Conclusions—Pravastatin modestly reduced the rate of kidney function loss in people with or at risk for cardiovascular function.1 Hyperlipidemia may play a role in the progression medication mediates progressive renal insufficiency.5 Drugs that inhibit HMG-CoA reductase (statins) reduce serum cholesterol and appear to have additional antiinflammatory effects.6 Data from animal models and several small studies in humans suggest that statins might reduce the rate of kidney function loss and reduce proteinuria in glomerular disease.7,8 A recent publication suggested that pravastatin reduced rates of kidney function loss in humans with renal insufficiency and concomitant coronary disease, especially in those with proteinuria or more advanced renal impairment.9 However, the number of subjects in these analyses was small.

The purpose of the present analysis was to determine the effect of pravastatin on rates of kidney function loss in a large group of subjects with or at high risk for coronary disease, with particular emphasis on those with concomitant moderate...
CKD, as defined by an estimated glomerular filtration rate (GFR) between 30 and 59.9 mL/min per 1.73 m². We tested the hypothesis that pravastatin would slow the rate of decline in renal function over ≈5 years.

Methods

Subjects in the Individual Trials

The design, conduct, and principal results of WOSCOPS, CARE, and LIPID have been described in detail, as has the justification and methods for the Prospective Pravastatin Pooling (PPP) project. All were randomized, double-blinded studies comparing pravastatin 40 mg/d with placebo for ≈5 years. The West of Scotland Coronary Prevention Study (WOSCOPS) studied high-risk men who had not previously experienced a myocardial infarction and had fasting LDL cholesterol >155 mg/dL after 4 weeks of a cholesterol-restricted diet. Cholesterol and Recurrent Events (CARE)12 and Long-Term Intervention With Pravastatin in Ischemic Disease (LIPID)13 were trials of men and women with previous acute coronary syndromes and average cholesterol levels (baseline total cholesterol <240 and 155 to 271 mg/dL, respectively). The maximum baseline serum creatinine values for WOSCOPS, CARE, and LIPID were 1.7, 2.5, and 4.5 mg/dL, respectively; subjects with creatinine values above these levels were excluded. Outcomes in all 3 trials were assessed by blinded observers.

Indexes of Renal Function

Serum creatinine was measured at a central laboratory in CARE. In LIPID and WOSCOPS, serum creatinine was measured at local study laboratories rather than at a central facility, although measurements for a given participant were made at a single center. Baseline urinalyses were performed on all participants in CARE and LIPID but not for those in WOSCOPS. Proteinuria was defined as the presence of trace or greater protein on dipstick urinalysis. Estimated GFR was the primary index of kidney function. We estimated GFR using the Modified Diet and Renal Disease Study (MDRD-GFR) formula: 186×[(140−age)/(weight/72)]×(SCr)−1.154×age−0.203×1.210 (if black)×1.742 (if female), where age is in years, serum creatinine (SCr) is in mg/dL, and GFR is in mL/min per 1.73 m² body surface area (BSA).14

We also used the Cockcroft-Gault equation for creatinine clearance to estimate GFR (CG-GFR). Although creatinine clearance may overestimate glomerular filtration (because creatinine is secreted by renal tubules in addition to being filtered by the glomerulus), this equation has been widely used and validated as an estimate of CG-GFR.14 CG-GFR is defined for men as follows: (140−age)×weight/72×SCr×(1.73/BSA) mL/min per 1.73 m² BSA, where age and SCr are as defined earlier, weight is in kilograms, and BSA is in meters squared. For women, the equation for CG-GFR above is multiplied by 0.85 (or 85%).15 BSA was estimated from this formula: BSA = [height (cm)]²×[weight (kg)⁰.⁴²⁵]×0.007184.16

The primary outcome was the rate of change in MDRD-GFR (in mL/min per 1.73 m²/yr). We considered secondary outcomes, including the rate of change in CG-GFR, and 3 categorical outcomes: the occurrence of ≥25% reductions in estimated GFR during follow-up, the development of estimated GFR <60 mL/min per 1.73 m² during follow-up, and the occurrence of “acute renal failure” during follow-up. The last outcome was considered to have occurred if a study subject was diagnosed with acute renal failure by his or her personal physician (who was unaware of treatment assignment). Information on the occurrence of end-stage renal disease or death from renal disease was not recorded in the PPP data set. The indexes of renal function and outcomes to be studied were selected before analyses were begun.

