Use of the Statins in Patients After Acute Myocardial Infarction

Does Evidence Change Practice?

Cynthia A. Jackevicius, BScPhm, MSc; Geoffrey M. Anderson, MD, PhD; Lawrence Leiter, MD; Jack V. Tu, MD, PhD

Objective: To compare the use of lipid-lowering agents in 42628 elderly patients (aged ≥65 years) after acute myocardial infarction, before and after the publication of the Scandinavian Simvastatin Survival Study (4S), using the Ontario Myocardial Infarction Database.

Methods: Multivariate regression models were created to estimate changes in the rate of statin use over time in monthly cohorts of elderly patients after acute myocardial infarction in Ontario from April 1, 1992, to March 31, 1997. Changes in the rate of statin use over time were estimated using patient and prescriber characteristics.

Results: We found a 3.6-fold significant increase in the monthly rate of statin use after the publication of 4S compared with before the publication of 4S (P<.001); specifically, the rate of increase in simvastatin and pravastatin sodium use was higher after the publication of 4S (P<.001 for each). Before the publication of 4S, the rate of increase in statin use in younger patients (aged 65-74 years) was 2.7 times higher than in older patients (aged ≥75 years) (P=.02), while after the publication of 4S, the rate of increase in statin use was only 1.8-fold higher in the younger group (P<.001). After the publication of 4S, there was a 1.6-fold higher rate of increase in statin use in male compared with female patients (P=.006). Also after the publication of 4S, specialists (cardiologists and internists) had a 2-fold higher rate of increased use of the statins than did generalists (P<.001).

Conclusion: It is possible to shift practice if the evidence of benefit is strong, the intervention is easy to implement, and the intervention is marketed aggressively.

Arch Intern Med. 2001;161:183-188

From the Pharmacy Department, University Health Network–Toronto General Hospital (Ms Jackevicius), the Departments of Health Administration (Ms Jackevicius and Drs Anderson and Tu), Medicine (Drs Leiter and Tu), Nutritional Sciences (Dr Leiter), and Public Health Sciences (Dr Tu), University of Toronto, the Institute for Clinical Evaluative Sciences (Drs Anderson and Tu), St Michael's Hospital (Dr Leiter), and the Division of General Internal Medicine, Sunnybrook and Women's College Health Science Centre (Dr Tu), Toronto, Ontario. Dr Leiter has received research funding from and has been a speaker for Merck Canada, Montreal, Quebec, the manufacturer of simvastatin.

The Scandinavian Simvastatin Survival Study (4S), published in 1994, was the first large, randomized, clinical trial to demonstrate that lipid lowering with simvastatin resulted in a clear and substantial decrease in total mortality and in fewer coronary heart disease events and less cardiovascular mortality when used in patients with coronary heart disease (history of angina or myocardial infarction) who also had high low-density lipo-protein cholesterol levels. Subsequent trials have reaffirmed these initial findings.

New research evidence, even evidence from landmark clinical trials, often has a delayed or minimal impact on practice. For example, although aspirin (formerly acetylsalicylic acid) and β-blockers have been shown to increase survival in patients with acute myocardial infarction (AMI) since the 1980s, uptake (use of an innovation or intervention in practice) of these interventions has been sub-optimal. The diffusion (or uptake) of innovations in medical care is a complex process that is driven by the features of the innovation and the explicit efforts to change physician behavior. The uptake of drugs that are easy to use and are not costly (eg, β-blockers and aspirin) may be related to behavior change efforts. Randomized trials have shown that it is possible to increase the use of β-blockers and aspirin using interventions based on marketing techniques (opinion leaders using small-group discussions), and the failure of these agents to be used more commonly in everyday practice may be in part the result of a lack of a systematic effort to promote their use. Aspirin and most β-blockers are available in generic forms, and proprietary firms have little to gain by marketing their use. It is also possible that there are barriers that make practice change related to AMI care difficult, no matter how simple and effective the intervention. The use of statins in patients after AMI represents a proven innovation that is not complex to use, that has been
PATIENTS AND METHODS

A time series design and regression techniques were applied to administrative data that identified patients with AMI and their subsequent prescription drug use, and were used to study the association between the release of results from 4S and the proportion of patients after AMI who filled a prescription for a statin within 6 months of hospital discharge.

