PETER H. JONES, MD
Associate Professor of Medicine; Director of Clinical Trials; Co-director, Lipid Metabolism and Atherosclerosis Clinic; Section of Atherosclerosis and Lipid Research, Baylor College of Medicine, Houston, TX

Statins: The case for higher, individualized starting doses

ABSTRACT

If patients with hypercholesterolemia were started on higher doses of statins tailored to their lipid levels and risk, more of them would achieve their low-density lipoprotein cholesterol (LDL-C) goals, possibly leading to fewer cardiovascular events and deaths.

KEY POINTS

Statin therapy reduces the risk of a first or repeat cardiovascular event in patients at moderate to high short-term risk.

Undertreatment of hypercholesterolemia remains a problem, especially as guidelines have extended the eligible patient population.

An initial statin dose should be prescribed according to a patient's risk, baseline LDL-C level, and degree of LDL-C reduction needed to attain his or her goal.

The risk of liver toxicity or myopathy with statin use is very low, even at high doses, and is far outweighed by the benefits of therapy.

The author has indicated that he has received research grants from the Pfizer, AstraZeneca, Kos, and Abbott corporations.

MOST PATIENTS on statin therapy aren't receiving high enough doses to get their low-density lipoprotein cholesterol (LDL-C) down to recommended goal levels. I believe that instead of starting with a low dose and titrating upward, we would do better by starting at a higher dose if the patient has a higher baseline LDL-C level or is otherwise at higher risk of coronary heart disease (CHD).

See related editorial, page 751

This article aims to increase awareness of undertreatment of hypercholesterolemia and to recommend a starting dose commensurate with a patient's global CHD risk.

STATINS PREVENT CHD EVENTS

Therapy for preventing CHD and its complications focuses on controlling modifiable risk factors, including dyslipidemia—a major cardiovascular risk factor identified in epidemiologic studies.[1]

The development of statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-Co A] reductase inhibitors) was a significant advance. Multiple studies have shown that statins improve clinical outcomes in patients with a broad range of baseline cholesterol levels both with and without established CHD.[2,3]

The benefit was first demonstrated in the Scandinavian Simvastatin Survival Study (4S),[4] in which a statin reduced the incidence of cardiovascular events and total mortality in patients with established CHD (angina pectoris or previous myocardial infarction). Most recently, the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA)[5] found that patients with hypertension but with-

out CHD had significantly fewer cardiovascular events with statin therapy regardless of their baseline total cholesterol levels.

These studies highlight the safety and benefit of statin therapy in patients at moderate-to-high short-term risk. LDL-C goals can also be achieved by drugs that inhibit cholesterol absorption, taken alone or combined with statins. However, not all such therapies have demonstrated clinical benefit.

TOUGHER GOALS FOR THOSE AT HIGHER RISK

Organizations in the United States and other countries have developed specific guidelines for estimating cardiovascular risk and for decreasing it. The guidelines focus on lowering serum LDL-C; secondary goals are to raise low levels of high-density lipoprotein cholesterol and to lower high levels of serum triglyceride.

The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III),[6] published in 2001 and updated in 2004,[7] sets the current standard for testing and managing cholesterol in the United States.

Most physicians agree with the guidelines but do not follow them aggressively enough

The ATP III guidelines set a lower LDL-C goal for patients with documented CHD and for those at equally high risk due to noncoronary atherosclerotic disease, type 2 diabetes mellitus, or a 10-year CHD risk of greater than 20% according to Framingham risk prediction charts. This concept of "CHD risk equivalents" was new in the ATP III report and it substantially increased the number of patients who qualify for the most intensive LDL-C target (< 100 mg/dL).[6] The 2004 update included an even lower target (< 70 mg/dL) as an option for patients at very high risk.[7]

The Third Joint European Task Force[8,9] uses a different system for estimating cardiovascular risk, but for people at high risk the goals are similar to those in the 2001 ATP III guidelines: an LDL-C concentration of 100 mg/dL or less and a total cholesterol concentration of 175 mg/dL or less.

