Use and Monitoring of “Statin” Lipid-Lowering Drugs Compared With Guidelines

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Background: In patients with high cholesterol, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (or “statins”) have been shown to reduce overall mortality in primary and secondary prevention. The National Cholesterol Education Program expert panel’s guidelines (Adult Treatment Panel II) recommend evaluation and treatment of high cholesterol based on stratification of patients according to cardiovascular risk. While evidence suggests that many patients are undertreated, comparatively few data are available regarding overtreatment.

Objectives: To assess the appropriateness of statin therapy compared with national guidelines and to examine the appropriateness of monitoring for adverse effects.

Methods: For all patients at a tertiary medical center, electronic medical records were evaluated for presence or absence of statin use and for presence of established coronary heart disease or cardiac risk factors. Therapy was compared with the recommendations of the National Cholesterol Education Program guidelines. Our primary outcome measures included, for all patients taking statins, prevalence of appropriateness vs overuse, and for all patients with coronary heart disease, prevalence of appropriateness vs underuse.

Results: Overuse of statin therapy was found among 69% of patients undergoing primary prevention, and among 47% of patients undergoing secondary prevention. In addition, among patients with coronary heart disease who were not taking statins, 88% were undertreated. Monitoring of liver function varied widely, and did not correlate with the risk of adverse events secondary to statin use.

Conclusions: Overtreatment and undertreatment for hyperlipidemia were frequent. Decision support may help physicians improve their performance compared with guidelines.

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Any epidemiologic studies over the past several decades have established the relation between an elevated serum cholesterol level and the development of coronary heart disease (CHD). In 1993, the expert panel of the National Cholesterol Education Program (NCEP) proposed guidelines to stratify patients according to risk of CHD, based on cholesterol values and other risk factors. The guidelines recommend drug therapy for individuals at greatest risk.

More recently, controlled trials have demonstrated a conclusive reduction in overall mortality and mortality from CHD among patients whose low-density lipoprotein (LDL) cholesterol values were lowered with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (“statin”) drug therapy. Initial trials demonstrated a survival benefit in patients with established CHD and significantly elevated serum cholesterol values; these results were later extended to patients with CHD whose LDL cholesterol levels were only modestly elevated and even to patients with CHD who had LDL cholesterol values in the average range. In patients without established CHD, the benefit of lowering LDL cholesterol levels with statin therapy has been shown in clinical trials to reduce the incidence of myocardial infarction and mortality from coronary events, supporting their use in primary prevention. These findings were also extended to show a reduction in coronary events among patients with modest LDL cholesterol elevations, using aggressive LDL cholesterol lowering.

Despite the evidence of preventable deaths among patients with CHD, several studies have suggested undertreatment...
PATIENTS AND METHODS

STUDY SITE AND PATIENTS

This study was performed at a tertiary care center, the Brigham and Women’s Hospital, Boston, Mass, and its affiliated sites. Data were drawn from an electronic outpatient medical record, which is used at most sites affiliated with the hospital, including hospital-based practices, free-standing community practices, and community health centers. The electronic medical record includes coded problem lists, medication lists, and laboratory data.

To assess the accuracy of the electronic medical record, we performed manual medical record reviews. In an analysis of 670 records, we found that if a specific disease state was on the electronic problem list (coronary artery disease, diabetes, or hypertension), then the problem was also found on medical record review 98% of the time. Conversely, of 177 patient records manually reviewed, a disease state found on medical record review on average had a 94% likelihood of also being on the electronic problem list. Similarly, if certain drugs (statins or hormone replacement agents) were on the electronic medication list, then more than 95% of the time these agents appeared on medical record review; if these drugs were found on medical record review, then they were found on the electronic medication list roughly 90% of the time. Demographic variables (age and sex) and laboratory data (LDL and high-density lipoprotein cholesterol levels and the results of liver function tests) were 100% accurate. Information regarding certain risk factors (smoking and family history of heart disease) was variably documented in patient medical records and electronic problem lists; however, when the risk factor information appeared, it appeared in both places.

To determine overuse, we evaluated the cohort of all patients taking statins as of January 1, 1996. Among patients taking statins, records were further studied to determine the indication for statin use (primary or secondary prevention), lipid profiles, and concomitant agents. In addition, we evaluated the amount of monitoring for liver function abnormalities, the impact of monitoring, and coexisting medications or disease conditions that could increase the risk of adverse effects.