Moderate CKD was defined by estimated GFR between 30 and 59.9 mL/min per 1.73 m². Recently published guidelines suggest that values <90 mL/min per 1.73 m² should be considered mildly reduced GFR.15 In the present data set, the risk of renal function loss and the renal effects of pravastatin appeared to be homogeneous in groups defined by 60 to 74.9 and 75 to 89.9 mL/min per 1.73 m². Therefore, we defined mild CKD and normal renal function by estimated GFR of 60 to 89.9 and ≥90 mL/min per 1.73 m², respectively.

Statistical Analysis

Descriptive statistics of each measure of renal function loss were computed for all 3 trials combined. Longitudinal changes in renal function (MDRD-GFR or CG-GFR) were estimated by maximum-likelihood random-coefficients regression models. Treatment-specific slopes and tests for differences were computed by fitting a set of “basic” models that included only baseline (prerandomization) renal function, an indicator of study (CARE, LIPID, or WOSCOPS), and treatment group assignment. Additional models included the basic set plus other covariates thought to be important predictors of renal function. The following baseline covariates were selected prospectively for inclusion: age, history of diabetes, insulin dependence, history of hypertension, systolic and diastolic blood pressures, LDL cholesterol, LDL cholesterol, triglycerides, glucose, ACE inhibitor use, black race, BSA, and gender.

Because subjects with more rapid renal function loss might be more likely to die of coronary disease and because pravastatin would be expected to reduce this risk, the possibility existed that pravastatin recipients would be more likely to live long enough to experience an adverse renal outcome. The potential impact of this informative censoring was assessed by examining Spearman rank correlation coefficients between simple 2-stage slope estimates of renal function decline and follow-up times. Analyses of relations between treatment group assignment and dichotomous outcomes were performed by χ² tests. For dichotomous outcomes, relative risks (RRs) and associated 95% CIs for pravastatin versus placebo assignment were computed after adjustment for trial. All analyses were performed with SAS statistical software. All analyses were performed using the treatment groups to which participants were assigned, and significance tests used 2-sided probability values. The CARE, LIPID, and WOSCOPS trials and this substudy on CKD are investigator-initiated studies funded by Bristol-Myers Squibb. All 3 studies were approved by local institutional review boards, and the University of Alberta institutional review board approved this analysis on CKD.

Results

Baseline Characteristics

Of 19,727 patients, renal function could be calculated for 18,569 (94.2%) on at least 2 occasions (median, 6); these patients were eligible. Of these, 3,402 (18.3%) had moderate CKD as defined by an estimated GFR of 30 to 59.9 mL/min per 1.73 m² at baseline. An additional 14 (0.08%) had a GFR <30 mL/min per 1.73 m², 12,843 (69.1%) had mild CKD (estimated GFR, 60 to 89.9 mL/min per 1.73 m²), and the remainder were considered to have normal renal function. The median interval between first and last GFR estimations was 5.0 years. There were no significant differences in the use of ACE inhibitors between the pravastatin and placebo groups at baseline (10.5% versus 10.2%, respectively; P = 0.8) or during follow-up (24.5% versus 25.4%, respectively; P = 0.17). Systolic and diastolic blood pressures did not differ between the pravastatin and placebo groups at baseline (P = 0.18 and P = 0.70, respectively) or at last follow-up (both P > 0.8).

