Adherence With Statin Therapy in Elderly Patients With and Without Acute Coronary Syndromes

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STATINS (3-HYDROXY-3-METHYL-glutaryl coenzyme A [HMG-CoA] reductase inhibitors) have been shown to significantly reduce morbidity and mortality in patients with coronary artery disease (CAD) and in patients with hyperlipidemia but only if taken on a regular basis.1-5 In clinical trials, statins demonstrated benefit only after 1 to 2 years of continuous treatment. Although the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study6 showed some early benefits in acute coronary syndromes (ACSs), benefits were on nonfatal outcomes only and the absolute effect was modest. Thus, for both primary and secondary prevention, statins are intended to be used long-term to achieve their full benefit. In addition, withdrawal of statins in ACSs may increase cardiovascular event rates.7

Studies assessing adherence in periods prior to the landmark statin trials found 1-year adherence rates of only 25% to 85% for patients initiated on lipid-lowering therapy.8-12 These earlier studies mainly assessed the older lipid-lowering drugs, a limited number of statins (mainly lovastatin) for 1 year or less of follow-up, and did not separate patients into primary and secondary prevention cohorts. Some evidence suggests that patients at higher risk for CAD may be more likely to adhere to therapy than those patients treated for primary prevention.13 In addition, in patients with CAD, adherent behavior may be an indicator of better prognosis or confer a protective effect.13 Adherence is a complex process with potential for nonadherence by

Context Landmark clinical trials have demonstrated the survival benefits of statins, with benefits usually starting after 1 to 2 years of treatment. Research prior to these trials of older lipid-lowering agents demonstrated low levels of 1-year adherence.

Objective To compare 2-year adherence following statin initiation in 3 cohorts of patients: those with recent acute coronary syndrome (ACS), those with chronic coronary artery disease (CAD), and those without coronary disease (primary prevention).

Design and Setting Cohort study using linked population-based administrative data from Ontario.

Patients All patients aged 66 years or older who received at least 1 statin prescription between January 1994 and December 1998 and who did not have a statin prescription in the prior year were followed up for 2 years from their first statin prescription. There were 22379 patients in the ACS, 36106 in the chronic CAD, and 85020 in the primary prevention cohorts.

Main Outcome Measures Adherence to statins, defined as a statin being dispensed at least every 120 days after the index prescription for 2 years.

Results Two-year adherence rates in the cohorts were only 40.1% for ACS, 36.1% for chronic CAD, and 25.4% for primary prevention. Relative to the ACS cohort, nonadherence was more likely among patients receiving statins in the chronic CAD (relative risk [RR], 1.14; 95% CI, 1.11-1.16) and primary prevention cohorts (RR, 1.92; 95% CI, 1.87-1.96).

Conclusions Elderly patients with and without recent ACS have low rates of adherence to statins. This suggests that many patients initiating statin therapy may receive no or limited benefit from statins because of premature discontinuation.

See also pp 455 and 495.
the patient prior to filling a prescription, failing to retrieve a filled prescription, and failing to refill a prescription.14

We compared long-term adherence of patients with acute and chronic CAD (secondary prevention) vs those without prior CAD (primary prevention) for a 2-year period after initiating statin therapy, focusing on failure to refill a prescription. A secondary objective was to identify patient characteristics associated with nonadherence.

METHODS
Sources of Data
Four separate population-based data sources were deterministically linked using the patient’s encrypted Ontario health insurance number to obtain the data to conduct the analyses: the Ontario Drug Benefit (ODB) prescription claims database, the Canadian Institutes of Health Information (CIHI) hospital discharge abstract database, the Ontario Health Insurance Plan (OHIP) database, and the Ontario Registered Persons Database (RPDB). The ODB prescription claims database contains information on outpatient prescription drug use and costs for all 1.4 million elderly residents of Ontario. Residents may fill prescriptions at any pharmacy within Ontario and have a minimum copayment with each prescription (Can $2/prescription or yearly deductible of Can $100). This database has been used in other pharmacoepidemiology studies assessing drug use in patients with cardiac disease.15,16 All Ontario residents have universal, publicly-funded health insurance for hospital care, with each discharge from the hospital resulting in the production of a discharge abstract that must be submitted to the provincial government. The CIHI hospital discharge abstracts contain information pertaining to the hospital admission, demographic characteristics of patients, coexisting illnesses, in-hospital procedures, and mortality. The OHIP database contains information on physician claims, and the RPDB database contains information on vital status.

