Background—Limited data describe the cardiovascular benefit of HMG-CoA reductase inhibitors (statins) in people with moderate chronic kidney disease (CKD). The objective of this analysis was to determine whether pravastatin reduced the incidence of cardiovascular events in people with or at high risk for coronary disease and with concomitant moderate CKD.

Methods and Results—We analyzed data from the Pravastatin Pooling Project (PPP), a subject-level database combining results from 3 randomized trials of pravastatin (40 mg daily) versus placebo. Of 19,700 subjects, 4491 (22.8%) had moderate CKD, defined by an estimated glomerular filtration rate of 30 to 59.99 mL/min per 1.73 m² body surface area. The primary outcome was time to myocardial infarction, coronary death, or percutaneous/surgical coronary revascularization. Moderate CKD was independently associated with an increased risk of the primary outcome (adjusted HR 1.26, 95% CI 1.07 to 1.49) compared with those with normal renal function. Among the 4491 subjects with moderate CKD, pravastatin significantly reduced the incidence of the primary outcome (HR 0.77, 95% CI 0.68 to 0.86), similar to the effect of pravastatin on the primary outcome in subjects with normal kidney function (HR 0.78, 95% CI 0.65 to 0.94). Pravastatin also appeared to reduce the total mortality rate in those with moderate CKD (adjusted HR 0.86, 95% CI 0.74 to 1.00, \( P = 0.045 \)).

Conclusions—Pravastatin reduces cardiovascular event rates in people with or at risk for coronary disease and concomitant moderate CKD, many of whom have serum creatinine levels within the normal range. Given the high risk associated with CKD, the absolute benefit that resulted from use of pravastatin was greater than in those with normal renal function.

(Circulation. 2004;110:1557-1563.)

Key Words: kidney failure ■ statins ■ pravastatin ■ trials

Chronic kidney disease (CKD) is a potent risk factor for cardiovascular disease. Individuals requiring dialysis treatment have cardiovascular mortality rates that are 10 to 20 times greater than age- and sex-matched controls in the general population. More striking is that 1-year mortality after myocardial infarction (MI) in dialysis patients exceeds 90%. Recent evidence shows that even mild renal insufficiency is associated with increased rates of cardiovascular events and that cardiovascular disease is the major cause of death among people with CKD. Despite this burden of illness, data demonstrating how cardiovascular disease may be prevented in people with renal disease are scarce. Perhaps because of the paucity of data, medications that reduce cardiovascular risk in the general population are infrequently prescribed to people with CKD. HMG CoA reductase inhibitors (“statins”) reduce coronary events in individuals with no history of coronary disease and also stroke and mortality rates in patients with preexisting stable or unstable angina or previous MI. Patients with serum cholesterol levels as low as 3.5 mmol/L are known to benefit, as do other important subgroups such as those with diabetes mellitus.

Although no direct evidence indicates that statins are less effective in people with CKD, renal dysfunction may alter the pathophysiology of cardiovascular disease, and therefore therapies that reduce cardiovascular risk in the general population are...
population might be less effective when renal function is impaired.\textsuperscript{16,17} Risk factors related to CKD, such as anemia, abnormal calcium and phosphate metabolism, malnutrition (and complications thereof), and chronic inflammation, have been proposed as potential mediators of cardiovascular disease among people with renal insufficiency. Data from the National Health and Nutrition Examination Survey (NHANES) II and III studies show that the prevalence of these putative risk factors increases once estimated glomerular filtration rate (GFR) falls below 60 mL/min.\textsuperscript{3,18} Accordingly, aggressive cardiovascular risk reduction is recommended in people with GFRs below this threshold.\textsuperscript{3,19}

Pravastatin reduces coronary event rates in those with mild CKD and previous MI.\textsuperscript{20} However, limited data describe the benefit of statins in people with more severe impairment of renal function, such as those with estimated GFR <60 mL/min per 1.73 m\textsuperscript{2} body surface area. The purpose of the present analysis was to determine the effect of pravastatin on incident cardiovascular events in subjects with or at high risk for coronary disease and with concomitant CKD. Particular emphasis was placed on those with estimated GFRs between 30 and 59.9 mL/min per 1.73 m\textsuperscript{2}, corresponding to stage 3 CKD.\textsuperscript{15}

**Methods**

**Patients in the Individual Trials**

Design, conduct, and principal results of West of Scotland Coronary Prevention Study (WOSCOPS), Cholesterol And Recurrent Events (CARE), and Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) have been described in detail.\textsuperscript{8,11,21} All were randomized, double-blinded studies comparing pravastatin 40 mg daily with placebo for \textasciitilde5 years. WOSCOPS studied high-risk individuals who had not previously experienced an MI. CARE and LIPID were trials of subjects with previous acute coronary syndromes and average cholesterol levels. Outcomes in all 3 trials were assessed by blinded observers using prespecified criteria. The maximum baseline serum creatinine values for subjects included in WOSCOPS, CARE, and LIPID were 1.7, 2.5, and 4.5 mg/dL, respectively.