Demographic and clinical characteristics, which were well balanced between the pravastatin and placebo recipients, are shown in Table 1. Subjects with CKD tended to be older and were more likely to be female than those with normal kidney function. Subjects with CKD were also more likely to have diabetes mellitus or known vascular disease compared with those with normal kidney function, in part because of the inclusion criteria of the individual trials. For example, par-
participants with serum creatinine of 2.0 mg/dL would have been excluded from WOSCOPS but not from CARE or LIPID. Thus, PPP subjects with CKD would have been more likely to be drawn from CARE or LIPID (for which symptomatic coronary disease was a prerequisite) rather than WOSCOPS. A statistical test for interaction suggested that pravastatin reduced kidney function loss to a greater extent among those with moderate CKD compared with those with mild CKD or normal kidney function (P = 0.06). Pravastatin was associated with a 31% slower unadjusted rate of kidney function loss in those with MDRD-GFR of 30 to 59.9 mL/min per 1.73 m² at baseline compared with placebo (P = 0.002). However, the absolute magnitude of the difference was clinically small (0.24 ± 0.08 mL/min per 1.73 m²/y). This result was similar after adjustment for other variables that might influence rates of renal function loss (34% reduction; 0.22 ± 0.07 mL/min per 1.73 m²/y slower than placebo; P = 0.002).

Renal Effects of Pravastatin in Individuals With Moderate CKD at Baseline

Although of borderline significance, a statistical test for interaction suggested that pravastatin reduced kidney function loss to a greater extent among those with moderate CKD compared with those with mild CKD or normal kidney function (P = 0.06). Pravastatin was associated with a 31% slower unadjusted rate of kidney function loss in those with MDRD-GFR of 30 to 59.9 mL/min per 1.73 m² at baseline compared with placebo (P = 0.002). However, the absolute magnitude of the difference was clinically small (0.24 ± 0.08 mL/min per 1.73 m²/y). This result was similar after adjustment for other variables that might influence rates of renal function loss (34% reduction; 0.22 ± 0.07 mL/min per 1.73 m²/y slower than placebo; P = 0.002).

Renal Function Loss in Individuals With Moderate CKD at Baseline

Among the 3402 individuals with MDRD-GFR of 30 to 59.9 mL/min per 1.73 m² at baseline, the mean rate of decline in MDRD-GFR was 0.67 ± 0.04 mL/min per 1.73 m²/y. Results of urinalyses were available only for CARE and LIPID participants, 480 (16.4%) of whom had evidence of proteinuria. Rates of MDRD-GFR decline were greater in individuals with proteinuria at baseline (1.28 ± 0.10 mL/min per 1.73 m²/y) compared with those without (0.47 ± 0.05 mL/min per 1.73 m²/y; P < 0.001).

