Supplement to
Clinical Cardiology

Volume 26

1'03

Clinical Cardiology™

An International Indexed and Peer-Reviewed Journal for Advances in Treatment of Cardiovascular Disease

LDL and Beyond: New Therapeutic Approaches to Hypercholesterolemia

John C. LaRosa, M.D.
Guest Editor

January 2003
Foundation for Advances in Medicine and Science, Inc.

Clinical Cardiology™

Supplement I

LDL and Beyond: New Therapeutic Approaches to Hypercholesterolemia

John C. LaRosa, M.D.
Guest Editor

This supplement is based on a satellite symposium sponsored by AstraZeneca and held prior to the 74th Scientific Sessions of the American Heart Association, November 2001, Anaheim, California. The publication of the proceedings is funded by an unrestricted educational grant from AstraZeneca.

Clinical Cardiology™

A Journal for Advances
in Cardiovascular Disease

The editorial content of supplements is reviewed by the guest editor and approved by C. Richard Conti, M.D., Editor-in-Chief of the Journal. The findings presented in this supplement are those of the contributors and not necessarily those of the sponsor, the publisher, or the editors of *Clinical Cardiology*.

The Publisher

CLINICAL CARDIOLOGY: A Journal for Advances in Cardiovascular Disease (ISSN 0160-9289) is published monthly and copyrighted © 2003 by the Foundation for Advances in Medicine and Science, Inc., 111 Oweno Road, Mahwah, N.J. 07430. Periodicals postage paid at Mahwah, New Jersey, and additional mailing offices. POSTMASTER: Send address changes to Clinical Cardiology, Box 832, Mahwah, NJ 07430-0832.

Subscription per annum (12 issues plus supplements): Personal $80 U.S. and Canada; $126.50 outside U.S. and Canada. Institutional $150 U.S. and Canada; $196.50 outside U.S. and Canada; single copy $15.50. Subscriptions calendar year only. Payment for subscriptions should be in U.S. funds drawn on U.S. bank to Clinical Cardiology Publishing Co., Inc., Box 832, Mahwah, N.J. 07430-0832.

This journal is fully refereed and is included in Index Medicus, Current Contents/Clinical Practice, ISI BioMed, Science Citation Index, Index Internacional de Cardiologia, and EMBASE/Excerpta Medica.

Neither the editors nor the publisher guarantees, warrants or endorses any product advertised in this publication; nor do they guarantee any claim made by the manufacturer of said product or service.

Manuscript submission: Refer to last page of Table of Contents for Instructions to Authors page listing or visit www.clinicalcardiology.org.

Printed in USA by Cadmus-Mack Printing Co., Easton, PA.

January 2003

Publisher: John Bourgholtzer

Executive Editor: Joey Marie Bourgholtzer, Ph.D.

Art Director: John Romano

Circulation Manager: Lillian Conly

Copyreader: Helga Politzer

Advertising rates & information mailed on request.

Contact:
Clinical Cardiology Advertising Department
Box 832, Mahwah, New Jersey 07430-0832
Tel. (201) 818-1010
Telex 220883 TAUR
Fax (201) 818-0086
E-mail: clinicalcardiology@fams.org
Internet: http://www.clinicalcardiology.org/

To implement a change of address, please remove the mailing label affixed to your copy and send it together with your new address to Clinical Cardiology, Box 832, Mahwah, NJ 07430-0832.

The journal is not responsible for replacing missing issues unless the Circulation Department is notified of nonreceipt within 3 months of issue date for domestic addresses and 6 months for foreign addresses.

Clinical Cardiology™

A Journal for Advances in Cardiovascular Disease

Contents • Vol. 26, No. 1, January 2003 (Supplement I)

ARTICLES IN BRIEF

Original Contributions

Clin. Cardiol. Vol. 26 (Suppl. I), I-1–I-2 (2003)

Introduction

LDL and Beyond: New Therapeutic Approaches to Hypercholesterolemia

JOHN C. LAROSA, M.D, GUEST EDITOR

State University of New York Downstate Medical Center, Brooklyn, New York, USA

Investigators first noted the link between elevated serum cholesterol and cardiovascular disease almost a century ago.[1] Only after the Second World War, however, did coronary heart disease (CHD) emerge as the leading cause of premature death in the developed world, warranting a major research effort to identify and address its causes.[2] This effort gave rise to such landmark epidemiologic surveys as the Seven Countries Study, the Framingham Study, and the Multiple Risk Factor Intervention Study, which elucidated the major risk factors for heart disease and identified low-density lipoprotein (LDL) cholesterol as the main atherogenic component of serum cholesterol.

Still, numerous trials of lipid-lowering drugs (bile acid sequestrants, nicotinic acid, and fibrates) in the 1980s failed to demonstrate that patients who reduced their cholesterol with medication would have lower rates of CHD morbidity and mortality. Only in the mid 1990s, with the advent of the 3-hydroxy-3-methylglutaryl (HMG-CoA) reductase inhibitors, or statins, did controlled trials[3–7] begin to yield unequivocal proof that reduction of total and LDL cholesterol prevents CHD-related disability and death in persons with no history of heart disease as well as in those with confirmed CHD.

As always, progress has raised new questions, several of which are addressed in this collection of articles, adapted from a symposium entitled "LDL and Beyond: New Therapeutic Approaches to Hypercholesterolemia." The symposium, held just prior to the 74th Scientific Sessions of the American Heart Association in Anaheim, California, touched on both clinical and basic research issues arising from over a decade of experience with the statins.