The Ontario Myocardial Infarction Database was created by using the unique scrambled health insurance number to link data on hospital discharges to data on prescription drugs in a comprehensive cohort of elderly Canadian patients with AMI from April 1, 1992, to March 31, 1997.\(^3\) The Ontario Myocardial Infarction Database has been described in detail previously.\(^1,2\) Briefly, all Ontario residents have universal publicly funded health insurance for hospital care, and each discharge from an acute care hospital results in the production of a discharge abstract that is submitted to the provincial government, containing patient demographics and diagnoses and the specialty of the physician most responsible for the care of the patient during the hospital stay. The most responsible physician for a hospital admission is defined as "the attending physician most responsible for the care of the patient and/or for the longest length of stay." Specialists were defined as cardiologists and internists, with all other physician types being classified as nonspecialists.

All Ontario residents 65 years or older are covered under a comprehensive drug benefit plan. Each time a prescription is filled, a claim is submitted to the provincial government that contains the patient health insurance number and a unique drug identifier. The Ontario Myocardial Infarction Database provides data on all elderly patients treated for AMI in any Ontario hospital and records any prescriptions filled after hospital discharge. A patient was identified as having a statin prescription if the patient had been dispensed at least one prescription for a statin in the 6-month period after discharge for AMI treatment. This would allow enough time for clinicians to properly test patients' cholesterol levels and give a trial of dietary therapy as appropriate before initiating drug therapy.

Sixty monthly cohorts of elderly patients with AMI were used for the analysis during the study: 32 before the publication of 4S (April 1, 1992, to November 30, 1994, inclusive) and 28 after the publication of 4S (December 1, 1994, to March 31, 1997, inclusive). The monthly rate of statin use was calculated for each cohort, with the total number of elderly patients with AMI per cohort as the denominator.

The baseline clinical characteristics for 12-month periods during the study were compared by using a t test for continuous, normally distributed variables; the Kruskal-Wallis test for nonnormally distributed continuous variables; and a \(\chi^2\) test for categorical variables. The main analysis compared the primary end point of statin use within 6 months post-AMI before and after the publication of 4S by linear regression. Additional analyses investigated subgroup effects based on prescriber and patient characteristics.\(^1,4\) The regression model used 3 time variables as independent variables to model the time-related effects: a variable that indicated the monthly rate of statin use during the entire period (ie, monthly intervals 1, 2, 3, \ldots , 60); a variable that indicated the monthly rate of statin use after the publication of 4S, starting on December 1, 1994, and continuing until March 31, 1997; and a dummy variable indicating whether the period was either before or after the publication of 4S, with the change point at December 1, 1994.

All variables were entered into the model simultaneously without the use of stepwise or conditional procedures. All models were evaluated for appropriateness of fit using standard graphical and statistical methods, including use of the Durbin-Watson statistic for autocorrelation.\(^1\) Models using interaction terms were constructed for physician specialty, age, and sex with the same independent variables as in the base model. The purpose of the interaction models was to allow estimates of differences in the effects of different subgroups. Determining separate estimates for subgroups allowed for assessment of nonparallel effects over time, before and after the publication of 4S. By convention, all \(P\) values were 2-tailed, and were considered significant at the .05 level, without correction for multiple comparisons. Adjusting for age and sex distribution of the cohort over time did not change the results; therefore, all results are presented as unadjusted analyses.\(^1,4,5\)

Statistical analyses were performed using SAS statistical software, version 6.12 (SAS Institute Inc, Cary, NC).

RESULTS

The study sample consisted of 42628 patients aged 65 years or older who experienced an AMI as the primary reason for a hospital admission between April 1, 1992, and March 31, 1997. Baseline characteristics of the subjects by year are summarized in Table 1. During the 5-year period, substantial changes included a higher proportion of patients admitted by specialists, more prior use of statins, and more overall and individual statin use. Substantial increases in the level of statin use were apparent between fiscal years 1994-1995 and 1995-1996, the period in which 4S was published, with the exception of lovastatin, for which the use levels appeared to peak in fiscal year 1995-1996 and decline thereafter. Subjects treated by specialists were younger, were more likely to be men, were more frequently treated at teaching hospitals, had fewer strokes, had more prior statin use, and had a greater level of use of any statin post-AMI (Table 2).