### TABLE 1. Baseline Demographic and Clinical Characteristics of Study Subjects

<table>
<thead>
<tr>
<th></th>
<th>Pravastatin (n = 1702)</th>
<th>Placebo (n = 1700)</th>
<th>Pravastatin (n = 6479)</th>
<th>Placebo (n = 6364)</th>
<th>Pravastatin (n = 1157)</th>
<th>Placebo (n = 1153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63.1 (7.3)</td>
<td>63.5 (7.2)</td>
<td>63.0 (18.2)</td>
<td>63.0 (17.9)</td>
<td>63.1 (18.2)</td>
<td>63.0 (17.9)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>135 (20.2)</td>
<td>135 (19.4)</td>
<td>133 (18.2)</td>
<td>133 (17.9)</td>
<td>131.6 (18.2)</td>
<td>133.1 (18.4)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>80.4 (10.9)</td>
<td>80.3 (11.1)</td>
<td>81.4 (10.8)</td>
<td>81.4 (10.5)</td>
<td>81.3 (10.8)</td>
<td>81.9 (10.3)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>77.8 (13.1)</td>
<td>77.8 (13.1)</td>
<td>79.3 (12.7)</td>
<td>79.0 (12.5)</td>
<td>78.1 (13.8)</td>
<td>78.4 (13.3)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.9 (3.8)</td>
<td>26.9 (3.9)</td>
<td>26.7 (3.8)</td>
<td>26.6 (3.7)</td>
<td>26.4 (4.1)</td>
<td>26.6 (4.3)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>225.4 (33.9)</td>
<td>225.3 (33.5)</td>
<td>236.1 (38.2)</td>
<td>236.2 (37.9)</td>
<td>237.5 (37.2)</td>
<td>235.9 (37.4)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>38.3 (8.6)</td>
<td>38.5 (8.7)</td>
<td>39.9 (9.4)</td>
<td>40.0 (9.7)</td>
<td>40.9 (10.6)</td>
<td>40.5 (10.1)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>154.0 (29.5)</td>
<td>154.0 (29.7)</td>
<td>163.1 (32.0)</td>
<td>163.3 (31.6)</td>
<td>164.1 (31.0)</td>
<td>163.1 (31.4)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>163.4 (74.8)</td>
<td>162.9 (73.4)</td>
<td>160.0 (79.3)</td>
<td>158.4 (71.4)</td>
<td>159.4 (78.3)</td>
<td>156.6 (73.8)</td>
</tr>
<tr>
<td>MDRD-GFR, mL/min per 1.73 m²</td>
<td>52.7 (6.1)</td>
<td>52.7 (5.9)</td>
<td>73.8 (7.9)</td>
<td>73.8 (7.8)</td>
<td>100.3 (12.8)</td>
<td>99.8 (11.4)</td>
</tr>
<tr>
<td>CG-GFR, mL/min per 1.73 m²</td>
<td>53.0 (8.8)</td>
<td>52.7 (8.8)</td>
<td>74.0 (11.7)</td>
<td>73.8 (11.4)</td>
<td>97.9 (15.9)</td>
<td>98.2 (15.6)</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.38 (0.19)</td>
<td>1.37 (0.19)</td>
<td>1.08 (0.12)</td>
<td>1.08 (0.12)</td>
<td>0.84 (0.09)</td>
<td>0.84 (0.09)</td>
</tr>
<tr>
<td>Proteinuria, n (%)</td>
<td>249 (17.0)</td>
<td>231 (15.8)</td>
<td>474 (11.8)</td>
<td>489 (12.5)</td>
<td>65 (8.9)</td>
<td>65 (9.0)</td>
</tr>
</tbody>
</table>

Values are mean (SD) when appropriate.

*Proteinuria was defined by the presence of trace or greater protein on a prerandomization urinalysis. Because urinalyses were not routinely performed in WOSCOPS, participants, the number of subjects with moderate CKD, mild CKD, and normal renal function who had data on proteinuria was 7927 (4004 pravastatin, 4392 placebo), and 1452 (731 pravastatin, 721 placebo), respectively.
of pravastatin was slightly greater in those with MDRD-GFR of 30 to 39.9 mL/min per 1.73 m^2 at baseline (n = 145) than in those with MDRD-GFR of 40 to 59.9 mL/min per 1.73 m^2 (0.71 ± 0.34 and 0.22 ± 0.08 mL/min per 1.73 m^2/y slower than placebo).

When all subjects with MDRD-GFR of 30 to 59.9 mL/min per 1.73 m^2 were considered, there were no differences in the incidence of a ≥25% decline in MDRD-GFR (RR, 0.84; 95% CI, 0.66 to 1.06) or acute renal failure (RR, 0.71; 95% CI, 0.44 to 1.16) between groups during follow-up (Figure). We repeated analyses using CG-GFR rather than MDRD-GFR to define categories of CKD and changes in kidney function. In this analysis, the frequency of a ≥25% decline in CG-GFR was significantly lower in pravastatin recipients with a CG-GFR of 30 to 59.9 mL/min per 1.73 m^2 at baseline (RR, 0.73; 95% CI, 0.56 to 0.95).

Data from CARE/LIPID participants were used to perform analyses that stratified on the presence or absence of proteinuria, which has previously been suggested to predict renal benefit from statin treatment. We found no evidence of a significant interaction between proteinuria and the effect of pravastatin on the rate of change in estimated GFR (P for interaction = 0.41). However, pravastatin recipients with moderate CKD and proteinuria at baseline (n = 249) were significantly less likely to experience a ≥25% decrease in GFR (12.5% versus 19.9%; RR, 0.63; 95% CI, 0.41, 0.96) or acute renal failure (3.2% versus 8.7%; RR, 0.37; 95% CI, 0.17 to 0.82) during follow-up. Results were similar when CG-GFR was used to define kidney function (data not shown).

