

## Over-the-Counter Statins

Nitesh K. Choudhry, MD, PhD, and Jerry Avorn, MD

In late 2004, the British government decided to allow a lipid-lowering agent to be sold as an over-the-counter medication. In contrast, the U.S. Food and Drug Administration recently decided not to do so. The United States and other countries will soon face similar decisions for other statins. Although statins have infrequent side effects and have been shown to be effective in moderate-risk primary prevention populations, many questions remain unanswered about their effectiveness at lower doses in over-the-counter use, the ability of patients to self-select themselves for appropriate therapy, and the social and economic implications

associated with this method of distribution for preventive medications. A rational policy decision concerning over-the-counter statin use will require an effectiveness trial to provide data on how such drugs would be used in this context, as well as on the clinical outcomes that could be expected from this novel "route of administration."

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For author affiliation, see end of text.

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An advisory committee to the U.S. Food and Drug Administration (FDA) recently rejected an application to make a lipid-lowering agent, lovastatin, available over the counter. The committee was concerned that patients might not take this medication safely without physician supervision (1, 2). In contrast, Britain recently approved simvastatin for over-the-counter sale (3). Unlike prescription statins, which are intended for people whose 10-year risk for a cardiovascular event is high (>20% to 30%), low-dose over-the-counter statins have been advocated for use by patients with a moderate (10% to 20%) 10-year risk for a first major coronary event (4). Such moderate-risk patients have been defined as men 45 years of age or older or women older than 55 years of age who have low-density lipoprotein (LDL) cholesterol levels of 3.4 to 4.4 mmol/L (130 to 170 mg/dL) and who smoke or have a low high-density lipoprotein cholesterol level, high blood pressure, or a family history of coronary artery disease (5).

In 2000, the FDA initially considered and rejected applications to make lovastatin and pravastatin available over the counter. However, although the FDA again rejected the reclassification application for lovastatin in early 2005 (2), reconsideration for pravastatin is pending. If statins are ultimately approved for over-the-counter use in the United States, other preventive drugs, such as a "polypill" combination of multiple cardiac medications (6), may also be considered for over-the-counter status in the future. We sought to assess the criteria by which such drugs should be evaluated for over-the-counter reclassification and whether statins satisfy these standards.

### CRITERIA FOR RECLASSIFYING DRUGS AS AVAILABLE OVER THE COUNTER

Drugs that are to be sold over the counter presently must meet a minimum standard of safety and efficacy for such use (Table). However, we believe that the evaluation of a potential preventive drug for over-the-counter use must also consider aspects of the health care delivery system as well as certain ethical and social implications of this method of selling medication. A drug that is safe, is not

likely to be misused, and does not require the involvement of health practitioners for routine use may also be minimally effective; thus, it may have profound and potentially unjustified social implications if it is also expensive and consumed by great numbers of patients. Moreover, if only more affluent patients can afford the over-the-counter drug, concerns of equity may be raised, especially if many insurers reduce coverage for the prescription version of a drug once an over-the-counter preparation becomes available.

### DO STATINS MEET THE OVER-THE-COUNTER STANDARD?

One justification for targeting over-the-counter statins to moderate-risk patients comes from the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (13). Several randomized primary prevention trials have shown beneficial effects of statin therapy in patients at high risk for cardiovascular death (14, 15). However, trials in moderate-risk primary prevention populations, the target populations for over-the-counter statins, have yielded inconsistent results.

The application to allow 20-mg tablets of lovastatin to be sold over the counter relied primarily on results from the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) (8). In this trial, patients without clinically evident coronary artery disease and "average" cholesterol levels (mean LDL cholesterol level, 3.9 mmol/L [150 mg/dL]) were given lovastatin, 20 mg; the dose was titrated to 40 mg if necessary to reach the LDL cholesterol goal. The trial found that lovastatin reduced the relative

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**Table. Criteria for Evaluating Over-the-Counter Decisions\***