As shown in Figure 1, the rates of change in the use of all statins as a group and those of simvastatin and pravastatin sodium increased substantially following the publication of 4S (\(P<.001\)). Before the publication of 4S, the rate of increase in all statin use was 0.14% per month, which increased 3.6-fold to 0.51% per month after the publication of 4S. Simvastatin and pravastatin also showed

endorsed by professional societies and practice guidelines, and that has been aggressively marketed by drug manufacturers.\(^8,10\) Analysis of the use of statins may provide us with information on the extent to which it is possible to change prescribing behavior in a large population when strong clinical evidence and practice guidelines are combined with aggressive marketing.

(REPRINTED) ARCH INTERN MED/VOL 161, JAN 22, 2001 WWW.ARCHINTERNMED.COM

©2001 American Medical Association. All rights reserved.
significant increases in the rates of use before and after the publication of 4S. After the publication of 4S, there was a 6.6-fold (95% confidence interval, 2.0- to 8.6-fold) increase in the rate of pravastatin use and a 3.7-fold (95% confidence interval, 3.3- to 4.5-fold) increase in the rate of simvastatin use compared with before the publication of 4S. There was no statistically significant change in the rate of use of lovastatin or fluvastatin sodium.

Figure 2 illustrates that it was only after the publication of 4S that patients admitted to the hospital under the primary care of a specialist were more often dispensed statins compared with those admitted under the care of a nonspecialist. A regression model constructed to assess for differential rates of use based on physician specialty found that the overall rate of increase in statin use was significantly greater for specialists (0.60% per month) than for nonspecialists (0.29% per month) during the post-4S period ($P$, <.001).

Since patients admitted by specialist physicians were generally younger and more likely to be men, it was possible that the specialist effect we found was actually due to increased statin use in the younger, male patients, who are more likely to be treated by specialist physicians. Regression models were constructed to assess the specialist effect separately in 4 patient groups: men, women, patients aged 65 to 74 years, and patients aged 75 years and older. In each of these 4 groups, patients admitted to the hospital by specialists had a statistically significant greater rate of increase in statin use after the publication of 4S than did those admitted by nonspecialist physicians ($P$, <.05). The results of these models confirm an independent effect of physician specialty that cannot be attributed to sex or age differences of patients admitted by specialist physicians. In addition, further regression analyses demonstrate a significant specialist effect in teaching and non-teaching hospitals when analyzed separately.

There was a significantly higher rate of overall statin use before ($P$, = .02) and more substantially after ($P$, <.001) the publication of 4S in younger (aged 65-74 years) compared with older (aged $\geq$75 years) patients (Figure 3). A small but statistically significant 1.6-fold greater rate of statin use was found for men compared with women only after 4S was published ($P$, = .006).

We found that there was a steady increase in the overall rate of statin use before the publication of 4S, but that the rate increased significantly after publication. Interestingly, the rate of use of simvastatin and pravastatin increased after the publication of 4S, even though simva-