### Renal Effects of Pravastatin in Individuals With Mild CKD at Baseline

There was no significant effect of pravastatin on mean rates of kidney function loss in individuals with MDRD-GFR of 60 to 89.9 mL/min per 1.73 m^2 at baseline (adjusted rate of change, 0.06 ± 0.04 mL/min per 1.73 m^2/y slower than placebo; P = 0.15). In these subjects, pravastatin did not significantly reduce the proportion with a ≥25% reduction in MDRD-GFR (RR, 0.94; 95% CI, 0.85 to 1.03). However, the likelihood of acute renal failure was significantly less frequent in pravastatin recipients with baseline MDRD-GFR of 60 to 89.9 mL/min per 1.73 m^2 (RR, 0.42; 95% CI, 0.22 to 0.78), and the RR of developing moderate CKD was of borderline statistical significance (RR, 0.95; 95% CI, 0.90 to 1.00). Results were similar when CG-GFR was used to define kidney function (data not shown).

When all 18,569 PPP subjects were considered, pravastatin reduced the adjusted rate of kidney function loss by 8% (0.10 mL/min per 1.73 m^2/y; 95% CI, 0.02 to 0.17) and the risk of acute renal failure (RR, 0.60; 95% CI, 0.41 to 0.86) but did not significantly reduce the frequency of a ≥25% decline in kidney function (RR for MDRD-GFR, 0.94; 95% CI, 0.88 to 1.01), although the reduction was significant for CG-GFR (RR, 0.90; 95% CI, 0.83 to 0.98; Figure).

### Adverse Events in CKD

The frequencies of selected adverse events in pravastatin and placebo recipients in strata defined by renal function are compared in Table 3. Only 1 case of rhabdomyolysis was observed, and it occurred in a placebo recipient. Pravastatin was not associated with an increased incidence of any adverse event compared with placebo.

### Discussion

The hypothesis that dyslipidemia might cause kidney disease was first advanced more than a century ago, and there has been intense interest in the notion that lipid-lowering treatment might improve renal outcomes. To the best of our knowledge, this is the largest detailed examination of the renal effects of any statin. When all participants with moderate CKD at baseline were considered, pravastatin was associated with a 34% reduction in the adjusted rate of kidney function loss, although the absolute reduction in the rate of loss was clinically small. Although pravastatin appeared to reduce the rate of renal function loss to a greater extent in the 145 subjects with more severe renal impairment (GFR of 30 to 39.9 mL/min per 1.73 m^2), the absolute magnitude of the effect remained small (0.7 mL/min per 1.73 m^2/y slower than placebo). On the other hand, if this apparent beneficial effect of pravastatin extends to people with more severe CKD, this would be expected to translate into a clinically relevant reduction in the risk of kidney failure, because GFR may decline more rapidly at lower levels of kidney function.

Our primary analysis considered renal function as a continuous variable, which may not be an ideal surrogate measure for progression of kidney disease. For example, in a recent randomized study, the therapy associated with the

### Table 2. Effect of Pravastatin on Rate of Kidney Function Loss

<table>
<thead>
<tr>
<th>Unadjusted effect on rate of change in MDRD-GFR</th>
<th>Reduction in decline vs placebo group rate, %</th>
<th>Adjusted effect on rate of change in MDRD-GFR</th>
<th>Reduction in decline vs placebo group rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate CKD (MDRD-GFR 30–59.9 mL/min per 1.73 m^2)</td>
<td>Moderate CKD (MDRD-GFR 60–89.9 mL/min per 1.73 m^2)</td>
<td>All Levels of Kidney Function (n = 18,569)</td>
<td>All Levels of Kidney Function (n = 18,569)</td>
</tr>
<tr>
<td>0.24 (0.08–0.39)</td>
<td>0.08 (–0.01–0.16)</td>
<td>0.10 (0.02–0.17)</td>
<td>31.3 (12.5–50.2)</td>
</tr>
</tbody>
</table>

Values represent the difference (95% CI) in the rate of change in MDRD-GFR among subjects assigned to pravastatin compared with placebo. A positive value means that kidney function declined more slowly in subjects assigned to pravastatin.
The highest mean rate of kidney function loss had the lowest rates of progression to end-stage renal disease. This apparent paradox was driven by a strong protective effect in subjects at the highest risk of kidney failure such as those with lower baseline levels of kidney function and/or those with proteinuria. These observations suggest that the effect of pravastatin on outcomes such as a ≥25% decline in GFR may be more clinically relevant than its effect on the mean rate of change.