MOST PATIENTS ARE UNDERTREATED

Although the consensus guidelines have been broadly disseminated, most patients at risk for CHD are not attaining the defined LDL-C goals, owing to undertreatment.[10–13]

The European Action on Secondary Prevention Through Intervention to Reduce Events (EUROASPIRE) study[14] showed that 67% of CHD patients who were surveyed in 1995 to 1996 required more intensive cholesterol-lowering treatment than they were receiving, and only 33% were receiving lipid-lowering drugs. The follow-up survey in 1999 to 2000 found that the percentage of CHD patients who were receiving lipid-lowering drugs had increased to 63%, although most still had not attained the recommended cholesterol targets.[11,12]

Most physicians agree with the guidelines—they just don't follow them aggressively enough,[15] and they prescribe statin doses that are too low.[16–19] Irish pharmacy reimbursement claims show that although prescriptions for lipid-lowering drugs (92% of which were statins) increased by 263% (from 35,590 to 129,324) from 1994 to 1997, most patients received the lowest dose, ie, 10 mg of either simvastatin or pravastatin.[13]

In a study in Norway, physicians in general practice who were provided with clear information about the new guidelines still failed to modify the starting statin dose, such that only 17% of primary prevention patients (ie, without CHD) and 44% of secondary prevention patients (ie, with CHD) reached their lipid goals.[16]

Although some coaching and counseling programs improve adherence and achievement of goals, a substantial number of patients still receive a suboptimal statin dose, regardless of LDL-C profile.[20] National prescription data show that commonly prescribed statin doses are substantially lower than those used in the landmark statin trials, eg:

- Simvastatin 20 to 40 mg (used in the 4S study[4]) or 40 mg (used in the Heart Protection Study[21])
- Pravastatin 40 mg (used in the Cholesterol and Recurrent Events study,[22] the Long-Term Intervention With Pravastatin in Ischaemic Disease,[23] and the West of Scotland Coronary Prevention study[24]).

Because of undertreatment, the at-risk population is unlikely to receive the same

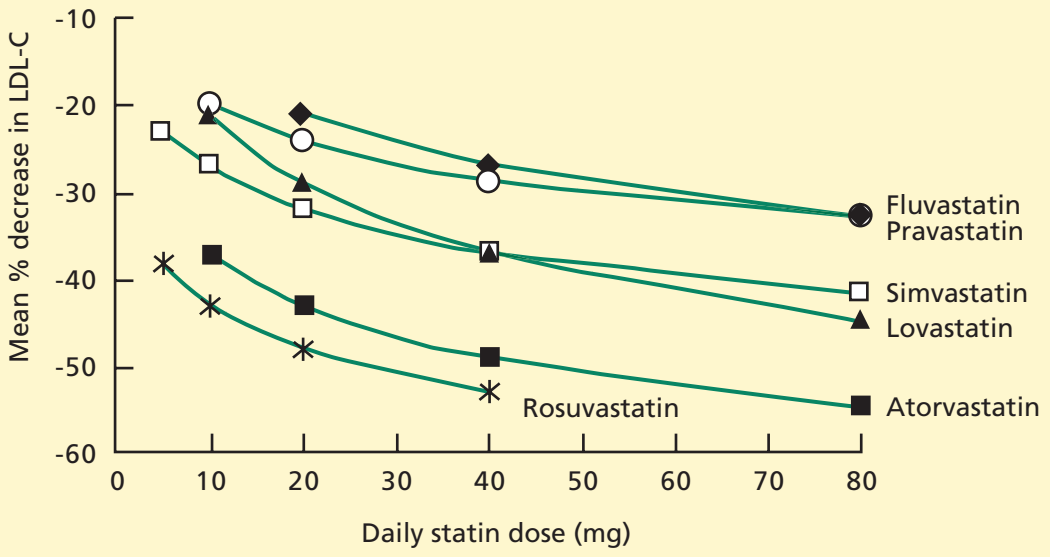

FIGURE 1. Percent reduction in low-density lipoprotein cholesterol (LDL-C) after 8 weeks of treatment with different statins in multiple trials. Data reflect effects observed up to the maximum approved dose for each drug.

DATA FROM LAW MR, WALD NJ, RUDNICKA AR. QUANTIFYING EFFECT OF STATINS ON LOW DENSITY LIPOPROTEIN CHOLESTEROL, ISCHAEMIC HEART DISEASE, AND STROKE: SYSTEMATIC REVIEW AND META-ANALYSIS. BMJ 2003; 326:1423–1429. BY PERMISSION OF THE BRITISH MEDICAL JOURNAL.

level of cardioprotective benefits as demonstrated in these trials.