**Table 1. Characteristics of an Elderly Acute Myocardial Infarction (AMI) Survivor Cohort in Ontario* **

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>8041</td>
<td>8395</td>
<td>8349</td>
<td>8618</td>
<td>9225</td>
<td>42828</td>
</tr>
<tr>
<td>Age, mean, y‡</td>
<td>75.0</td>
<td>74.9</td>
<td>75.1</td>
<td>75.2</td>
<td>75.3</td>
<td>75.1</td>
</tr>
<tr>
<td>Patients aged $\geq$75 y†</td>
<td>48.4</td>
<td>47.6</td>
<td>48.0</td>
<td>48.5</td>
<td>49.7</td>
<td>48.5</td>
</tr>
<tr>
<td>Male sex</td>
<td>55.2</td>
<td>56.6</td>
<td>55.7</td>
<td>55.5</td>
<td>55.2</td>
<td>55.6</td>
</tr>
<tr>
<td>Diabetes‡</td>
<td>18.6</td>
<td>19.5</td>
<td>20.3</td>
<td>19.9</td>
<td>22.0</td>
<td>20.1</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.8</td>
<td>4.2</td>
<td>4.2</td>
<td>4.9</td>
<td>4.7</td>
<td>4.5</td>
</tr>
<tr>
<td>Teaching hospital†</td>
<td>28.6</td>
<td>27.9</td>
<td>28.4</td>
<td>28.2</td>
<td>29.9</td>
<td>28.6</td>
</tr>
<tr>
<td>Admitted by a specialist‡§</td>
<td>66.4</td>
<td>67.3</td>
<td>69.3</td>
<td>68.6</td>
<td>70.3</td>
<td>68.4</td>
</tr>
<tr>
<td>Predispension statin use 90 d before the index AMI‡</td>
<td>3.3</td>
<td>4.0</td>
<td>4.4</td>
<td>4.6</td>
<td>6.6</td>
<td>5.5</td>
</tr>
<tr>
<td>6-mo postdischarge rates of use</td>
<td>5.5</td>
<td>6.9</td>
<td>9.6</td>
<td>17.3</td>
<td>24.9</td>
<td>13.2</td>
</tr>
<tr>
<td>Any statin‡</td>
<td>0</td>
<td>0</td>
<td>0.3</td>
<td>1.0</td>
<td>1.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Fluvastatin sodium‡</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Lovastatin‡</td>
<td>4.0</td>
<td>4.7</td>
<td>4.7</td>
<td>5.8</td>
<td>5.3</td>
<td>4.9</td>
</tr>
<tr>
<td>Pravastatin sodium‡</td>
<td>1.1</td>
<td>1.1</td>
<td>2.2</td>
<td>4.9</td>
<td>9.8</td>
<td>3.9</td>
</tr>
<tr>
<td>Simvastatin‡</td>
<td>0.6</td>
<td>1.3</td>
<td>2.5</td>
<td>6.7</td>
<td>9.6</td>
<td>4.3</td>
</tr>
</tbody>
</table>

* Data are given as percentage of patients unless otherwise indicated.
† $P$, <.05 for trend throughout years.
‡ $P$, <.001 for trend throughout years.
§ Cardiologist or internist.
||Four statins were available during the study period.

**Table 2. Characteristics of Patients in the Cohort by Physician Specialty* **

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Generalist</th>
<th>Specialist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>13,454</td>
<td>29,714</td>
</tr>
<tr>
<td>Male sex‡</td>
<td>51.99</td>
<td>57.28</td>
</tr>
<tr>
<td>Age, mean, y‡</td>
<td>76.18</td>
<td>74.59</td>
</tr>
<tr>
<td>Patient aged $\geq$75 y‡</td>
<td>54.47</td>
<td>45.71</td>
</tr>
<tr>
<td>Diabetes</td>
<td>20.08</td>
<td>20.15</td>
</tr>
<tr>
<td>Stroke‡</td>
<td>5.17</td>
<td>4.24</td>
</tr>
<tr>
<td>Teaching hospital‡</td>
<td>7.38</td>
<td>38.41</td>
</tr>
<tr>
<td>Prior statin use 90 d AMI‡</td>
<td>4.13</td>
<td>6.08</td>
</tr>
<tr>
<td>Statin use at 6 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any statin‡</td>
<td>9.64</td>
<td>14.91</td>
</tr>
<tr>
<td>Fluvastatin sodium‡</td>
<td>0.43</td>
<td>0.56</td>
</tr>
<tr>
<td>Lovastatin‡</td>
<td>3.49</td>
<td>5.60</td>
</tr>
<tr>
<td>Pravastatin sodium‡</td>
<td>2.97</td>
<td>4.39</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>3.08</td>
<td>4.87</td>
</tr>
</tbody>
</table>

* Data are given as percentage of patients unless otherwise indicated. AMI indicates acute myocardial infarction.
† Cardiologist or internist.
‡ $P$, <.001.
statin was the drug used in 4S. The publication of the West of Scotland Coronary Prevention Study in 1995, although it was a primary prevention trial, may have had an impact on prescribers, and some may have believed that the 4S trial indicated a drug class effect rather than a drug-specific effect. However, if there was a class effect, it did not seem to extend to lovastatin as the use of this drug continued to decline.