**Indices of Renal Function**

Two measures of renal function were used:

- The primary index used the Cockcroft-Gault equation to estimate GFR (CG-GFR). Although this equation was originally derived as an estimate of creatinine clearance, it has been widely used and validated as an estimate of GFR.\textsuperscript{15} CG-GFR is defined for males as

\[
\text{CG-GFR} = \frac{(140 - \text{age}) \times \text{weight}}{\text{SCr} \times 72 \times \text{BSA}},
\]

where age is in years, actual body weight in kilograms, serum creatinine (SCr) in milligrams per deciliter, and body surface area (BSA) in meters squared. For females, the equation for CG-GFR above is multiplied by 0.85.\textsuperscript{22}

- The Modified Diet and Renal Disease Trial formula was used for estimated GFR (MDRD-GFR):

\[
186 \times \text{SCR}^{-1.154} \times \text{Age}^{-0.203} \times 1.210 \times \text{black} \times 1.047 \times \text{female},
\]

where age and SCr are defined as in the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) Clinical Practice Guidelines for Chronic Kidney Disease.\textsuperscript{15} GFR was estimated using CG-GFR and MDRD-GFR, and participants were classified as having normal renal function (\textasciitilde90 mL/min per 1.73 m\textsuperscript{2}), mild CKD (60 to 89.99 mL/min per 1.73 m\textsuperscript{2}), or moderate CKD (30 to 59.99 mL/min per 1.73 m\textsuperscript{2}).\textsuperscript{15} Subjects with CG-GFR <30 mL/min per 1.73 m\textsuperscript{2} (n = 27) were excluded.

**Statistical Methods**

Analyses in this article were not prespecified in the original Pravastatin Pooling Project (PPP) protocol but were specified before examining information on kidney function and were undertaken on an intention-to-treat basis. The relation between renal function and cardiovascular risk was assessed in categorical analyses using the 3 groups (normal renal function, mild CKD, and moderate CKD) and also in analyses using continuous estimates of renal function (CG-GFR, MDRD-GFR). The relation between renal function and cardiovascular outcomes was assessed with and without adjustment for other cardiovascular risk factors.\textsuperscript{3}

Efficacy of pravastatin for preventing cardiovascular events was assessed in the 3 categories of renal function. The primary outcome was time to first occurrence of coronary death, nonfatal MI, or coronary revascularization. Time to an expanded composite cardiovascular outcome (first occurrence of cardiovascular death, nonfatal MI, coronary revascularization, or nonfatal stroke) and time to all-cause death were examined as secondary outcomes. Influence of CG-GFR and MDRD-GFR on follow-up outcomes was assessed with the use of proportional hazards regression models. The following covariates also were included in all models: treatment assignment; age; systolic blood pressure; diastolic blood pressure; HDL cholesterol; LDL cholesterol; triglycerides; an indicator for trial (CARE, LIPID, or WOSCPoS); current smoking status; history of stroke; history of coronary disease; history of diabetes; insulin dependence; and baseline use of aspirin, \textbeta-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 by tertiles of renal function, which showed no important departures from proportionality. Possible 2-way interactions between treatment and renal function were tested by including an additional effect for the continuous renal function measure of interest (CG-GFR or MDRD-GFR) in participants randomized to pravastatin.

**Results**

**Baseline Characteristics**

Participants with mild or moderate kidney disease more often were receiving antihypertensive medication and were more likely to have suffered a previous stroke. They were also older and more likely to be female, probably because such subjects have less kidney function for a given serum creatinine level. Baseline systolic blood pressure was higher and total and LDL cholesterol were lower in people with CKD (Table 1).

**Baseline Renal Function**

Of 19 700 participants with or at high risk for cardiovascular disease, 4491 (22.8%) had moderate CKD as defined by CG-GFR of 30 to 59.99 mL/min per 1.73 m\textsuperscript{2}, and 12 333 (62.6%) had mild CKD as defined by CG-GFR of 60 to 89.99 mL/min per 1.73 m\textsuperscript{2}. Notably, 44.6% of those with moderate CKD and 94.1% of those with mild CKD had serum creatinine levels within the normal range. A higher proportion of participants in CARE or LIPID had moderate CKD (34.2%) than those in WOSCOPS (7.6%). This difference appeared to be due to a higher prevalence of individuals at increased risk for CKD (because of presence of diabetes mellitus or established vascular disease) and older or female subjects in the 2 secondary-prevention trials.