For example, the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study[18] compared morbidity and mortality rates in patients with CHD and high cholesterol who were given either usual medical care as provided by a primary care physician (which may have included drug treatment) or structured care with open-label atorvastatin provided by a specialist. In the structured-care group, 95% of patients achieved their LDL-C goals vs 3% of usual-care patients, a particularly low number considering that 14% received hypolipidemic drug treatment, mostly statins, at a dose considered appropriate by the primary care physician. The rates of recurrent CHD-related events and deaths were half as high in patients who received structured care as in those who received usual care. This trial highlights that usual care is not optimal and that lipid reductions in line with guidelines are necessary for clinical benefits.

A TARGETED DOSING STRATEGY

An alternative to the traditional "start-low-and-titrate" strategy is to choose the initial statin dose according to a patient's baseline LDL-C level, global CHD risk profile, and percent reduction needed to attain his or her treatment goal. The ATP III update recommends that statins be prescribed at a dose capable of reducing LDL-C levels by at least 30% to 40%.[7]

All of the statins available in the United States and in some European countries come in a range of doses that permit a higher starting dosage.

The dose-response curves for statins are not linear: most of the LDL-C reduction occurs at the lowest dose, and each doubling in dose yields incremental reductions in LDL-C of 5% to 7% (FIGURE 1).[25] Clinicians can tailor therapy appropriately if they know approximately how much the six available statins reduce LDL-C at what dose.

Doubling the statin dose lowers LDL-C by 5%–7%

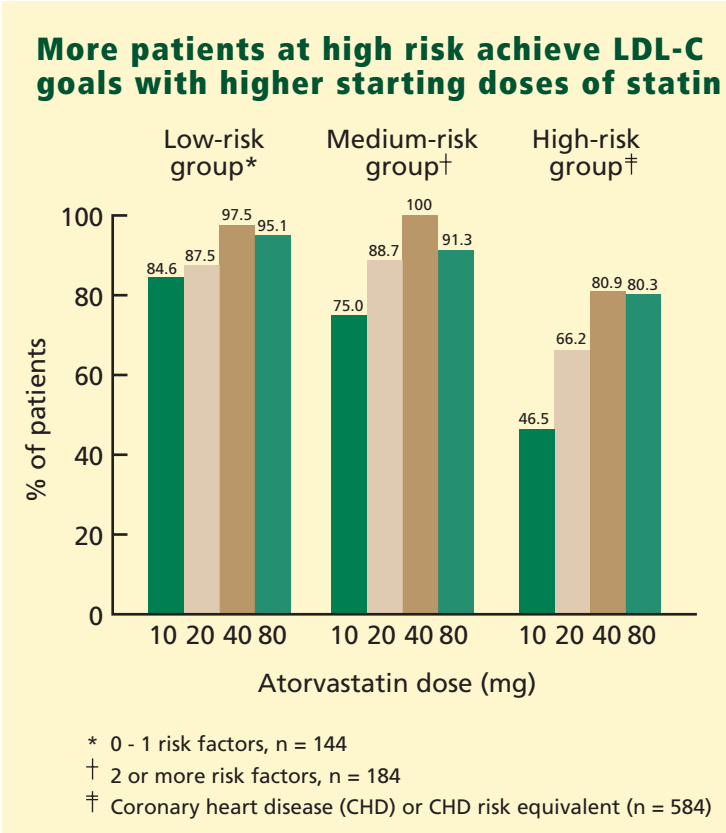

FIGURE 2. Percent of patients who attained the low-density lipoprotein cholesterol goals specified in the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) after being randomized to receive different doses of atorvastatin in the New Atorvastatin Starting Doses: A Comparison (NASDAC) study.

ADAPTED FROM JONES PH, MCKENNEY JM, KARALIS DG, DOWNEY J. COMPARISON OF THE EFFICACY AND SAFETY OF ATORVASTATIN INITIATED AT DIFFERENT STARTING DOSES IN PATIENTS WITH DYSLIPIDEMIA. AM HEART J 2005; 149:e1. WITH PERMISSION FROM ELSEVIER.

For example, if a patient needs to have his or her LDL-C level reduced by 40% from baseline to meet the goal, one should start with a statin dose expected to lower LDL-C by at least that much (eg, rosuvastatin 10 mg/day or atorvastatin 20 mg/day). This strategy reduces the number of follow-up visits and repeat laboratory tests necessary in the titration process, increases compliance and convenience for the patient, and minimizes management costs.