**Figure 1.** Use of each statin and overall statin use 6 months after myocardial infarction. For all statins, before the publication of 4S, $b = .14$ ($P < .001$); and after the publication of 4S, $b = .51$ ($P < .001$). For the all statins model, $F = 562.41$ ($P < .001$), $R^2 = 0.97$, and the Durbin-Watson statistic $= 1.89$. 4S indicates Scandinavian Simvastatin Survival Study.

**Figure 2.** Use of statins 6 months after myocardial infarction in patients admitted by a specialist (cardiologist or internist) vs a nonspecialist physician. Before the publication of 4S, $b = .13$ vs .15 ($P = .58$); and after the publication of 4S, $b = .29$ vs .60 ($P < .001$). For the model, $F = 320.07$ ($P < .001$), $R^2 = 0.95$, Durbin-Watson statistic $= 1.99$.

**Figure 3.** Use of statins 6 months after myocardial infarction by age category. Before the publication of 4S, $b = .20$ vs .08 ($P = .02$); and after the publication of 4S, $b = .68$ vs .38 ($P < .001$). For the model, $F = 465.77$ ($P < .001$), $R^2 = 0.97$, Durbin-Watson statistic $= 2.12$. 4S indicates Scandinavian Simvastatin Survival Study.
The present study confirms and expands on previous work on the prescribing of lipid-lowering agents. The time trend analysis of Baxter et al of changes in the prescribing of lipid-lowering drugs in the general population of southeast Thames, England, found an exponential increase from 1990 to 1996, with great regional variation in the uptake of the change in practice. The study by Lemaitre et al of a general population cohort of patients aged 65 years and older also found a significant 4-fold increase from June 1989 to May 1996, with an apparent significant undertreatment of many patients. We not only found a substantial rate of increase in statin use over similar periods but also uncovered differential use related to prescriber and patient characteristics.

Although there was no statistically significant difference in the rate of uptake in the use of statins between specialists and nonspecialists before the publication of 4S, there was a significant consistent effect of specialty after the study’s publication. This suggests that specialists take up new information from clinical trials at a greater rate and speed than nonspecialists. These results are congruent with those of previous studies, in which specialists’ prescribing practice was nearer to clinical trial evidence than was nonspecialists’ prescribing practice. Specifically, Whyte et al found that followed up by cardiologists were more than twice as likely to receive drug therapy for a low-density lipoprotein cholesterol level above the accepted target level than were patients treated by generalists. Most of these studies were conducted in the United States, where the nonspecialists used for comparison were interns who are often primary care physicians in the American health care system, similar to family physicians or general practitioners in the Canadian health care system. In Canada, the licensing body did not mandate formal continuing education for either generalists or specialists during the period of interest for our study. While generalist physicians have a broader area of knowledge to maintain, specialist physicians are able to read literature on a narrower range of topics pertinent to their specialty and to attend scientific specialty meetings where late-breaking results of clinical trials are first presented and discussed. Not only do specialist physicians inherently have a quicker uptake of new information, they also are often the first to be targeted for marketing of new drugs by pharmaceutical companies.

Based on reports of the range of serum cholesterol levels in patients with coronary heart disease and the target cholesterol level of 5.5 to 8.0 mmol/L (213-309 mg/dL) of patients in 4S, a conservative estimate of a potentially desirable target rate of statin use in post-AMI population would be approximately 50% to 60%. Previous surveys demonstrated that approximately 65% to 69% of older patients after AMI have an elevated total cholesterol (>5.5 mmol/L [>213 mg/dL]) or an elevated low-density lipoprotein cholesterol (>3.2 mmol/L [>124 mg/dL]) level, typically requiring therapy. If we assumed that the rates of increase in statin use were to continue at the rate estimated in this study and if we assumed an overall level of 60% of patients receiving statins at 6 months was a marker of appropriate uptake, we estimate that it would take until September 2000 for specialists and until November 2008 for nonspecialists to reach this level of prescribing. In other words, specialists would reach the “target” rates 6 years after the trial was published and nonspecialists would reach this level in 14 years. While the specialists had better rates of incorporating the 4S results into their prescribing practices, their rates were still far from optimal. Antman et al have shown that even clinical experts have difficulty keeping up with and summarizing the latest evidence in a timely fashion.