Patient Population
Outpatients were included in the study if they were 66 years or older and had at least 1 statin prescription dispensed during the period from January 1, 1994, to December 31, 1998, with the date of first dispensation as the index date. We only included patients who did not have a statin prescription in the last 12 months before the index date of statin prescription to allow for evaluation of relatively new users. Patients residing in chronic care hospitals were not included in the analysis.

Cohort Definition
This study assessed adherence in 3 separate patient cohorts: (1) those with a recent ACS, defined as a hospital discharge in the last year with a most responsible diagnosis of myocardial infarction (International Classification of Diseases, Ninth Revision [ICD-9] code 410) or unstable angina (ICD-9 code 411); (2) those with evidence of chronic CAD, defined by the diagnosis of ischemic heart disease (ICD-9 code 412-414), acute myocardial infarction or ACSs (ICD-9 code 410-411), coronary artery bypass graft (ICD-9 code 36.1) or angioplasty (ICD-9 code 36.0) procedures in hospital discharge abstracts 1 to 5 years before the index date of statin prescription, or the use of ni troglycerin in the prescription claims database within the year before the index date; and (3) all remaining patients without CAD who were dispensed a statin prescription within the study period. All patients were included in the cohort only once. Co- morbidities were defined as follows: diabetes by the presence of the diagnosis in CIHI (ICD-9 code 250), the use of insulin, or oral hypoglycemic agents in ODB; hypertension by the diagnoses listed in CIHI (ICD-9 code 401) or the use of thiazides, angiotensin-converting enzyme inhibitors (without furosemide), calcium channel blockers, or β-blockers (without any other marker for CAD). Patient CIHI hospital discharge records for 5 years before the index date were searched for an entry for the comorbidity of interest, and ODB records were searched for 1 year before the index date for an entry of a medication of interest.

Assessment of Adherence
The most reliable objective measure of adherence in large patient groups is failure to refill a prescription.17 The primary outcome of adherence was defined as having a statin prescription dispensed at least every 120 days after the index prescription date until the end of the 2-year monitoring period. Change from one statin to another was considered adherence with statin therapy. Six statins were available during part or all of the study period. Patients receiving medications in the ODB program should obtain a maximum of 100 days therapy with 1 physician’s prescription. A total of 120 days was chosen as the target refill date to allow a 20% grace period for prescription refills. The duration of adherence for each patient was calculated as the difference between the index date and the final consecutive prescription date plus 60 days (50% of assumed refill period). All patients were monitored for a 2-year period after their index statin prescription. Adherence at 0.5, 1, and 1.5 years was also calculated. Similar methods have been used successfully in adherence research using administrative data.10,12

We conducted a sensitivity analysis: defining adherence as having a statin prescription dispensed every 180 days after the index prescription date. In this analysis, the duration of adherence was calculated as the difference between the index date and the final consecutive prescription date plus 90 days. To estimate the extent of intermittent adherers, we determined the proportion of patients who filled a subsequent prescription in the year following the end point of nonadherence after their index prescription. As a sensitivity measure, we examined the tablet quantities dispensed with each statin prescription to calculate a cumulative tablet quantity per patient. We correlated the quantity dispensed with the estimated duration of adherence using our primary methods.

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Statistical Analysis
To examine differences in baseline characteristics between groups, we used χ² analysis for binary variables and the Kruskal-Wallis test for continuous variables. A Cox proportional hazards model was constructed by standard statistical tests on proportionality to compare 2-year adherence between the cohorts, while adjusting for potential confounders. Time to discontinuation was defined as the dependent variable. The independent variables were age (continuous), sex, diabetes, hypertension, number of medications (defined by number of different drug identification number prescriptions dispensed within 1 year before the index date), number of physician visits within 1 year before the index date (maximum 1 per day), and number of different physicians. Patients were censored if they died or reached the end of the 2-year follow-up period. We performed all analyses using SAS version 8.1 (SAS Institute Inc, Cary, NC) and P<.05 was the level of significance.