Criteria	Do Statins Meet Criteria?	Comments
<b>Current FDA criteria (7)</b>		
Benefits outweigh the risks	Yes (lovastatin); no (pravastatin)	Lovastatin efficacy based on data from AFCAPS/TexCAPS (8); lack of pravastatin efficacy for primary prevention based on ALLHAT-LLT (9) and PROSPER (10); rate of muscle toxicity and liver enzyme abnormalities low for both drugs
Potential for misuse and abuse is low	No	Results of CUSTOM (11, 12) indicate that 43% of patients who took OTC lovastatin were at low risk for CAD mortality and should not have taken any statin, 24% were at high risk for CAD death and should have taken higher-dose statins, and 10% had potential contraindications
Drug can be used safely and effectively without health practitioner involvement	Unclear	Health practitioner involvement should reduce misuse; however, even under the traditional prescription model, many high-risk patients do not receive statins and adherence to long-term statin use is poor
Consumers can use for self-diagnosed conditions	No	Only 10% of users of OTC lovastatin in CUSTOM met all of the label eligibility criteria
Labeling adequate	No	Current labeling appears insufficient to prevent misuse, although adequate labels could be developed
<b>Additional criteria</b>		
Ethical and socially acceptable	Unclear	Cost of OTC statin use will be high; cost likely to be substantially offset by decreased cardiac expenditure only for higher-risk patients; in the absence of subsidies, some patients will not be able to pay for OTC statins, which may compound existing disparities

\* Numbers in parentheses are reference numbers. AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid-Lowering Trial; CAD = coronary artery disease; CUSTOM = Consumer Use Study of Over-the-Counter Lovastatin; FDA = U.S. Food and Drug Administration; OTC = over-the-counter; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk.

risk for major coronary events (fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death) by 37% compared with placebo. However, over-the-counter lovastatin would have been appropriate for only half of the patients in this sample (16). There is no evidence evaluating lovastatin at a fixed dose of 20 mg.

Pravastatin, 40 mg, did not affect outcome rates in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid-Lowering Trial (ALLHAT-LLT), which enrolled hypertensive patients with 1 or more risk factors for coronary artery disease and a mean LDL cholesterol level of 3.8 mmol/L (146 mg/dL) (9). These results may have been attributable in part to large numbers of patients in the control group also receiving statin therapy. A similar negative finding at this dose was seen in the primary prevention arm of the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), which included patients 70 to 82 years of age who had a history of smoking, diabetes, or hypertension and a mean LDL cholesterol level of 3.8 mmol/L (146 mg/dL) (10). There are no primary prevention trials with clinical end points of pravastatin at the proposed over-the-counter dose of 20 mg.

The relatively low rate of adverse drug events associated with statins is reassuring. In the primary prevention trials, rates of muscle toxicity and liver enzyme abnormalities in patients receiving statin therapy were similar to those in patients receiving placebo (8, 10, 14, 15). A meta-analysis of safety data from 35 000 patients enrolled in both primary and secondary prevention trials found that the absolute risks for rhabdomyolysis and liver failure due to statin use are low (17). However, with the widespread

use of statins, a small excess risk for toxicity will probably translate into large numbers of adverse drug events. Moreover, adverse event rates may be higher when drugs are used in actual practice, especially over the counter, compared with use in closely supervised clinical trials. This may be particularly relevant for rare toxicities, such as fetal central nervous system defects when statins are taken by pregnant women (16). The recently reported Consumer Use Study of Over-the-Counter Lovastatin (CUSTOM) (5, 11) seems to validate these concerns, which were central to the FDA's recent rejection of lovastatin's reclassification application (12). An industry-funded study, CUSTOM was designed to assess use of over-the-counter statins sold in simulated retail pharmacies, with participants recruited by mass-media advertising. Of the 1061 individuals who purchased and took at least 1 over-the-counter lovastatin pill, 10.3% had a potential contraindication to the drug (for example, pregnancy, breast feeding, or liver disease) (12).

Unrestricted access to statins may also encourage unnecessary use by low-risk patients. In CUSTOM, 43% of purchasers had 2 or fewer cardiac risk factors and should not have taken statins. Some patients with multiple risk factors have a 10-year risk of less than 10% for coronary death and should not be treated unless their LDL cholesterol levels are high (18). Other patients may use over-the-counter statins as a substitute for the cornerstones of prevention of coronary artery disease (for example, diet, exercise, and smoking cessation). Finally, patients who require more intensive lipid-lowering therapy may be falsely reassured by use of a low-dose statin. One third of users in CUSTOM did not know their LDL cholesterol level when

they decided to purchase the medication (19), and about one quarter were actually at high risk and required more intensive statin therapy (11). Overall, only 10% of users of over-the-counter lovastatin met all of the label eligibility criteria (19).

