and the effect of pravastatin on these outcomes were nonsignificant (*P* = 0.99 and 0.71, respectively). Although pravastatin reduced the relative likelihood of the primary outcome to a similar extent in all four groups, the absolute risk reduction was highest in participants with both CKD and diabetes and lowest in those with neither characteristic (Table 3). Specifically, after adjustment for trial, pravastatin reduced the absolute risk for the primary outcome by 3.5% (neither CKD nor diabetes), 4.5% (CKD alone), 5.0% (diabetes alone), and 6.4% (both CKD and diabetes), respectively, over the median follow-up of 64 mo (Figure 1).

Pravastatin significantly reduced the adjusted risk for all-cause mortality in participants with neither CKD nor diabetes (HR 0.71; 95% CI 0.63 to 0.81) but not in the other three subgroups (Table 3). Although the HR associated with the effect of pravastatin on mortality was qualitatively higher when CKD and diabetes both were present (HR 0.98; 95% CI 0.69, 1.39), there was no evidence that pravastatin reduced mortality to a lesser extent in this group (*P* = 0.27 for interaction). Results were similar when estimated creatinine

Table 2. Incidence of clinical outcomes by baseline category of kidney function and diabetic status[a]

	No CKD Nondiabetic	CKD Nondiabetic	No CKD Diabetic	CKD Diabetic
N	14,194	4099	873	571
Outcome Events (rate [95% CI])				
coronary heart disease death, nonfatal MI, CABG, or PTCA	15.2 (14.6 to 15.8)	18.6 (17.6 to 19.8)	21.3 (19.2 to 23.7)	27.0 (24.1 to 30.1)
coronary heart disease death, nonfatal myocardial infarction, CABG, PTCA, or stroke	16.7 (16.1 to 17.4)	21.2 (20.1 to 22.4)	25.2 (22.9 to 27.7)	31.7 (28.7 to 34.9)
all-cause mortality	6.4 (6.0 to 6.8)	10.3 (9.4 to 11.2)	11.6 (9.9 to 13.6)	18.5 (15.9 to 21.6)
coronary heart disease death or nonfatal MI	8.9 (8.5 to 9.5)	13.3 (12.3 to 14.3)	14.8 (12.7 to 17.1)	20.1 (18.1 to 24.3)
CABG or PTCA	7.4 (6.9 to 7.9)	7.5 (6.8 to 8.2)	8.6 (7.3 to 10.1)	10.0 (8.4 to 12.0)
any stroke	2.2 (1.9 to 2.4)	3.6 (3.0 to 4.2)	5.8 (4.5 to 7.4)	7.5 (5.7 to 9.9)

[a]Median follow-up period was 64 mo. CI, confidence interval; CAD, coronary artery disease; CABG, coronary artery bypass graft surgery; PTCA, percutaneous coronary angiography. %, adjusted for treatment assignment and trial (CARE, LIPID, or WOSCOPS). Parentheses contain 95% CI.

Table 3. Adjusted effect of pravastatin on clinical outcomes by CKD status and diabetic status[a]

	No CKD Nondiabetic	CKD Nondiabetic	No CKD Diabetic	CKD Diabetic
N	14194	4099	873	571
Coronary heart disease death, nonfatal MI, CABG, or PTCA	0.76 (0.70 to 0.82)	0.77 (0.68 to 0.87)	0.73 (0.57 to 0.94)	0.75 (0.57 to 0.98)
Coronary heart disease death, nonfatal MI, CABG, PTCA, or stroke	0.77 (0.71 to 0.83)	0.80 (0.71 to 0.90)	0.68 (0.54 to 0.86)	0.79 (0.62 to 1.03)
All-cause mortality	0.71 (0.63 to 0.81)	0.97 (0.82 to 1.15)	0.87 (0.61 to 1.23)	0.98 (0.69 to 1.39)
Coronary heart disease death or nonfatal MI	0.68 (0.61 to 0.76)	0.85 (0.73 to 1.00)	0.79 (0.57 to 1.09)	0.84 (0.60 to 1.18)
CABG or PTCA	0.81 (0.72 to 0.90)	0.72 (0.61 to 0.86)	0.58 (0.41 to 0.82)	0.69 (0.47 to 1.01)
Any stroke	0.77 (0.61 to 0.96)	0.96 (0.71 to 1.30)	0.48 (0.28 to 0.82)	1.12 (0.63 to 1.97)

[a]Values are for hazard ratios with 95% confidence intervals in parentheses. Hazard ratios have been adjusted for age; systolic BP; HDL cholesterol; LDL cholesterol; triglycerides; an indicator for trial (CARE, LIPID, or WOSCOPS); current smoking status; history of stroke; history of coronary disease; insulin dependence; and baseline use of aspirin, β blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers. Median follow-up period was 64 mo.

clearance rather than MDRD-GFR was used to classify participants with respect to CKD status (data not shown).