In people with moderate CKD, pravastatin did not significantly reduce the risk of a ≥25% decline in kidney function as estimated by MDRD-GFR (RR, 0.94; 95% CI, 0.85 to 1.03). When the C-G equation was used instead, pravastatin significantly reduced the risk of a ≥25% reduction in kidney function by approximately one quarter. The reduction in risk was also significant in subjects with moderate CKD and concomitant proteinuria and was of borderline significance when all PPP subjects were considered. Although these findings are provocative, they should be interpreted with caution, because pravastatin did not significantly reduce the incidence of this outcome in all subgroups.

As expected, acute renal failure occurred infrequently in study participants. Although pravastatin did not reduce the incidence of acute renal failure among those subjects with moderate CKD at baseline, a significant reduction was observed in the subgroup with moderate CKD and proteinuria (absolute risk reduction, 5.5%; number needed to treat, 18). Smaller but statistically significant reductions were observed in the larger group with mild CKD and when all PPP participants were considered (0.3%; number needed to treat, 301). To the best of our knowledge, no other trial demonstrates that statins prevent acute renal failure in humans. However, experimental studies suggest that the severity of ischemic acute renal failure may be ameliorated by statin treatment, perhaps through hemodynamic or antiinflammatory mechanisms. The effect of pravastatin in the present study might have been mediated through prevention of contrast nephropathy (by reducing the need for coronary angiography) or by reducing the risk of atheroembolic renal disease.

Clinically relevant renal outcomes by treatment group. A, Acute renal failure; B, percent with 25% decline in MDRD-GFR; C, percent with 25% decline in CG-GFR; D, percent developing moderate CKD.

Statins are infrequently used in patients with CKD despite the high cardiovascular risk associated with this condition. Despite concerns about the safety of statins in people with kidney disease, we found that pravastatin was well tolerated in subjects with and without renal insufficiency, with no evidence of clinically relevant toxicity. Our previous work showed that pravastatin reduces mortality in people with or at risk for coronary disease who have concomitant moderate CKD. Given the high rates of morbidity and mortality associated with kidney failure, preventing progressive loss of renal function is an important public health objective. The present study suggests that in addition to reducing cardiovascular risk, the use of pravastatin may also modestly slow the rate of kidney function loss in this population.

Our findings are generally consistent with the results of previous studies. A meta-analysis of all studies published...
before 2001 suggested that lipid-lowering medications (statins were used in 11 of 13 trials) significantly reduced the rate of kidney function loss by \( \approx 1.9 \text{ mL} \cdot \text{min}^{-1} \cdot \text{y}^{-1} \). Because many of the participants in the included trials had glomerulonephritis or diabetes mellitus, the lower absolute magnitude of the benefit in the present study might reflect a lower underlying rate of kidney function loss compared with subjects in the meta-analysis. More recently, a small randomized trial \((n=56)\) showed that atorvastatin significantly slowed renal loss in people with proteinuric renal disease, and the Heart Protection Study showed a beneficial effect of simvastatin on the rate of kidney function loss that was similar in magnitude to that observed in the present study. Although a large randomized study in renal transplant recipients found no evidence that fluvastatin improved graft survival, it is unclear whether these findings are applicable to native kidney disease, in which the causes and mechanisms of progressive renal loss might differ substantially. A subgroup analysis of the CARE study suggested that pravastatin reduced the rate of kidney function loss, especially in those with baseline glomerular filtration rate \( < 40 \text{ mL/min per 1.73 m}^2 \). However, the small number of such subjects \((n=32)\) was the rationale for the present study, which included the subjects from CARE and expanded the number in this subgroup to 145.