We defined patients as meeting criteria for secondary prevention if they had CHD; we did not include a broader definition of atherosclerotic disease for this analysis. Patients were identified as having CHD if their computerized problem lists indicated coronary artery disease, myocardial infarction, coronary artery bypass graft, angina, or percutaneous transluminal coronary angioplasty; patients without these problems were considered to be taking statins for primary prevention. Patients undergoing primary prevention were examined for the presence of factors widely accepted as conferring risk for heart disease. These include hypertension, current smoking status, diabetes mellitus, family history of premature heart disease, male sex and age older than 45 years, female sex and age older than 55 years, not taking hormone replacement therapy, and low (<0.91 mmol/L [<35 mg/dL]) high-density lipoprotein cholesterol values. A high-density lipoprotein cholesterol level greater than 1.35 mmol/L (>50 mg/dL) was considered a negative risk factor. The total number of risk factors for each patient was summed. Since established guidelines stratify patients according to whether they have 2 or more risk factors or less than 2, we also categorized patients this way.

GUIDELINES

Guidelines for using pharmacological therapy to treat hypercholesterolemia are based on LDL cholesterol values. Thus, we retrieved the most recent LDL cholesterol value before the initiation of statin therapy. This value, combined with the number and type of risk factors, was compared with guidelines for initiating statin therapy. Patients were considered appropriate if their risk factor status and LDL cholesterol value before statin initiation were in accordance with guidelines.

For patients undergoing primary prevention, those with less than 2 risk factors were considered appropriate if their LDL cholesterol level before drug initiation was greater than 4.92 mmol/L (>190 mg/dL); those with 2 or more risk factors were considered appropriate if their prior LDL cholesterol value was greater than 4.14 mmol/L (>160 mg/dL).

RESULTS

Among 29,543 outpatients who visited their primary care physician during 1996, 1,575 (5%) were taking statins. Patients taking statins were 60% female, and their mean age was 63 years (Table 1). Among patients taking statins, 69% were treated for primary prevention, and 31% had established CHD. Total cholesterol values were measured of this group by primary care physicians and cardiologists. In contrast, relatively little is known about the frequency of overtreatment, particularly among patients undergoing primary prevention. Furthermore, little is known about how practice patterns for monitoring the safety of these medications vary or compare with recommendations. Since primary care physicians hold a strategic position in the detection and management of health problems, their adherence to standards such as consensus guidelines may have a widespread effect.

To address these issues, we performed a study with several goals. Our primary aim was to assess the prevalence of appropriateness of statin therapy compared with previously established recommendations. Secondary aims included evaluating the impact that monitoring had on clinical outcomes, estimating the safety of statins in this cohort, and estimating the financial burden of monitoring. We sought to quantify the occurrence of less obvious adverse effects, in addition to hepatotoxicity. We also assessed the potential costs and savings associated with inappropriate and appropriate statin use and liver function monitoring.

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We considered patients with CHD (secondary prevention) to be inappropriately taking statin therapy if their LDL cholesterol value before drug therapy was below 2.59 mmol/L (<100 mg/dL). To estimate underuse of statins, we reexplored our database for patients who met our criteria for CHD and who were not taking statins. When patients had LDL cholesterol values greater than 2.59 mmol/L (>100 mg/dL) in the presence of CHD and were not taking statins, we considered this inappropriate underuse. For the sake of this analysis, patients with CHD who were taking statins but had not reached the goal LDL cholesterol level of 2.59 mmol/L (100 mg/dL) were not considered inappropriately treated.

ANALYSIS

Patient demographics, overall lipid values, and the range of lipid and liver function monitoring were assessed. The proportions of inappropriate use were calculated, including overuse in primary and secondary prevention and underuse in secondary prevention. Patient demographics were compared between those meeting and not meeting guidelines.

Logistic regression modeling was used to identify predictors of overuse of statin therapy. Indication (primary vs secondary) and patient sex were binary covariates. The 2 continuous variables—patient age and number of risk factors—were assessed to determine the most appropriate form to be used in the model. Both variables, when grouped into categories, showed a nonlinear relation to overuse when used in a logistic regression model. Thus, for the final model, age was categorized into clinically relevant groups, and “number of cardiac risk factors” was collapsed into a binary variable to correlate with guidelines (<2 vs ≥2).