Alternative Definitions of CKD

Our primary definition of CKD included patients with mildly reduced GFR and trace proteinuria on routine dipstick. Although this definition may have increased sensitivity for detecting early diabetic nephropathy, it likely reduced specificity for other forms of CKD. To address this possibility, we repeated analyses defining CKD as the presence of GFR <60 ml/min per 1.73 m², without considering results of urinalysis. The resulting number of patients in each subgroup when this classification was used was 15,013 (neither CKD nor diabetes), 3280 (CKD alone), 1058 (diabetes alone), and 386 (both CKD and diabetes). In these analyses, the benefit of pravastatin was statistically nonsignificant among par-

ticipants with both CKD and diabetes. However, point estimates for the treatment effect were very similar to those in the primary analysis, suggesting that the definition of CKD is unlikely to have affected results. For example, the HR of the primary outcome associated with pravastatin treatment was 0.75 (95% CI 0.70 to 0.82), 0.79 (0.69 to 0.91), 0.77 (0.62 to 0.96), and 0.77 (0.55 to 1.08) in the four groups of participants. Similar results were obtained for the other clinical outcomes when this definition of CKD was used and also when a third definition of CKD (GFR <60 or GFR 60 to 89.9 ml/min per 1.73 m² with 1+ proteinuria or greater) was used (data not shown).

Discussion

We studied a large population of people who had or were at high risk for coronary disease, approximately 24% of whom
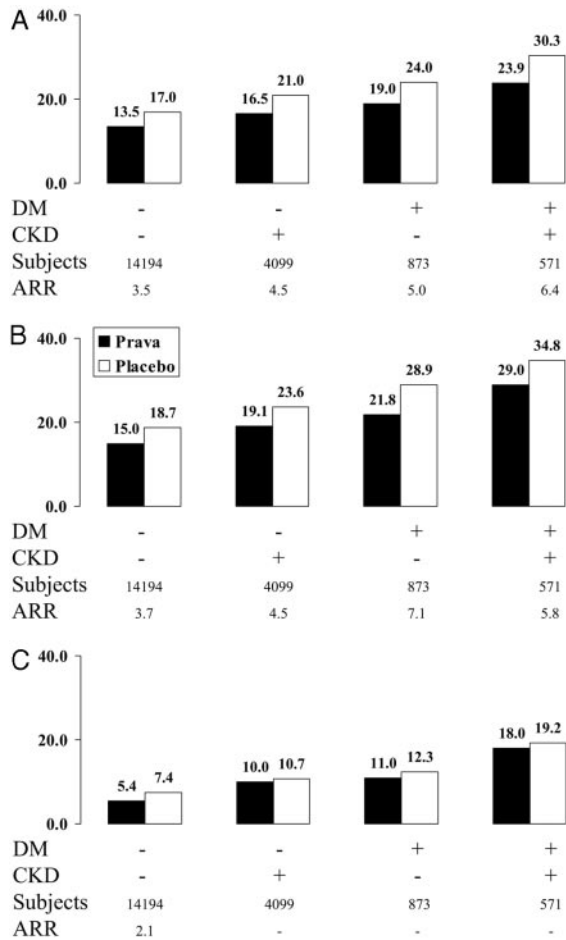
Figure 1. Effect of pravastatin on the absolute risk reduction in adverse clinical events by chronic kidney disease (CKD) and diabetic status. (A) Primary outcome (fatal coronary disease, nonfatal myocardial infarction, or coronary revascularization). (B) Expanded outcome (fatal coronary disease, nonfatal myocardial infarction, coronary revascularization, or stroke). (C) All-cause mortality. Diabetes and CKD were more frequent in patients with a history of coronary disease. Therefore, the incidence of each outcome in this analysis was adjusted for trial (CARE/LIPID *versus* WOSCOPS). Absolute risk reductions (ARR) are presented only for outcomes that were significantly less likely in pravastatin recipients.

had stage 2 to stage 3 CKD. As previously shown, patients with either CKD or diabetes had a substantially increased risk for cardiovascular events, compared with those with neither characteristic (2,10,12,20–22). However, individuals with CKD and concomitant diabetes were at quantitatively higher risk than those with one or neither of these conditions. After adjustment for trial, the primary outcome occurred in 27.0% of participants with diabetes and CKD but only 15.2% of nondiabetic participants without CKD, and 21.3% of those with diabetes alone. This increased risk persisted after adjustment for other factors that might influence the rate of cardiovascular events.

In this population of patients with symptomatic coronary disease or high-risk status, pravastatin was associated with a similar relative reduction in the likelihood of incident cardiovascular

events regardless of the presence or absence of CKD or diabetes ($P > 0.6$ for interaction). However, the markedly higher event rate in patients with CKD and concomitant diabetes translated into a greater absolute benefit of pravastatin on the risk for cardiovascular events. The benefit of pravastatin in this group seemed to be qualitatively largest for prevention of coronary revascularization. However, the negative tests for interaction suggest that the effect of pravastatin on harder outcomes such as cardiovascular death did not differ in patients with both CKD and diabetes, compared with those with one or neither characteristic.