When MDRD-GFR rather than CG-GFR was used to estimate kidney function, the total numbers of participants in
Influence of Baseline Renal Function on Cardiovascular Risk

Because moderate CKD was more common in the secondary-prevention studies, we considered the relation between kidney function and cardiovascular event rates primarily in the CARE and LIPID studies to avoid confounding by baseline cardiovascular risk. Moderate CKD (CG-GFR 30 to 59.99 mL/min per 1.73 m²) was associated with a crude hazard ratio (HR) of 1.64 (95% confidence interval [CI] 1.48 to 1.83) for the primary outcome of coronary death, nonfatal MI, or the need for coronary revascularization, and 1.74 (95% CI 1.57 to 1.93) for the expanded outcome of coronary death, nonfatal MI, coronary revascularization, or stroke, compared with individuals with normal renal function. Figure 1 shows the inverse relation between the crude incidence of the clinical outcomes and level of renal function. Even after adjustment for age, comorbidity, and medication use, moderate CKD was independently associated with an increased risk of the primary (HR 1.26, 95% CI 1.07 to 1.49) and expanded outcomes (HR 1.25, 95% CI 1.07 to 1.47).

When kidney function was treated as a continuous variable, there was a strong and independent relation between cardiovascular outcome and severity of renal impairment. When the primary outcome of coronary death, nonfatal MI, or the need for coronary revascularization was considered, a 20–mL/min per 1.73 m² decrease in CG-GFR or MDRD-GFR was independently associated with a 9% increase in risk (hazard ratio 1.09). Similar results were obtained when the expanded cardiovascular outcome or all-cause mortality were considered and when all 3 trials were included in analyses (Figure 2).

Effect of Pravastatin on Serum Lipid Levels

Among individuals with moderate CKD (CG-GFR 30 to 59.99 mL/min per 1.73 m²), pravastatin reduced LDL cholesterol levels by 47.9±24.1 mg/dL and triglyceride levels by 17.3±56.3 mg/dL and raised HDL cholesterol by 2.3±6.0 mg/dL at 12 months, compared with baseline (Table 2). LDL was reduced by a significantly greater extent in subjects with more severe renal insufficiency (P<0.001, Table 2).
Effect of Pravastatin on Cardiovascular Events in Moderate Renal Insufficiency

In the primary analysis, the effect of pravastatin was studied among those with moderate CKD (CG-GFR 30 to 59.99 mL/min per 1.73 m²) from all 3 studies, comprising a population of subjects that had or were at high risk of cardiovascular disease. Pravastatin significantly reduced the adjusted incidence of the primary outcome of coronary mortality, nonfatal MI, and coronary revascularization (HR 0.77, 95% CI 0.68 to 0.86) and the expanded outcome (cardiovascular mortality, nonfatal MI, coronary revascularization, or stroke; HR 0.79, 95% CI 0.71 to 0.88) in people with moderate CKD (Figure 3). Statistical tests for interaction revealed no significant differential effect of pravastatin in people with and without CKD or in those with and without symptomatic coronary disease at baseline (P for interaction for both analyses >0.5). Figure 3 also demonstrates the relative risk reductions in cardiovascular events for people with other levels of kidney function. Pravastatin significantly reduced rates of all-cause mortality and cardiovascular events in people with mild CKD at baseline. The magnitude of the relative risk reduction in the incidence of the primary outcome was similar in all 3 categories of renal function (Figure 3). Analyses repeated with MDRD-GFR as the index of renal function gave similar results (Figure 4).

Discussion

We found that moderate CKD was a powerful risk factor for cardiovascular disease, with event rates that remained ≈25% higher compared with those who had normal kidney function, after adjustment for potential confounders. Among people with moderate CKD and concomitant coronary disease or high-risk status, pravastatin was associated with a similar relative risk reduction to that observed in the overall trial cohorts, including a reduction in all-cause mortality. This translates to a greater absolute benefit of pravastatin in those with moderate renal impairment. The magnitude of these reductions in risk was similar regardless of which index of kidney function was used and was similar in subjects with or without documented coronary disease at baseline.

Previous studies either have examined the cardiovascular effects of statins in subjects with mild renal dysfunction or have not distinguished between mild and moderate CKD. It is tempting to speculate that statins would be both beneficial and cost-effective as primary prevention of coronary disease in individuals with moderate CKD and other cardiovascular risk factors.