RESULTS
The median population of Ontario for the study period was more than 11.1 million, with those persons 66 years or older accounting for 12.6% of the population. Approximately 10% of the total population of elderly persons in Ontario received statin prescriptions. There were 22 379 patients in the ACS, 36 106 patients in the chronic CAD, and 85 020 patients in the primary prevention cohorts. Baseline characteristics of the 3 cohorts are presented in Table 1. Patients in the ACS and CAD cohorts were older, more likely to be men, have a history of diabetes or prior revascularization, were receiving more medications, and visited more physicians more frequently compared with the primary prevention cohort. Simvastatin was the most frequently prescribed statin (30.1%), followed closely by atorvastatin (29.0%) and pravastatin (25.4%), with relatively little use of lovastatin (9.6%), fluvastatin (3.8%), and cerivastatin (2.0%).

The Figure illustrates that patients’ adherence continually diminished from initiation of therapy through 2 years follow-up in a progressive manner with at least 25% of patients discontinuing statin therapy by 6 months in all groups. Patients in the secondary prevention cohorts had higher levels of adherence at all times compared with those without evidence of coronary disease (primary prevention). The crude proportion of patients receiving statin prescriptions continuously for 2 years was 40.1% in the ACS, 36.1% in the CAD, and 25.4% in the primary prevention cohorts. Even after accounting for possible confounders, relative to the patients in the ACS cohort, non-adherence was more likely among patients receiving statin prescriptions in the CAD (relative risk [RR], 1.14; 95% confidence interval [CI], 1.11-1.16) and primary prevention cohorts (RR, 1.92; 95% CI, 1.87-1.96). Other factors associated with nonadherence are summarized in Table 2.

Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Acute Coronary Syndrome (n = 22 379)</th>
<th>Coronary Artery Disease (n = 36 106)</th>
<th>Primary Prevention (n = 85 020)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>72.5 (5.0)</td>
<td>72.4 (4.9)</td>
<td>71.5 (4.6)</td>
</tr>
<tr>
<td>Sex</td>
<td>1010 (9.2)</td>
<td>1010 (2.8)</td>
<td>0</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>3523 (15.7)</td>
<td>3523 (15.7)</td>
<td>0</td>
</tr>
<tr>
<td>Prior PTCA</td>
<td>2061 (9.2)</td>
<td>1010 (2.8)</td>
<td>0</td>
</tr>
<tr>
<td>No. of medications in prior year</td>
<td>12.8 (6.8)</td>
<td>11.4 (6.3)</td>
<td>7.9 (5.4)</td>
</tr>
<tr>
<td>Mean (IQR)</td>
<td>12 (8-16)</td>
<td>10 (7-14)</td>
<td>7 (4-10)</td>
</tr>
<tr>
<td>No. of different physicians</td>
<td>11.2 (6.3)</td>
<td>8.9 (5.1)</td>
<td>6.7 (4.0)</td>
</tr>
<tr>
<td>Mean (IQR)</td>
<td>10 (7-14)</td>
<td>8 (5-11)</td>
<td>6 (4-9)</td>
</tr>
<tr>
<td>No. of physician visits in prior year</td>
<td>27.3 (19.3)</td>
<td>20.8 (16.4)</td>
<td>15.1 (12.7)</td>
</tr>
<tr>
<td>Mean (IQR)</td>
<td>23 (14-35)</td>
<td>17 (10-26)</td>
<td>12 (7-19)</td>
</tr>
</tbody>
</table>

*CABG indicates coronary artery bypass graft surgery; PTCA, percutaneous transluminal coronary angioplasty; and IQR, interquartile range.

Figure. Survival Curves for Adherence With Statins in 3 Cohorts

All curves are based on a Cox proportional hazards model adjusted for covariates. The median follow-up was 494 days for acute coronary syndrome, 430 days for coronary artery disease, 235 days for primary prevention, and 303 days for overall.

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Sensitivity analysis, using a definition of adherence as having a statin dispensed every 180 days, revealed similar patterns of progressive discontinuation of statins over time. At 2 years following the index date, using a more lenient definition of adherence, with a statin prescription being dispensed every 180 days, greater adherence rates were found (61.7%, 58.5%, 46.8%, respectively, in the ACS, CAD, and primary prevention cohorts), although the 2-year adherence rates were still low.