Studies of individualized statin dosing

The Atorvastatin Matrix study[26] tested a strategy of choosing the appropriate statin dose to attain LDL-C goals. Patients with hypercholesterolemia who did not achieve European Atherosclerosis Society lipid-lowering targets received open-label treatment for 12 weeks with atorvastatin 10, 40, or 80 mg/day. The dosage was determined by baseline LDL-C levels and other CHD risk factors. More than 85% of the patients at low or moderate risk without existing CHD achieved their cholesterol goal with this strategy, as did 69% of the patients at high risk (who had CHD, peripheral vascular disease, or familial hypercholesterolemia).

Two newer trials undertaken specifically to determine the optimum starting atorvastatin dose also support the use of higher doses for achieving LDL-C goals.

In the New Atorvastatin Starting Doses: A Comparison (NASDAC) study,[27] 919 patients with CHD or at risk for it were randomized to receive atorvastatin 10, 20, 40, or 80 mg/day.

The Atorvastatin Goal Achievement Across Risk Levels (ATGOAL) study[28] also evaluated atorvastatin 10, 20, 40, or 80 mg/day. However, instead of being randomized, patients (N = 1,295) were assigned a starting dose according to an algorithm based on their risk factors and baseline LDL-C levels. After 4 weeks the dose was titrated upward until patients reached either their goal or the highest dose.

In both studies, atorvastatin produced dose-dependent reductions in LDL-C (36%–52%), and each of the higher doses significantly reduced LDL-C levels vs all lower doses. Patients were more likely to achieve ATP III LDL-C goals with a higher starting dose, regardless of CHD risk level (FIGURE 2, FIGURE 3).

RISKS OF HIGH STATIN DOSES ARE LOW

The primary clinical concerns with higher doses of statins are liver toxicity and myopathy.

The available statins have a strong record of safety and tolerability across the range of approved doses. More than 70,000 people have participated in controlled randomized statin trials, with no serious morbidity or mortality attributed to drug treatment.[3]

After cerivastatin was withdrawn from the market in 2001 because of reports of myopathy, the American College of Cardiology, the American Heart Association, and the National Heart, Lung, and Blood Institute produced a clinical advisory report to update recommendations about the use and safety of statins.[29] The report emphasized the lifesaving potential of statins, stating that the benefits of therapy in at-risk patients greatly outweigh the risks of adverse effects. It concluded that improved safety monitoring can limit adverse effects and alleviate physician and patient concerns.

Liver toxicity

In early clinical trials of statins, alanine aminotransferase and aspartate aminotransferase levels increased to more than three times the normal values in approximately 1% of participants.[4,22,24,30]

In the Prospective Pravastatin Pooling (PPP) project,[31] which combined data from three trials involving more than 19,000 subjects, pravastatin 40 mg/day did not affect the incidence of elevated hepatic transaminase levels compared with placebo.

In pooled safety data from 44 completed clinical trials involving more than 9,400 patients treated with atorvastatin, fewer than 1% had persistently elevated hepatic transaminase levels across the full dosage range, which was not significantly different from the incidence in the placebo groups.[32]

Myopathy

Myopathy is an important adverse event: in rare cases, it leads to acute rhabdomyolysis and irreversible renal failure.[33]

With simvastatin treatment, the incidence of myopathy, rhabdomyolysis, or both has been reported as 0.02% at 20 mg/day, 0.07% at 40 mg/day, and 0.3% at 80 mg/day.[34,35]

Rosuvastatin, the newest statin approved in the United States, has the same low, dose-related incidence of myopathy.[36]

With atorvastatin, a pooled safety analysis of 44 trials revealed no cases of myopathy or rhabdomyolysis, and the incidence of muscle-related side effects was low and no different from that of placebo.[32]

In a meta-analysis of patients treated with fluvastatin 20 to 80 mg per day, the frequency of elevated creatine phosphokinase levels was similar in the treatment and placebo groups.[37]

These data for the clinically established statins confirm good tolerability and impressive safety across their approved doses.