While selling over-the-counter statins could eliminate barriers created by the need to see a physician for a prescription, there is little evidence that this would enhance adherence. Unlike patients who use other over-the-counter remedies, such as those for allergies or gastrointestinal discomfort, patients who need over-the-counter statins will be asymptomatic. They will not feel better when taking therapy and will not know whether the drugs are “working” as expected. Labeling and promotion could theoretically help in this regard. However, CUSTOM reported adherence rates of 59% (11) compared with 41% to 80% for prescription therapy (20, 21), and the FDA advisory committee was concerned that this was an overestimate of actual rates because of the analytic strategy used (12). For those without insurance, paying for statins out of pocket may further challenge adherence (22) and could paradoxically increase the burden of cardiovascular disease.

The involvement of pharmacists and physicians in prescribing and dispensing statins should, in principle, reduce misuse. However, even the traditional prescription-based model of statin use has not resulted in optimal care. Many high-risk patients do not receive statins (23), and adherence to long-term therapy is poor (20, 24). This may reflect the lack of a reliable system of primary care providers in the United States, especially for patients with inadequate insurance coverage. Interaction between pharmacists and patients was required in Britain’s simvastatin policy, but it is not clear whether the more attenuated pharmacist–patient interaction that prevails in the United States would work as well.

The economic implications of selling statins over the counter could be profound. An estimated 23 million Americans have a 10-year risk for cardiovascular events that is moderate (25). If low-dose over-the-counter lovastatin had been approved, its estimated cost would have been approximately \$1 per day (26). Thus, if all of the patients for whom over-the-counter statins are intended took lovastatin, the aggregate cost for U.S. consumers would be more than \$8 billion per year. Of course, these costs could be justified if statins at the proposed doses effectively reduced other cardiac expenditures. A formal cost-effectiveness analysis would be necessary to evaluate this question. However, if other patients were to take statins also, the costs could be higher—an important concern in the U.S. system where drug advertising to consumers is so prominent.

It is likely that some patients, in the absence of subsidies, will be unable to pay for over-the-counter statins regardless of the price. This raises issues of fairness and may compound existing disparities: Patients of lower socioeconomic status are, on average, at higher risk for death from

coronary artery disease (27) and are less likely to receive cardiovascular care (28). Because prescription statins are a major economic burden for payers, for-profit providers and insurers may see reclassification of statins as an opportunity to shift the cost of these drugs to consumers (29), as has been done when other prescription drugs became available over the counter. Similar criticisms have been leveled against Britain’s National Health Service but are even more salient in a market in which many entities, such as health maintenance organizations, have a profound economic interest in reducing expenditures.

## ISSUES FOR FURTHER EVALUATION

Allowing consumers to purchase preventive medications over the counter represents an innovation in drug delivery. The idea is worth considering, since the present use of cardioprotective medications falls far short of recommendations. However, although some statins in low doses may benefit moderate-risk patients, too many questions about over-the-counter use of these drugs remain unanswered. This delivery method cannot be justified at present. After all, one of the best cardioprotective drugs, aspirin, is already available over the counter, yet its use still falls far short of public health goals. Decisions about over-the-counter availability should be based on evidence of both the efficacy and the effectiveness of a daily preventive medication taken without specific instructions from physicians. Although CUSTOM is a good start in assessing this approach, it has substantial shortcomings. Evaluations of the consequences of Britain’s decision to make simvastatin available over the counter may provide valuable insights (30), but without a priori planning, such studies will probably be confounded by indication and other biases and may not yield meaningful conclusions.

The health care delivery system itself is an “active ingredient” that helps determine the effectiveness of most medications (31). Therefore, reclassifying a drug to over-the-counter status or changing the way in which it is reimbursed can impact patient outcomes as surely as changing its salt formulation or its route of administration. A randomized, controlled trial will be required to provide an optimal assessment of the benefits, risks, and cost-effectiveness of making low-dose statins available over the counter. Such “policy experiments” were once thought impossible but have recently been conducted in other contexts (32). Given increasing consumerism in health care and the obvious failure of our current means of getting many drug treatments to patients who need them, this should be both a research and a regulatory priority. An adequate assessment would be population-based and would collect complete data on patient self-selection, effectiveness, adverse events, and costs. We must explore strategies to ensure equitable, affordable access before embracing an unevaluated and possibly problematic approach to the most common health problem in the United States.

From Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts.

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**Requests for Single Reprints:** Nitesh K. Choudhry, MD, PhD, Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, 1620 Tremont Street, Boston, MA 02120.

Current author addresses are available at [www.annals.org](http://www.annals.org).

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**Current Author Addresses:** Drs. Choudhry and Avorn: Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, 1620 Tremont Street, Boston, MA 02120.