Statin Use in Outpatients With Obstructive Coronary Artery Disease

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Background—Clinical trials have shown that statin therapy reduces cardiovascular morbidity and mortality in patients with coronary artery disease (CAD), even among patients with low-density lipoprotein cholesterol levels $<100$ mg/dL. We sought to determine the extent to which patients with obstructive CAD in routine outpatient care are treated with statins, nonstatins, or no lipid-lowering therapy.

Methods and Results—Within the American College of Cardiology’s Practice Innovation and Clinical Excellence (PINNACLE) outpatient registry, we examined rates of treatment with statin and nonstatin medications in 38 775 outpatients with obstructive CAD (history of myocardial infarction or coronary revascularization) and without documented contraindications to statin therapy. Among these patients, 30 160 (77.8%) were prescribed statins, 2042 (5.3%) were treated only with nonstatin lipid-lowering medications, and 6573 (17.0%) were untreated. Lack of medical insurance was associated with no statin treatment, and male sex, coexisting hypertension, and a recent coronary revascularization were associated with statin treatment. Among those not on any lipid-lowering therapy, low-density lipoprotein cholesterol levels were available for 51.2% (3365/6573). Among these untreated patients, low-density lipoprotein cholesterol levels were $<100$ mg/dL in 1794 patients (53.3%) and $\geq 100$ mg/dL in 1571 patients (46.7%).

Conclusions—Despite robust clinical trial evidence, a substantial number of patients with obstructive CAD remain untreated with statins. A small proportion were treated with nonstatin therapy, and 1 in 6 patients was simply untreated; half of the untreated patients had low-density lipoprotein cholesterol values $<100$ mg/dL. These findings illustrate important opportunities to improve lipid management in outpatients with obstructive CAD. (Circulation. 2011;124:2405-2410.)

Key Words: cholesterol reduction ■ coronary artery disease ■ lipids ■ statins

Although randomized clinical trials$^1$–$^5$ have consistently demonstrated that secondary prevention treatment with statins substantially reduces recurrent cardiovascular events and mortality in patients with obstructive coronary artery disease (CAD), the extent to which these high-risk patients are treated with statin, nonstatin, or no lipid-lowering therapy in the outpatient cardiology setting is largely unknown. This is because prior studies have primarily examined rates of statin treatment for dyslipidemia or nonspecific diagnoses of CAD in population-based or health insurance databases.$^6$–$^10$ However, statin treatment rates among outpatients with documented obstructive CAD (ie, patients with prior myocardial infarction or coronary revascularization who are at high risk of recurrent events) may be different.

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Moreover, among untreated patients, it is unclear whether patients are untreated because they have normal-range low-density lipoprotein cholesterol (LDL-C) levels. Although current guidelines recommend that high-risk patients be treated to LDL-C levels $<100$ mg/dL, implicit within these guidelines are that patients are treated with a lipid-lowering agent (preferentially statins).$^11$ In addition, despite the guideline recommendations of LDL-C targets, clinical trials have found that the benefits of statin therapy are consistent across all subgroups, including those with LDL-C levels $<100$ mg/dL.$^1,12,13$ Therefore, nontreatment with statins because of a “normal-range” LDL-C level in patients at high risk for...
recurrent cardiovascular events may represent a gap in the quality of CAD care.

Recently, the American College of Cardiology’s National Cardiovascular Disease Registry (NCDR) initiated the Practice Innovation and Clinical Excellence (PINNACLE Registry) program, the first prospective registry of cardiovascular outpatient care in the United States. The emergence of this outpatient registry provides a unique opportunity to better understand lipid therapy in outpatients with CAD. Specifically, it affords the opportunity to quantify the proportion of patients with known obstructive CAD who are not treated with statins or any lipid-lowering medications. It can also describe the prevalence of undertreatment with statins among those with LDL-C levels of <100 and ≥100 mg/dL.