Liver function monitoring was reviewed to assess the range and variability of monitoring frequency compared with recommendations. To evaluate whether more vigilant monitoring occurred with increased risk of adverse events due to statin use, Spearman rank correlations were used to compare the degree of abnormality of the laboratory result with the frequency of monitoring. The effect of monitoring was further assessed to determine whether the abnormalities had an impact on therapy, such as discontinuation or replacement of the statin drug. Records showing patients with abnormal liver function were individually analyzed to determine the impact of these abnormal results on their statin therapy and to determine whether these patients had any clinically significant abnormality.

Patient problem lists, which included medical conditions that would increase the risk of using statins (such as hepatitis or liver disease), were individually reviewed to determine if monitoring was appropriate. Records were also reviewed to determine if the problem preceded or resulted from statin use.

We also evaluated whether monitoring was more frequent if medications interacting with statins were being taken concurrently. These medications were itraconazole, nefazodone hydrochloride (Serzone), gemfibrozil, clofibrate, cyclosporine, and niacin.

Potential adverse reactions to the statin medications were identified by searching patient records for problems that might be related to statin use, including rhabdomyolysis, myositis, sleep disorder or insomnia, and thrombocytopenia. If any of these problems were present, the individual patient records were manually reviewed to determine if the problems appeared to have any relation to use of the statin medication.

We estimated potential annual medication and liver monitoring charges and savings that might be realized if guidelines for use and monitoring were followed. To assess the drug costs of overuse, we used weighted averages of the statin drugs in our cohort and their 1996 average wholesale prices. We estimated the drug cost of correcting underuse by choosing a particular statin (atorvastatin calcium) and calculating the cost using its 1996 average wholesale price. This statin was chosen because its average wholesale price was the lowest among the statins and would, therefore, result in the most conservative estimate of the cost of correcting underuse.

The expected cost of liver function monitoring was estimated using an average of 2 episodes of monitoring per person appropriately undergoing therapy. Excess cost, due to overmonitoring patients appropriately undergoing therapy or monitoring patients who were inappropriately undergoing therapy, was estimated using prices in the Brigham and Women’s Hospital laboratory.

All data analyses were performed using SAS statistical software.

Older, being treated for primary prevention, and having fewer than 2 risk factors were significant (P < .001) predictors of statin overuse, but patient sex was not (Table 4). Reintroducing the covariate of sex to our model did not reveal confounding.

Among patients with CHD who were not receiving statin therapy (n = 1459), 88% met the criteria for being able to receive a statin and were thus undertreated. Among patients with CHD who were taking statins (n = 544), 47% did not meet the criteria and were, therefore, being over-treated according to guidelines (Figure 2).

We found that liver function monitoring during a 1-year period varied widely (Table 5). Among approximately 5000 liver function tests performed on the cohort of 1575 patients taking statins, 37 (2%) of the patients had values greater than 3 times normal. Thirty-five patients had their statin medication changed or discontinued within 90 days of an abnormal result; 10
of these were confirmed, on individual record review, to be related to the abnormal laboratory result. Two patients remained off statins as a result of abnormal liver values, and none had clinical manifestations of hepatitis. The frequency of monitoring did not correlate with the level of test abnormality.

We also evaluated whether monitoring was more intensive among patients receiving a drug that interacted with statins. Ninety-eight patients (6%) were found to be taking other medications with important drug-drug interactions, including niacin, gemfibrozil, cyclosporine, and itraconazole. However, these patients were not monitored more frequently. None of these patients had clinically significant adverse events. Nine patients had other documented problems that may be considered adverse reactions to the statin drugs, including sleep disorder and thrombocytopenia, but none required discontinuation of the drug.

One impact of inappropriate overuse and liver function monitoring is cost. Based on the average wholesale price with weighted averages of specific statin drugs, from the payer perspective an estimated $1338449 in annual cost savings might have been realized if statin use in primary and secondary prevention were restricted to NCEP guidelines. If recommended liver function monitoring were followed, we estimated a further potential annual cost savings of $26620. The cost of correcting underuse among patients with CHD would be $841020.
The potential pharmacy and laboratory savings that would occur by eliminating overuse are substantial. Also, the cost of correcting underuse would be more than offset by the savings of eliminating overuse, and might also reduce the morbidity of CHD. These cost and savings estimates represent drug and laboratory charges; they do not include social costs of treatment, such as lost work days, or costs of treating adverse drug events.