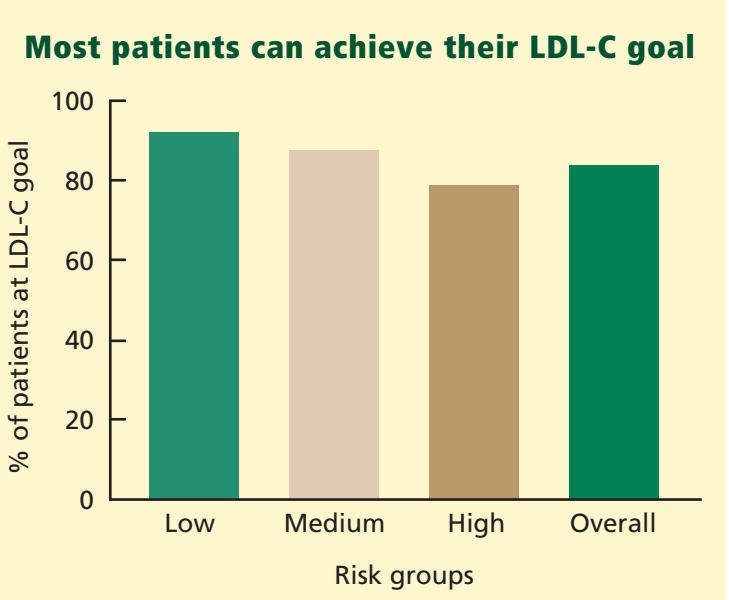

FIGURE 3. Attainment of ATP III goals with single-dose atorvastatin treatment according to risk in the Atorvastatin Achievement Across Risk Levels (ATGOAL) study.

DATA FROM MCKENNEY J, DAVIDSON M, SAPONARO J, THOMPSON P, BAYS H, FOR THE ATGOAL INVESTIGATORS. EFFICACY AND SAFETY OF ATORVASTATIN INITIATED AT OPTIMAL STARTING DOSES IN ACHIEVING LDL-C GOALS IN PATIENTS WITH DYSLIPIDEMIA [ABSTRACT]. PRESENTED AT THE 74TH EUROPEAN ATHEROSCLEROSIS SOCIETY CONGRESS; 2004; SEVILLE, SPAIN. WWW.DRUGSTUDY.MD/ATGOAL.HTML. REPRINTED BY PERMISSION OF THE AUTHORS.

REFERENCES

1. **American Heart Association.** Heart disease and stroke statistics—2004 update. Dallas; American Heart Association, 2003.
2. **Wilt TJ, Bloomfield HE, MacDonald R, et al.** Effectiveness of statin therapy in adults with coronary heart disease. Arch Intern Med 2004; 164:1427–1436.
3. **Vaughan CJ, Gotto AM Jr.** Update on statins: 2003. Circulation 2004; 110:886–892.
4. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344:1383–1389.
5. **Sever PS, Dahlof B, Poulter NR, et al; ASCOT investigators.** Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations in the Anglo-Scandinavian Cardiac Outcomes Trial—

Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 2003; 361:1149–1158.
6. **Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.** Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001; 285:2486–2497.
7. **Grundy SM, Cleeman JI, Merz CN, et al.** Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004; 110:227–239. Erratum in: Circulation 2004; 110:763.
8. **Conroy RM, Pyörälä K, Fitzgerald AP, et al.** Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003; 24:987–1003.
9. **De Backer G, Ambrosioni E, Borch-Johnsen K, et al.** European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J 2003; 24:1601–1610.
10. **EUROASPIRE.** A European Society of Cardiology survey of secondary prevention of coronary heart disease: principal results. EUROASPIRE Study Group. European Action on Secondary Prevention through Intervention to Reduce Events. Eur Heart J 1997; 18:1569–1582. Erratum in: Eur Heart J 1998; 19:356–357.
11. **EUROASPIRE II Study Group.** Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries; principal results from EUROASPIRE II Euro Heart Survey Programme. Eur Heart J 2001; 22:554–572.
12. **EUROASPIRE I and II Group; European Action on Secondary Prevention by Intervention to Reduce Events.** Clinical reality of coronary prevention guidelines: a comparison of EUROASPIRE I and II in nine countries. EUROASPIRE I and II Group. European Action on Secondary Prevention by Intervention to Reduce Events. Lancet 2001; 357:995–1001.
13. **Pearson TA, Laurora I, Chu H, Kafonek S.** The lipid treatment assessment project (L-TAP): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. Arch Intern Med 2000; 160:459–467.
14. **Vanuzzo D, Pilotto L, Ambrosio GB, et al; EUROASPIRE Study Group.** Potential for cholesterol lowering in secondary prevention of coronary heart disease in Europe: findings from EUROASPIRE study. European Action on Secondary Prevention through Intervention to Reduce Events. Atherosclerosis 2000; 153:505–517.
15. **Hobbs FD, Erhardt L.** Acceptance of guideline recommendations and perceived implementation of coronary heart disease prevention among primary care physicians in five European countries: the Reassessing European Attitudes about Cardiovascular Treatment (REACT) survey. Fam Pract 2002; 19:596–604.
16. **Svilaas A, Risberg K, Thoresen M, Ose L.** Lipid treatment goals achieved in patients treated with statin drugs in Norwegian general practice. Am J Cardiol 2000; 86:1250–1253, A6.
17. **Ruof J, Klein G, Marz W, Wollschlager H, Neiss A, Wehling M.** Lipid-lowering medication for secondary prevention of coronary heart disease in a German outpatient population: the gap between treatment guidelines and real life treatment patterns. Prev Med 2002; 35:48–53.
18. **Athyros VG, Papageorgiou AA, Mercouris BR, et al.** Treatment with atorvastatin to the National Cholesterol Educational Program goal versus 'usual' care in secondary coronary heart disease prevention. The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. Curr Med Res Opin 2002; 18:220–228.
19. **Howell N, Trotter R, Mottram DR, Rowe PH.** Compliance with statins in primary care. Pharmacol J 2004; 272:23–26.
20. **van Dam M, van Wissen S, Kastelein JJ.** Declaring war on undertreatment: rationale for an aggressive approach to lowering cholesterol. J Cardiovasc Risk 2002; 9:89–95.
21. **Heart Protection Study Collaborative Group.** MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360:7–22.
22. **Sacks FM, Pfeffer MA, Moyé LA, et al.** The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial Investigators. N Engl J Med 1996; 335:1001–1009.
23. **The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group.** Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998; 339:1349–1357.
24. **Shepherd J, Cobbe SM, Ford I, et al.** Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 1995; 333:1301–1307.
25. **Law MR, Wald NJ, Rudnicka AR.** Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ 2003; 326:1423–1429.
26. **McVey D, Patel H, Eminton Z, Maton S.** An assessment of the efficacy of atorvastatin in treating patients with dyslipidaemia to target LDL-cholesterol goals: the atorvastatin matrix study. Int J Clin Pract 1999; 53:509–513.
27. **Jones PH, McKenney JM, Karalis DG, Downey J.** Comparison of the efficacy and safety of atorvastatin initiated at different starting doses in patients with dyslipidemia. Am Heart J 2005; 149:e1.
28. **McKenney J, Davidson M, Saponaro J, Thompson P, Bays H, for the ATGOAL Investigators.** Efficacy and safety of atorvastatin initiated at optimal starting doses in achieving LDL-C goals in patients with dyslipidemia [abstract]. Presented at the 74th European Atherosclerosis Society Congress; 2004; Seville, Spain. www.drugstudy.md/atgoal.html. Accessed 4/19/05.
29. **Pasternak RC, Smith SC Jr, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C; American College of Cardiology; American Heart Association; National Heart, Lung and Blood Institute.** ACC/AHA/NHLBI clinical advisory on the use and safety of statins. J Am Coll Cardiol 2002; 40:567–572.
30. **Bradford RH, Shear CL, Chremos AN, et al.** Expanded Clinical Evaluation of Lovastatin (EXCEL) study results. I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholesterolemia. Arch Intern Med 1991; 151:43–49.
31. **Pfeffer MA, Keech A, Sacks FM, et al.** Safety and tolerability of pravastatin in long-term clinical trials: prospective Pravastatin Pooling (PPP) Project. Circulation 2002; 105:2341–2346.
32. **Newman CB, Palmer G, Silbershatz H, Szarek M.** Safety of atorvastatin derived from analysis of 44 completed trials in 9,416 patients. Am J Cardiol 2003; 92:670–676.
33. **Pierce LR, Wysowski DK, Gross TP.** Myopathy and rhabdomyolysis associated with lovastatin-gemfibrozil combination therapy. JAMA 1990; 264:71–75.
34. Zocor (Simvastatin) [package insert]. Whitehouse Station, NJ: Merck & Co., Inc; 2004. Available at: http://www.zocor.com/zocor/shared/documents/english/pi.pdf. Accessed August 23, 2004.
35. **de Lemos JA, Blazing MA, Wiviott SD, et al.** Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA 2004; 292:1307–1316.
36. **Shepherd J, Hunninghake DB, Stein EA, et al.** Safety of rosuvastatin. Am J Cardiol 2004; 94:882–888.
37. **Benghozi R, Bortolini M, Jia Y, Isaacsohn JL, Troendle AJ, Gonasun L.** Frequency of creatine kinase elevation during treatment with fluvastatin. Am J Cardiol 2002; 89:231–233.

ADDRESS: *Peter H Jones, MD, FACP, 6565 Fannin Street, A601, Houston, TX 77030; e-mail jones@bcm.tmc.edu.*