**Methods**

**Study Population**

The NCDR PINNACLE Registry was launched in 2008 by the American College of Cardiology and represents the first national, prospective, office-based, quality improvement registry of cardiac patients in the United States. Within participating practices, longitudinal patient data were collected at the point of care and included patients’ symptoms, vital signs, medications, laboratory values, and recent hospitalizations with the use of a standard data collection tool with written definitions, uniform data entry and transmission requirements, and data quality checks. For the purposes of this study, we assessed clinical data from 179,608 patients enrolled from 30 practices between July 1, 2009, and June 30, 2010. We included only those adult patients with documented obstructive CAD (n = 39,601), which was defined as a prior myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft surgery. If a patient had >1 clinic visit during the study period, data from only the index encounter were used to minimize overrepresentation by patients with multiple visits. Of the 30 practices enrolled in PINNACLE, we excluded 5 practices with <10 CAD patients and 1 practice with inconsistent data entry (total patients excluded = 311). We also excluded 515 patients with documented contraindications to statins (determined by the treating physician as a medical, patient, or system reason for exclusion). Our final study sample thus included 38,775 patients from 24 practices representing 111 practice locations in 18 states across the United States (Figure 1).

**Study Outcomes and Variables**

There were 2 principal outcomes for this study. First, we examined the proportion of patients with obstructive CAD who were treated with a statin, a nonstatin, or no lipid-lowering therapy. This was determined by whether a patient was prescribed a statin or nonstatin agent during the clinical encounter, and these rates include treatment decisions made during the office encounter. Second, among patients on no lipid-lowering therapy, we further examined the distribution of LDL-C levels in this population and quantified the proportion of patients with known obstructive CAD who are not treated with statins or any lipid-lowering medications. It can also describe the prevalence of undertreatment with statins among those with LDL-C levels of <100 and ≥100 mg/dL.

**Statistical Analyses**

Demographic and clinical characteristics were compared between those treated and not treated with statins with the use of χ² tests for categorical variables and t tests for continuous variables. To determine independent predictors for statin nontreatment, hierarchical log-Poisson regression models, with a random effect for site to adjust for clustering by site, were constructed. Patient-level covariates were entered as fixed effects in the multivariable model and included the following: age, sex, body mass index, diabetes mellitus, hypertension, prior myocardial infarction, recent percutaneous coronary intervention or coronary artery bypass graft surgery within the past 12 months, current tobacco use, and insurance status (none versus public versus private). Race was not included in the models because of a high (51.4%) missing rate. Because the rate of statin nontreatment exceeded 10%, we estimated relative risks (RRs) directly by using log-Poisson or modified Poisson regression models at all steps (as opposed to logistic regression) to avoid overestimation of estimates of effect. Nonlinearity between the covariates and outcomes was tested, and cubic spline terms were added to the model as appropriate, which was required for age (Table I and Figure I in the online-only Data Supplement) and body mass index (Table II and Figure II in the online-only Data Supplement).
To better characterize patients who were not treated with any lipid-lowering therapy, we examined the distribution of LDL-C levels in this group. Furthermore, the proportion of untreated patients with an LDL-C level of <100 and ≥100 mg/dL was determined.

Besides race, data were missing for 17% of patients (7% were missing 1 value, 5% were missing 2 values, and 4% were missing ≥3 values; the highest missing rate for any single variable was body mass index at 10%). Missing data were assumed to be missing at random and imputed with the use of 10 imputation data sets.18 All clinical and demographic variables available in PINNACLE were used to inform the imputation model.19 For each analysis, the null hypothesis was evaluated at a 2-sided significance level of 0.05 with 95% confidence intervals (CIs) calculated. All analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC), R version 2.7.0 (Foundation for Statistical Computing, Vienna, Austria), and IVEWare (Institute for Social Research, University of Michigan, Ann Arbor).