Recent work in experimental and human renal disease demonstrates that statins reduce urinary protein excretion. Because proteinuria is associated with more rapid rates of kidney failure or a \( \geq 25\% \) decrease in kidney function in subjects with moderate CKD and proteinuria, which is consistent with this hypothesis. Our study has several strengths and limitations that should be considered. To the best of our knowledge, this is the largest study to describe the renal effects of statins in detail. Although this was a post hoc, pooled analysis using data from 3 randomized, double-blind, placebo-controlled trials, there were several important similarities in the designs of the individual studies, including use of pravastatin at the same daily dose \((40 \text{ mg})\) and ascertainment of outcomes by individuals who were unaware of treatment status. Second, kidney function was estimated from equations based on serum creatinine rather than directly measured. It is therefore possible that our findings were due in part to effects of statins on nonrenal organs (such as muscle) rather than kidney function. However, although prediction equations 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 epidemiological studies. Third, much of the error associated with these equations is related to calibration of the serum creatinine assay, especially when true GFR is \( < 60 \text{ mL/min per 1.73 m}^2 \). Although serum creatinine measurements were not made in a central laboratory for 2 of the 3 studies included in the PPP, measurements were made in the same laboratory for each participant, suggesting that the lack of a central study laboratory is unlikely to have affected our results. Nonetheless, it is possible that undetected assay drift over time might have resulted in random error. Because any such measurement error should have been similar in both groups, it is unlikely to have appreciably influenced our findings, although it may have biased our results toward the null. Fourth, although the diagnosis of acute renal failure was determined by physicians who were unaware of treatment status, this outcome was not adjudicated through the use of standardized criteria. Therefore, the finding that pravastatin prevents acute renal failure requires confirmation. Fifth, because the cause of reduced GFR in PPP participants was unknown and because all had or were at high risk for coronary disease, the generalizability of these findings is uncertain. In addition, it is unclear whether these findings can be extrapolated to individuals who are followed up by nephrologists for CKD or to those with rapid and progressive loss of kidney function. However, given the frequent coexistence of renal and cardiovascular disease, such individuals are common in the general...
population and in cardiology practice. Finally, additional randomized trials are required to determine whether statins exert renal effects in individuals with severe CKD (estimated GFR <30 mL/min per 1.73 m²),30,38 those with heavy proteinuria, or those at low risk for coronary events.

In conclusion, pravastatin reduced the rate of kidney function loss and the risk of acute renal failure in people with or at risk for cardiovascular disease. Although these effects might be of public health importance, their clinical significance requires further study. Consequently, the primary rationale for the use of statins in people with or at risk for coronary events remains the reduction in cardiovascular mortality and mortality that results from their use.

Acknowledgments
Dr Tonelli was supported by a Population Health Investigator Award from the Alberta Heritage Foundation for Medical Research and a New Investigator Award from the Canadian Institutes for Health Research.

Disclosure
The CARE, LIPID, and WOSCOPS trials and this substudy on kidney disease are investigator-initiated studies funded by Bristol-Myers Squibb. Statistical analyses were performed at Wake Forest University, Winston-Salem, NC, independently of the sponsor. 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 regulation.

Dr Tonelli has received a research grant from Bristol-Myers Squibb and has received honoraria from and has served on the advisory board of Pfizer. Dr Craven has served as a consultant to Bristol-Myers Squibb. Dr Tonkin has received a research grant as co-chairman of the management committee of study of rosuvastatin (AstraZeneca) and has received honoraria for speaking at symposia sponsored by AstraZeneca, Pfizer, and Sankyo. Dr Pfeiffer has received honoraria from and has served as a consultant to Bristol-Myers Squibb. Dr Sacks has served on the speakers’ bureaus of and/or received honoraria from Bristol-Myers Squibb and Sankyo and has served as a consultant to Bristol-Myers Squibb. Dr Furbeger has received research grants from GlaxoSmithKline. Dr Curhan has received a research grant from NIDDK. Dr Cobbe has received research grants from Bristol-Myers Squibb and AstraZeneca and has served on the speakers’ bureau of and/or received honoraria from AstraZeneca.

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Circulation. 2005;112:171-178; originally published online July 5, 2005; doi: 10.1161/CIRCULATIONAHA.104.517565

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/112/2/171

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