These results are consistent with those of several other studies20-22 that demonstrate lack of adherence to available guidelines. Our findings extend prior evidence of undertreatment to show that overtreatment is also a significant concern, and that a substantial financial burden is associated with overtreatment. Moreover, we assessed adherence to the NCEP guidelines, which tend to be aggressive regarding therapy; use of other guidelines23,24 might have suggested that overtreatment is even more frequent.

Several studies25-27 have shown that publication of guidelines without more intensive accompanying information has little impact on clinical practice. This suggests that research evidence and consensus statements are not primary determinants of physician behavior. Practice-based interventions may be more effective at having an impact on practice behavior.27-29

Tools for improving compliance, and reducing the number of errors, include reminders and computerized alerts.30,31 A growing body of evidence suggests that such computerized decision support, especially when presented at key times such as when physicians are writing orders, can modify ordering behavior.32 In addition, decision support is effective for helping physicians remember to implement an order that follows from another order, such as ordering laboratory tests to monitor liver function after the initiation of statin therapy.32

This study also illustrates the power of the electronic medical record for measuring quality. Although such records are not yet widely used, they have many benefits,33 and facilitation of quality measurement is high on the list.

Our study has several limitations. While some misclassifications undoubtedly occurred because of inaccuracies in the database, they could not account for these figures; guideline adherence could clearly be improved. We may have overestimated the amount of underuse among patients undergoing secondary prevention, since our manual medical record review revealed 1 patient of 20 to be actually taking a statin. If this is the actual proportion of underascertainment, then the rate of underuse would fall to 84%, which is still a formidable figure. Also, some people consider that other populations should be included in the secondary prevention group, such as patients with a history of cerebrovascular accident or peripheral vascular disease, but we followed a strict interpretation of the NCEP guidelines. In addition, we did not address whether patients undergoing secondary preven-

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Table 5. Range of Monitoring Liver Function for 1575 Patients Taking Statins*

<table>
<thead>
<tr>
<th>Laboratory Value Checked</th>
<th>Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td></td>
</tr>
<tr>
<td>No. of times checked</td>
<td>2545</td>
</tr>
<tr>
<td>No. (%) of times abnormal</td>
<td>145 (6)</td>
</tr>
<tr>
<td>No. of patients with an abnormal result</td>
<td>57</td>
</tr>
<tr>
<td>Frequency of monitoring, mean (SD)</td>
<td>3 (3.9)</td>
</tr>
<tr>
<td>Frequency of monitoring correlated with level</td>
<td>0.08†</td>
</tr>
<tr>
<td>AST</td>
<td></td>
</tr>
<tr>
<td>No. of times checked</td>
<td>2509</td>
</tr>
<tr>
<td>No. (%) of times abnormal</td>
<td>343 (14)</td>
</tr>
<tr>
<td>No. of patients with an abnormal result</td>
<td>165</td>
</tr>
<tr>
<td>Frequency of monitoring, mean (SD)</td>
<td>3 (3.9)</td>
</tr>
<tr>
<td>Frequency of monitoring correlated with level</td>
<td>0.09†</td>
</tr>
</tbody>
</table>

*Statins are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase.
†Spearman coefficients.
tion actually achieved the recommended LDL cholesterol values; many undoubtedly did not. Another limitation is that this study was done at one site, so our results may not be generalizable to other populations. However, poor adherence to guidelines has been found in other studies, and is extended herein to show overtreatment in primary prevention and to show inappropriate safety monitoring.

One possible explanation of our findings of statin overuse is that physicians may be extrapolating from recent trials supporting a more aggressive approach to lipid lowering instead of following the NCEP guidelines. However, our data are drawn from physician behavior as of January 1, 1996, before many of the clinical trials, particularly those in primary prevention. An additional implication may be that the guidelines are outdated, and should be revised to reflect more current evidence.

We conclude that, taken together, these results suggest a substantial and costly burden of statin overtreatment and undertreatment, and widely varying liver function monitoring for adverse effects. Decision support, offered during the prescribing and laboratory test-ordering processes, may help physicians optimize use of these medications from the population perspective.

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