### Results

Of 38 775 patients with obstructive CAD, 30 160 (77.8%) were treated with statins, 2042 (5.3%) were treated with only nonstatin lipid-lowering medications, 6441 (16.6%) were treated with both statin and nonstatin lipid-lowering medications, and 6573 (17.0%) were untreated (Figure 2). Patients not treated with statins (n=8615; 22.2%) were more likely to be younger and female and to have a history of prior myocardial infarction, prior coronary artery bypass grafting, and atrial fibrillation. Patients not treated with statins were also less likely to have prior percutaneous coronary interventions and to have coexisting heart failure, diabetes mellitus, hypertension, and peripheral artery disease (Table; P<0.001 for all).

In multivariable hierarchical modified Poisson regression models, adjusted for clustering of patients within sites, lack of medical insurance was associated with a lower likelihood of being treated with a statin (adjusted RR, 0.94; 95% CI, 0.89–1.00; P=0.039), whereas male sex (adjusted RR, 1.10; 95% CI, 1.07–1.13; P<0.001), coexisting hypertension (adjusted RR, 1.07; 95% CI, 1.02–1.12, P=0.003), prior coronary artery bypass grafting (adjusted RR, 1.09; 95% CI, 1.05–1.14; P<0.001), and prior percutaneous coronary intervention (adjusted RR, 1.11; 95% CI, 1.06–1.16; P<0.001) were associated with a higher likelihood of being treated with a statin (Figure 3). Coexisting diabetes mellitus and a history of prior myocardial infarction were weakly associated with a higher likelihood of statin therapy. Age and body mass index were nonlinearily associated with statin treatment, with patients aged 60 to 80 years (Table I and Figure I in the online-only Data Supplement) and patients with body mass index of 30 to 35 (Table II and Figure II in the online-only Data Supplement) having the highest rates of statin treatment.

Among patients who were not on any lipid-lowering therapy (n=6573; 17.0%), LDL-C levels were available for 3365 patients (51.2%). Of those with LDL-C results, 1794 (53.3%) had LDL-C levels of <100 mg/dL, and 644 (19.1%)
had LDL-C levels <70 mg/dL. There were an additional 1571 patients (46.7%) who were not treated with any lipid-lowering medications who had LDL-C levels of ≥100 mg/dL (Figure 4).

Discussion

In this large, national, contemporary registry of cardiac outpatients, we found that >1 in 5 patients with obstructive CAD and without documented contraindications were not treated with statins, a class of medications with demonstrated efficacy in secondary prevention, and a small proportion were treated with nonstatin lipid-lowering medications. Importantly, 17% of patients were not treated with any lipid-lowering therapy at all. Notably, half of these untreated high-risk patients had LDL-C levels <100 mg/dL. Collectively, these findings suggest there are significant opportunities for improvement in the quality of lipid management for a substantial number of outpatients with obstructive CAD.

Our report extends the work of prior studies, which have reported statin treatment rates of 60% to 70% in outpatients with CAD.6–10,20 Among 290 patients with CAD in a Maryland health maintenance organization, 69% were on lipid-lowering therapy.7 An evaluation of 108 patients with CAD in the 2003–2004 National Health and Nutrition Examination Survey found that 63% were treated with statins.10 Similarly, among 1960 post–myocardial infarction patients in a multicenter US registry from 2003 to 2004, ~70% of patients were on statins at 12 months after their myocardial infarction.20 These studies, however, were limited by smaller study samples and the specificity of the diagnosis of CAD and were all conducted before 2005, before the publication of current guidelines and recent studies.4,11,12 Our study extends these findings in a large, contemporary sample of patients with obstructive CAD. Additionally, we were able to examine the LDL-C profiles of patients not treated with any lipid-lowering therapy and rates of treatment with other lipid-lowering agents among those not treated with statins.