We specifically assessed those patients who had an index statin prescription but did not have another statin prescription dispensed in the next 120 days, therefore, meeting the criteria for nonadherence to determine whether these patients were intermittent adherers. Approximately 46% of these patients had a subsequent statin prescription dispensed at sometime in the year following their initial nonadherence. We also examined the correlation between the estimated duration using the technique described and the number of pills dispensed and found a high degree of correlation ($r = 0.93; P < .001$), which enhances the validity of the estimated duration method. When considering specific drugs, there was slightly better adherence with simvastatin (RR, 0.90; 95% CI, 0.88-0.92), pravastatin (RR, 0.93; 95% CI, 0.91-0.95), and atorvastatin (RR, 0.95; 95% CI, 0.94-0.97) relative to lovastatin, but slightly worse adherence was obtained with cerivastatin (RR, 1.34; 95% CI, 1.28-1.40) and fluvastatin (RR, 1.06; 95% CI, 1.02-1.10).

**COMMENT**

In our study to assess long-term statin adherence since the publication of definitive studies showing benefit, we found a low 2-year adherence rate following initiation of therapy. Given as early as 120 days from the index prescription, at least 25% of patients discontinued therapy at 6 months after the index prescription date. It appears that the publication of landmark trials and the strong supportive evidence about morbidity and mortality benefits from statins has done little to change adherence rates. One could argue that earlier studies may have had worse adherence because the evidence was less compelling. It is possible that the low rate of adherence we found underestimates the magnitude of the problem in the United States because the issue of high drug cost was avoided in our study setting. In the Canadian population we assessed, all the medication costs are covered except for a small co-payment per prescription.

Our study indicates that patients with existing coronary disease, and those with comorbidities (diabetes, hypertension) were the most likely to be adherent to therapy. While those with acute or chronic cardiac disease fared better, at 2 years, less than 50% of patients were adherent to therapy for a sufficiently long duration to possibly achieve substantial morbidity and mortality benefits. The landmark secondary prevention trials had 5-year discontinuation rates of only 6% to 19%, while the primary prevention trials had 5-year discontinuation rates of 30% for both. While there was a gradient of nonadherence between secondary and primary prevention in the landmark trials, in both groups we found substantially higher rates in our cohorts than those reported in the clinical trials. Using administrative data from 2 health maintenance organizations from 1988-1990, Andrade et al found similar rates of discontinuation for lovastatin in clinical trials (16%) and in practice (15%). Earlier studies have found the factors most associated with adherence to lipid-lowering therapy include receipt of statins and a history of cardiac disease. Nonadherent patients are less likely to reach target lipid values and subsequently less likely to achieve benefit from therapy. Recent evidence demonstrating the early benefit of starting statin therapy and the potential harm of suddenly stopping statins after an ACS highlight the importance of early and chronic statin therapy.

**Table 2. Factors Associated With Nonadherence***

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
</tr>
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<tbody>
<tr>
<td>Coronary artery disease group†</td>
<td>1.14 (1.11-1.16)</td>
</tr>
<tr>
<td>Primary prevention group‡</td>
<td>1.92 (1.87-1.96)</td>
</tr>
<tr>
<td>Age, y†</td>
<td>1.009 (1.008-1.011)</td>
</tr>
<tr>
<td>Sex, men</td>
<td>1.02 (1.01-1.04)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.87 (0.85-0.88)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.80 (0.78-0.81)</td>
</tr>
<tr>
<td>Total prescriptions‡</td>
<td>1.012 (1.011-1.014)</td>
</tr>
<tr>
<td>No. of physician visits‡</td>
<td>0.996 (0.996-0.997)</td>
</tr>
<tr>
<td>No. of different physicians‡</td>
<td>1.004 (1.002-1.006)</td>
</tr>
</tbody>
</table>

*Outcome of interest in Cox proportional hazards model is discontinuation (>120 days between subsequent prescriptions). †Compared with acute coronary syndrome cohort. ‡For each additional unit.