Previous work has examined the cardiovascular effects of statins in patients with CKD or with diabetes but have generally not evaluated the benefit of these medications in people with both conditions (10,11,23–25). Our analysis confirms that statins reduce cardiovascular risk in diabetic individuals with mild or moderate CKD. This finding contrasts with results from the 4D trial, which recently found no benefit of atorvastatin 20 mg daily compared with placebo in 1255 dialysis-dependent individuals with diabetes (13). The 4D investigators reported a very high cardiovascular event rate but found that the risk reduction associated with treatment was qualitatively different from that in other statin trials (HR 0.92 for cardiovascular death, nonfatal MI, and stroke; 95% CI 0.77 to 1.10), raising the possibility that statins are less effective in this population.

Possibilities for the discrepant findings in 4D include differences in the study treatment regimens or the pathophysiology of atherosclerosis in the study populations (26–28). For example, because many cardiovascular events in dialysis patients are due to sudden death (perhaps as a result of electrolyte abnormalities) (29,30) or to cardiomyopathy (perhaps from chronic extracellular fluid volume overload) (26,29), it is possible that a beneficial effect of statin therapy on atherosclerotic events might have been diluted. A larger study therefore may be required to detect a benefit of statin treatment in dialysis patients, especially given the frequency with which atorvastatin recipients discontinued therapy (25%) and placebo recipients used nonstudy statins (15%) in 4D.

In one study, statins seemed to be equally effective for preventing cardiovascular events in participants with both diabetes and CKD, compared with those with one or neither characteristic, and the markedly higher event rate in this group translated into a greater absolute benefit of pravastatin on the risk for cardiovascular events. The nonsignificant effect of pravastatin on harder clinical outcomes such as cardiovascular death in patients with both diabetes and CKD may be due to low statistical power or, alternatively, to a true biologic difference in effect. Unfortunately, our analysis cannot differentiate between these possibilities, and further studies will be required. In the meantime, reducing the need for coronary revascularization (with the attendant possibility of acute or chronic renal failure) and possibly other adverse cardiovascular events seems to be a valid indication for statin therapy in this population.

Because our definition of kidney disease tended to select individuals with stage 2 or early stage 3 CKD, our findings may not apply in the setting of more advanced disease. In addition, although we found no evidence of an interaction between the coexistence of CKD and diabetes and the effect of pravastatin, our study may have lacked statistical power to demonstrate this,

especially for all-cause mortality. This uncertainty about the benefit of statin therapy in the setting of more advanced CKD highlights the urgent need to recruit to ongoing clinical trials such as the Study of Heart and Renal Protection (31).

Mortality after coronary heart disease events is several-fold higher among people with renal dysfunction than those with normal kidney function (32,33), emphasizing the potential importance of prevention in this population. However, most individuals with CKD do not receive statins, even those with previous coronary heart disease or with concomitant diabetes (6,34). The high cardiovascular risk associated with the combination of non–dialysis-dependent CKD and diabetes, and the favorable absolute risk reduction as a result of pravastatin treatment suggest that physicians should attempt to increase rates of statin use in this population. Because concomitant CKD and diabetes occur in nearly 40% of incident dialysis patients in the United States (10), prescription of statins at earlier stages of renal impairment might reduce the burden of cardiovascular disease among people with ESRD.

In addition to the considerations noted above concerning the interpretation of our findings, this analysis has several methodologic limitations. Although it was a *post hoc* analysis using participant-level data from three randomized, double-blind, placebo-controlled trials, there were several important similarities in the designs of the individual studies, including the same daily dose of pravastatin (40 mg), uniform definitions of prespecified outcomes, and careful ascertainment of outcomes. Second, although we followed published guidelines for classification of CKD (17), kidney function was estimated using equations based on serum creatinine rather than measured directly. Although prediction equations that are based on serum creatinine are less accurate than nuclear isotope estimates of GFR, they are the recommended method for estimating kidney function in clinical practice and epidemiologic studies (17). However, serum creatinine was measured on a single occasion and was not calibrated to the Cleveland Clinic reference laboratory, which may have influenced our ability to classify patients accurately with respect to CKD status. A related issue is that determination of proteinuria was based on a single random dipstick urinalysis rather than repeated quantitative measures such as urinary albumin to creatinine ratio. Because we did not have information on microalbuminuria, we used trace (rather than 1+) proteinuria to define CKD in patients with mildly reduced GFR, recognizing that this probably increased sensitivity for earlier forms of diabetic nephropathy while reducing specificity for other types of CKD (35,36). For these reasons, some patients may have been misclassified with respect to CKD status. Although the effect of pravastatin was nonsignificant when GFR alone was used to define CKD, the point estimate for the benefit of treatment was not qualitatively affected. Therefore, although we cannot exclude the possibility that our results were influenced by such potential misclassification, we believe that it is unlikely.

In conclusion, pravastatin reduced rates of cardiovascular events in people who had or were at risk for coronary heart disease and the combination of diabetes and stage 2 or early stage 3 CKD. Because of the extremely high risk associated with the coexistence of these two conditions, more widespread use of statins in this population likely would result in a clinically important benefit. However, additional studies are needed to determine the efficacy of statins in patients with more severe kidney disease, especially those who require chronic dialysis.

Acknowledgments

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