Our finding that half of untreated patients had an LDL-C of <100 mg/dL raises concerns about missed opportunities for intensive secondary prevention in patients with documented obstructive CAD. Although appearing to have reached established LDL-C treatment targets for secondary prevention, these patients were not receiving any active lipid-lowering treatment. Although we can only speculate as to the actual reasons for nontreatment of these patients, our data suggest that some physicians may be making decisions about lipid management for these patients based on baseline LDL-C levels alone. However, prior analyses from clinical trials have reported that there is a constant relative risk reduction for recurrent cardiac events of 20% with statins across the spectrum of baseline LDL-C levels.1,12,13 Others have posited that the only definitive inference from secondary prevention clinical trials of statin therapy is that empirical statin therapy in high-risk patients reduces cardiovascular events, independent of LDL-C levels. These investigators contend that, because these studies randomized patients to fixed-dose statin therapy regardless of LDL-C level, a treat-to-target strategy has yet to be studied in a clinical trial.11,21,22 Therefore, a strategy of initiating lipid-lowering therapy (preferably statins) in patients with known CAD only when they have LDL-C levels ≥100 mg/dL may reflect a misapplication of the current evidence base and clinical guidelines. Further study is needed, however, to better understand the reasons for nontreatment of these patients at high risk of a recurrent cardiovascular event, including patients’ baseline LDL-C levels.

Finally, we identified many patients with CAD and elevated LDL-C levels who were not treated with any lipid-lowering medications. The reasons why these patients remain untreated despite poor lipid control were not documented. If this practice were to be pervasive, it would mean that a significant number of patients are not even considered for lipid-lowering therapy for their CAD.

Our study findings should be interpreted in light of the following limitations. First, the PINNACLE program enrolled patients from highly motivated practices dedicated to quality improvement. Rates of statin use among patients with CAD in other US practices are likely to be lower than those reported in this study. Second, although we have data regarding patients’ LDL-C levels, we are unable to establish the underlying reasons why patients were not treated with statins. Although a low untreated LDL-C level may be contributing to the decision not to treat these patients, further
study is required to test this hypothesis. Third, the PINNACLE program allows clinicians to designate exclusions for statin therapy without adjudication, such that they are removed from the denominator of eligible patients. The number of patients with documented exclusions (n=515; 1.3%) was lower than the discontinuation rates that had been observed in clinical trials (ranging from 4% to 33%), which may indicate that exclusions were underdocumented in PINNACLE or possibly improved tolerance when the choice and dosing of statins are allowed to vary according to patient preference (ie, a patient may have myalgias with a particular type or dose of statin but would tolerate a lower dose of the statin or a difference type). Regardless, if underdocumentation of contraindications to statin therapy occurred, many patients still remained untreated with other nonstatin lipid-lowering agents. Fourth, LDL-C levels were not available for half of the patients who were not treated with lipid-lowering medications compared with one third of treated patients. Differential missing rates in LDL-C may lead to potential confounding in our study findings. Fifth, we did not have specific information regarding statin type, statin dose, or type of nonstatin medication used, which limited our ability to provide additional insights in regard to how these patients were treated. Furthermore, we did not have information regarding prescription drug coverage or actual adherence to the selected lipid-lowering strategy. Nonetheless, our study was interested in assessing physician treatment of patients, and therefore actual patient adherence, although of interest, would not affect our findings of physician undertreatment of patients with CAD at high risk of recurrent cardiovascular events. Sixth, we did not have information on race in half of the patients in PINNACLE, but this variable is unlikely to have affected our primary study findings. Finally, although this study was not designed to examine the association of statin therapy with specific clinical outcomes, such as readmission and mortality, treatment with statins is a recognized advancement in outpatients with obstructive CAD who are at high risk for recurrent cardiovascular events. The manuscript underwent internal review by an NCDR Research and Publications committee; the views expressed in this manuscript represent those of the authors and do not necessarily represent the official views of the NCDR or its associated professional societies identified at http://www.ncdr.com.

Disclosures
Dr Krumholz chairs a cardiac scientific advisory board for UnitedHealth and is the recipient of a research grant from Medtronic, Inc through Yale University. The other authors report no conflicts.