While it is possible that patients discontinued therapy for good reasons, such as the development of adverse effects given the known tolerability of the statins, this explanation is less likely given the magnitude of nonadherence we found. In the Scandinavian Simvastatin Survival Study (4S) study, the rates of discontinuation due to adverse effects was only 6%, making up 50% of all patients stopping therapy, while in the West of Scotland Coronary Prevention Study, adverse effects accounted for only 2% of discontinuations, with the overall discontinuation rate of 30% at 5 years. Since we assessed the entire drug class, if a patient was intolerant to 1 statin, switching to another statin was possible and would not have been interpreted as nonadherence. Like hypertension, hyperlipidemia is an asymptomatic condition. Patients, particularly those without CAD, may perceive no immediate benefit and discontinue medication without appreciating the long-term consequences of their actions. Although patients in Ontario are man-
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dated to receive education on all initial prescriptions by pharmacists, patients refilling prescriptions may not necessarily receive the same attention and education regarding the importance of continued use of their statin. In addition, no systematic, automated process is in place to encourage all pharmacists and physicians to monitor ongoing adherence to medications.

In the landmark statin trials for primary prevention, the proportion of elderly patients is quite small (West of Scotland Coronary Prevention Study: mean age, 55 years; Air Force/Texas Coronary Atherosclerosis Prevention Study [AFCAPS/TexCAPS]: 21% of patients ≥ 65 years) compared with the secondary prevention trials (4S: 51% ≥ 60 years; Coronary and Recurrent Events: 51% ≥ 60 years; the Long-Term Intervention with Pravastatin in Ischemic Disease [LIPID]: 39% ≥ 65 years; MIRACL: mean age, 65 years). Given the strength of evidence and greater generalizability of the secondary prevention trials to elderly patients and better adherence we found for secondary prevention and patients with CAD risk factors, efforts to improve adherence may be more worthwhile for secondary prevention and for high-risk CAD-equivalent patients, such as those with diabetes.

It appears that these patients are intermittent adherers, in that they fill their statin prescriptions on an irregular and noncontinuous basis. The benefit of statins taken in this manner is unknown, because it does not match the administration methods in the clinical trials.

In comparison with lovastatin, patients adhered somewhat better to simvastatin, pravastatin, and atorvastatin. While atorvastatin appeared to have good adherence rates in comparison with lovastatin, the clinical trials evidence for atorvastatin is limited to the MIRACL trial, a short-term, composite end point study. Simvastatin and pravastatin are the 2 statins with the strongest clinical trial evidence to support their use. We found that the majority of the patients in the cohorts were prescribed these 2 evidence-based statins and that patients adhered to these statins a little better in comparison with lovastatin. Adherence with fluvastatin and cerivastatin was slightly less. Of note, cerivastatin was recently withdrawn from the US and Canadian markets due to serious concerns about rhabdomyolysis, with or without gemfibrozil, in rates greater than that observed with the other statins. Potential reasons for lack of adherence with fluvastatin include the inferior potency compared with other statins.

Some limitations of our study include the lack of comprehensive clinical data on each patient, such as lipid values, actual drug doses, incidence of adverse effects, and the exact reason for discontinuation. We used the marker of a patient filling their statin prescription for actual medication use; however, we cannot determine whether the patient actually took their medication once it was dispensed. Also, our study was restricted to elderly patients because of data availability; the adherence rates may be different in nonelderly patients. Failure to adhere may occur at 2 stages of the adherence process: the patient stops daily dosing without using all of the current prescription or the patient continues daily dosing and then fails to refill a new prescription. Our study was not able to discern which type of patient nonadherence occurred.

The results observed in our study were based on a large, population-based cohort. It is likely that our results are generalizable to other similar populations. Although statin trials have shown important benefits, many patients starting on statins likely receive no or limited benefit from these drugs. Given the low rates of adherence demonstrated in our study, there is a great need to identify strategies that will lead to improved statin adherence if the benefit of clinical trials are to lead to improved population health. Initiation of therapy in the hospital is one possible step toward ensuring patient adherence. Ongoing reminders during physician office visits or by community-based pharmacists, or detailed patient education programs could also potentially increase adherence rates.

Author Contributions: Study concept and design: Jackevicius, Mamdani. Acquisition of data: Mamdani. Analysis and interpretation of data: Jackevicius, Mamdani, Tu. Drafting of the manuscript: Jackevicius. Critical revision of the manuscript for important intellectual content: Jackevicius, Mamdani, Tu. Statistical expertise: Jackevicius, Mamdani. Obtained funding: Tu. Administrative, technical, or material support: Jackevicius. Study supervision: Tu.

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The greatest happiness for the thinking man is to have fathomed the fathomable, and to quietly revere the unfathomable.
—Johann Wolfgang von Goethe (1749-1832)