Although we found an increase in the rate of statin use in elderly patients, the rate of increase was much higher in the younger patients. Since patients in 4S were 70 years or younger at enrollment, lower rates of use in the very elderly (>75 years old) may be appropriate. In contrast to the significantly lower observed rates of use of blockers and aspirin in women in previous studies, we found a negligible sex difference in our study, despite the fact that in 4S women represented only 18% of the study population and in subgroup analysis they did not achieve a statistically significant mortality benefit. Marketing efforts of the statins after the publication of 4S may not have differentiated between the effects due to sex and likely influenced the achievement of similar rates of statin use in men and women.

It is impossible to separate the effects of the publication of 4S, the subsequent continuing education efforts, and the effects of marketing by the pharmaceutical industry. Therefore, the results of this study show the effects of the combined efforts among many different parties to promote appropriate medication prescribing with lipid-lowering therapy in patients after AMI. The impact of marketing by the pharmaceutical industry must not be unexpected or underestimated. Surveys demonstrate that physicians often do rely on pharmaceutical representatives as a main source of their continuing medical education. Potential effects of the pharmaceutical industry that were demonstrated in this study include the continual decline in the use of lovastatin, possibly due to the genericization of this preparation in Canada and subsequent decreased promotion, and the transient decline in the rates of use of pravastatin shortly after the publication of 4S. The key questions are related to how marketing should be used to promote high-quality, evidence-based care. Who should market low-cost effective therapies that are not patented, such as blockers? Why has the use of blockers continually remained well below target levels despite solid evidence of benefit? Can marketing of some agents have unexpected negative results? For example, previous research with blockers and calcium channel blockers has demonstrated that properly targeted marketing can inhibit the use of well-proven therapies with the substitution of less well-proven therapies in patients after AMI.

Our study has some limitations. Use of statin therapy was available solely for patients 65 years and older. It is possible that even higher rates of uptake of statin use would have been found with a younger post-AMI population given the existing age bias in post-AMI prescribing. Our database did not have access to actual cholesterol profiles for the patients in our cohort, which limits...
our ability to determine, based on post-AMI guidelines, which individual patients should have received cholesterol-lowering therapy. However, since our study relied on a large, population-based database, our results are likely quite generalizable to many post-AMI populations. Our study did not assess the adherence of patients to their statin prescriptions. It has been reported\(^4\) that up to half of the patients prescribed a lipid-lowering agent discontinue the medication within 1 year. Since the benefits of lipid lowering with simvastatin on mortality started after 1 1/2 to 2 years of therapy, nonadherence represents a lost opportunity for prevention of cardiovascular disease events.

This study has demonstrated that one large randomized clinical trial, 4S, was associated with a significant change in the prescribing of lipid-lowering agents in patients 65 years and older after AMI. Differential prescribing was associated with age and physician specialty status. While rates of statin use significantly increased during the period of interest, additional efforts need to be put into place to sufficiently increase the prescribing rates to target levels. This study suggests that it is possible to shift practice if the evidence of benefit is strong, the intervention is easy to implement, and the intervention is marketed aggressively.

Accepted for publication July 13, 2000.

This study was funded by an operating grant from the Medical Research Council of Canada, Ottawa, Ontario, and in part by a Medical Research Council Scholar award (Dr Tu).

Presented at the Canadian Cardiovascular Society Meeting, Quebec City, Quebec, October 20, 1999.

We thank Peter Austin, PhD, for his consultation on statistical issues.

Corresponding author and reprints: Cynthia A. Jackevicius, BScPhm, MSc, Pharmacy Department, University Health Network–Toronto General Hospital, 200 Elizabeth St, Toronto, Ontario, Canada MSG 2C4 (e-mail: cynthia.jackevicius@uhn.on.ca).

REFERENCES