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In the large, contemporary Practice Innovation and Clinical Excellence (PINNACLE) outpatient registry, we examined rates of guideline-based treatment with lipid-lowering therapy in 38,775 patients with obstructive coronary artery disease (defined as history of myocardial infarction or prior coronary revascularization) and without contraindications to statin therapy. We found that 78% of patients were receiving guideline-based treatment with statins, 5% were treated only with nonstatin lipid-lowering medications, and 17% of patients were not treated with any lipid-lowering therapy at all. Among untreated patients, half had low-density lipoprotein cholesterol (LDL-C) levels ≥100 mg/dL. Despite multiple clinical trials that have shown that statin therapy reduces cardiovascular morbidity and mortality in this population, a substantial number of high-risk patients remained untreated with statins despite elevated levels of LDL-C. We also found that half of untreated patients had LDL-C levels <100 mg/dL. Although appearing to have reached established LDL-C treatment “targets” for secondary prevention, these patients were not receiving guideline-based care because they were not treated with any lipid-lowering therapy. Our data suggest that some physicians may be making decisions about lipid management for these patients on the basis of baseline LDL-C levels alone rather than on the basis of clinical trial evidence, which has demonstrated a consistent benefit with statin therapy in secondary prevention regardless of baseline LDL-C levels. These findings highlight important opportunities to improve the use of statin therapy in outpatients at high risk for recurrent cardiovascular events.
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SUPPLEMENTAL MATERIAL

Relationship of age with statin treatment in patients with CAD.

eTable 1. Unadjusted rates of statin treatment by decade of age

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>&lt;20</th>
<th>20 to &lt;30</th>
<th>30 to &lt;40</th>
<th>40 to &lt;50</th>
<th>50 to &lt;60</th>
<th>60 to &lt;70</th>
<th>70 to &lt;80</th>
<th>80 to &lt;90</th>
<th>≥90</th>
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<tbody>
<tr>
<td>n</td>
<td>14</td>
<td>140</td>
<td>525</td>
<td>2475</td>
<td>6915</td>
<td>11286</td>
<td>10655</td>
<td>6049</td>
<td>716</td>
</tr>
<tr>
<td>Statin Treatment</td>
<td>0 (0.0%)</td>
<td>27 (19.3%)</td>
<td>265 (50.5%)</td>
<td>1809 (73.1%)</td>
<td>5377 (77.8%)</td>
<td>9168 (81.2%)</td>
<td>8469 (79.5%)</td>
<td>4606 (76.1%)</td>
<td>439 (61.3%)</td>
</tr>
</tbody>
</table>

eFigure 1. Risk ratio of statin therapy by age. Reference age is 70 years.
Relationship of body mass index with statin treatment in patients with CAD.

eTable 2. Unadjusted rates of statin treatment by body mass index

<table>
<thead>
<tr>
<th>Body Mass Index (kg/m²)</th>
<th>Statin Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15</td>
<td>24 (66.7%)</td>
</tr>
<tr>
<td>15 to &lt;20</td>
<td>662 (67.2%)</td>
</tr>
<tr>
<td>15 to &lt;30</td>
<td>15127 (78.0%)</td>
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<tr>
<td>20 to &lt;35</td>
<td>6741 (80.1%)</td>
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<td>30 to &lt;40</td>
<td>2898 (78.8%)</td>
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<tr>
<td>35 to &lt;45</td>
<td>1063 (78.2%)</td>
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<tr>
<td>40 to &lt;50</td>
<td>363 (75.2%)</td>
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<tr>
<td>45 to &lt;55</td>
<td>126 (71.6%)</td>
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<tr>
<td>50 to &lt;55</td>
<td>39 (65.0%)</td>
</tr>
<tr>
<td>≥ 55</td>
<td></td>
</tr>
</tbody>
</table>

n = 50

Statin Treatment

eFigure 2. Risk ratio of statin therapy by body mass index. Reference body mass index is 35 kg/m².