Until recently, the terms “renal insufficiency” and “kidney disease” were applied only to patients with unequivocally raised serum creatinine levels. However, because creatinine
production is reduced at older age and in those with lower muscle mass, significant renal impairment may be present even when serum creatinine is within normal limits. For example, in the present study, 44.6% of subjects with moderate CKD and 94.1% of those with mild CKD had serum creatinine within the normal range. This insensitivity of serum creatinine for detecting clinically relevant renal dysfunction is thus at least partially responsible for the high proportion of PPP subjects who had mild or moderate CKD. Recent work shows that the mortality rate after coronary events is substantially higher among people with mild or moderate renal impairment than those with normal kidney function,6,25,26 which highlights the potential importance of prevention in this population. Surprisingly, the rate of statin use in those with kidney disease is low. For example, among Canadian patients followed up by nephrologists for CKD and concomitant cardiovascular disease, less than 25% were receiving statins, and statin use in other at-risk populations appears to be directly proportional to the level of kidney function.5–7 The benefit of pravastatin seen in the present work suggests that physicians should attempt to increase rates of statin use in people with mild or moderate CKD, who account for the vast majority of people with renal impairment worldwide.15

The excess cardiovascular risk in people with renal disease is only partially attenuated by adjustment for traditional risk factors. Table 2 presents selected clinical outcomes in subjects with or at high risk for coronary disease, stratified by baseline category of kidney function and treatment assignment. The table includes data on baseline cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and outcomes such as fatal/nonfatal CAD, CABG or PTCA, fatal/nonfatal CAD, CABG, or stroke, and all-cause mortality. The values are mean (SD) or No. (%) where appropriate. CAD indicates coronary artery disease; CABG, coronary artery bypass graft; and PTCA, percutaneous coronary angioplasty.

Values are mean (SD) or No. (%) where appropriate. CAD indicates coronary artery disease; CABG, coronary artery bypass graft; and PTCA, percutaneous coronary angioplasty.

This analysis included subjects from all 3 studies and used CG-GFR to define strata of kidney function.
cardiovascular risk factors.\textsuperscript{4,27} In addition, hypercholesterolemia does not necessarily imply higher cardiovascular risk in CKD\textsuperscript{16,28}—a finding noted also in the present study (in which subjects with moderate CKD had lower cholesterol levels but higher cardiovascular risk than those with normal kidney function). Accordingly, it has been proposed that so-called CKD-related risk factors might mediate cardiovascular disease in people with renal impairment. Such factors are incompletely elucidated but might include anemia, abnormal calcium and phosphorus metabolism, and oxidative stress,\textsuperscript{15} as well as chronic inflammation.\textsuperscript{29} If factors such as chronic inflammation and endothelial dysfunction are of heightened importance in CKD, statins might be particularly beneficial in people with renal disease because of their pleiotropic effects.\textsuperscript{16} On the other hand, CKD may simply identify subjects at high cardiovascular risk by marking for more severe atherosclerosis.\textsuperscript{30} Although our results do not address the pathophysiology of cardiovascular disease in CKD, they show that statins prevent cardiovascular events in people with renal impairment, at least in those whose estimated GFR exceeds 30 mL/min per 1.73 m\textsuperscript{2}.

This study has some limitations. Although it was a post hoc analysis that used data from 3 randomized, double-blind, placebo-controlled trials, there were several important similarities in the designs of the individual trials, including use of pravastatin at the same daily dose (40 mg), rigorous uniform definitions of prespecified outcomes, and meticulous ascertainment of outcomes. Although there may be disagreement about which marker of renal function is most appropriate, the results were consistent regardless of which definition was used. Finally, an additional randomized trial would be required to determine whether our results apply to individuals with severe CKD (estimated GFR <30 mL/min per 1.73 m\textsuperscript{2}).\textsuperscript{16,17}

In conclusion, pravastatin reduced rates of cardiovascular events and all-cause mortality in people with or at risk for coronary disease and concomitant mild or moderate renal impairment. Because of the high risk associated with CKD,
the absolute risk reduction in cardiovascular event rates that would result from additional uptake of statins in this population appears to be meaningful to clinical practice and should be encouraged.

Disclosure

Dr Pfeffer receives honoraria from Bristol-Myers Squibb.

Acknowledgment

Dr Tonelli was supported by a salary award from the Alberta Heritage Foundation for Medical Research.

References


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Circulation. 2004;110:1557-1563; originally published online September 13, 2004;
doi: 10.1161/01.CIR.0000143892.84582.60
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
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:
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