Address for reprints:

John C. LaRosa, M.D.
President, SUNY Downstate Medical Center
Health Science Center at Brooklyn
450 Clarkson Avenue, Box 1
Brooklyn, NY 11203, USA
e-mail: jclarosa@downstate.edu

The opening article answers the question of how, over the first half of the twentieth century, CHD evolved from being a relatively rare condition to causing more deaths than any other disease worldwide. It summarizes several important milestones in the history of cardiovascular medicine, from the first recorded description of atherosclerosis in a late–seventeenth-century autopsy to recent studies showing that CHD risk ratios are lower among populations in undeveloped regions than among migrant populations from the same regions—sometimes from the same families—living in urban environments. It also reviews the landmark autopsy studies that found signs of mild to severe coronary artery disease in U.S. soldiers killed in Korea and Vietnam,[8, 9] as well as in trauma victims—some still in their teens—in the United States.[10, 11] These studies proved that atherosclerosis begins early, progresses with age, and is positively related to an atherogenic blood lipid profile.

Apart from LDL cholesterol, what components of the blood-lipid profile contribute to atherogenicity, and how does lipid-lowering therapy alter them? M. John Chapman, B.Sc., Ph.D., D.Sc., and colleagues Muriel Caslake, B.Sc., Ph.D., Chris Packard, B.Sc., Ph.D., D.Sc., and Fergus McTaggart, B.Sc., Ph.D., discuss the other atherogenic lipid particles—the apolipoprotein B (apoB)–containing lipoprotein subfractions—namely, very-low-density lipoprotein (VLDL), VLDL remnants, and intermediate-density lipoproteins. The statins appear to reduce circulating concentrations of apoB-containing lipoproteins by both decreasing production of VLDL in the liver and increasing the number of LDL receptors. The authors also present data showing that rosuvastatin, the newest agent in the statin class, effectively lowers both LDL and apoB subfractions in patients with type IIa or IIb dyslipidemia.

Peter Libby, M.D., answers the question of how the statins reduce the risk of coronary thrombosis, revealing that mechanisms less straightforward than cholesterol lowering per se are involved. He discusses several cellular-level changes characteristic of plaque formation and disruption and shows how statins interrupt the biochemical pathways that destabilize the atherosclerotic plaque and precipitate most fatal cases of coronary thrombosis. Dr. Libby also examines the possible mechanisms of the statins' vasodilating and anti-inflammatory properties.

What are the similarities and differences among the statins? Peter H. Jones, M.D., reviews the current data on the pharmacodynamic and pharmacokinetic variations within the class,

reaching some preliminary conclusions about their clinical implications. In clinical trials, the statins have all produced significant reductions in LDL cholesterol, although atorvastatin and rosuvastatin seem to be the most powerful. Dr. Jones also summarizes current perspectives on the statins' effects on triglycerides and high-density lipoprotein (HDL) cholesterol.

Finally, what future direction is lipid-lowering therapy likely to take? In a concluding article, Antonio M. Gotto, Jr., M.D., D.Phil., praises the National Cholesterol Education Program (NCEP) for increasing public awareness of hypercholesterolemia as a risk factor for heart disease but notes that lipid disorders remain underdiagnosed and undertreated, even among high-risk patient groups. The statins, which are effective, generally safe, and remarkably well tolerated, should help clinicians begin to address the gaps in treatment of lipid disorders with greater success. The newest member of this drug class, rosuvastatin, may have stronger LDL cholesterol–lowering effects than the older statins.

While the value of the statins cannot be overstated, additional lipid-lowering agents will undoubtedly have a place in the future management of hypercholesterolemia. Several agents in the early stages of development work by inhibiting cholesterol or bile transport rather than interrupting cholesterol synthesis, bypassing the HMG-CoA reductase pathway entirely. With a wider range of therapeutic tools and a better understanding of optimal management for distinct subgroups of hyperlipidemic patients, significant CHD risk reduction should be widely attainable.

References

1. Haust MD, More RH: Development of modern theories on the pathogenesis of atherosclerosis. In *The Pathogenesis of Atherosclerosis* (Eds. Wissler RW, Geer JC), p. 1–19. Baltimore, Md.: Williams and Wilkins, 1972
2. Paul O: *Take Heart. The Life and Prescription for Living of Paul Dudley White, the World's Premier Cardiologist*, p. 131–149. Boston, Mass.: Harvard University Press, 1986
3. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM Jr: Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *J Am Med Assoc* 1998;279:1615–1622
4. 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
5. Sacks FM, Pfeffer MA, Moyé LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JMO, Wun C-C, Davis BR, Braunwald E, for the Cholesterol and Recurrent Events Trial Investigators: The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001–1009
6. Scandinavian Simvastatin Survival Study Group: Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–1389
7. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ: Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301–1307
8. Enos WF, Holmes RH, Beyer J: Coronary disease among United States soldiers killed in action in Korea. Preliminary report. *J Am Med Assoc* 1953;152:1090–1093
9. McNamara JJ, Molo MA, Stremple JF, Cutting RT: Coronary artery disease in combat casualties in Vietnam. *J Am Med Assoc* 1971;216:1185–1187
10. Strong JP, Malcom GT, McMahan CA, Tracy RE, Newman WP III, Herderick EE, Cornhill JF, for the Pathobiological Determinants of Atherosclerosis in Youth Research Group: Prevalence and extent of atherosclerosis in adolescents and young adults. Implications for prevention from the Pathobiological Determinants of Atherosclerosis in Youth Study. *J Am Med Assoc* 1999;281:727–735
11. Relationship of atherosclerosis in young men to serum lipoprotein cholesterol concentrations and smoking. A preliminary report from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *J Am Med Assoc* 1990;264;3018–3024

Clin. Cardiol. Vol. 26 (Suppl. I), I-3–I-6 (2003)

Understanding Risk in Hypercholesterolemia

JOHN C. LAROSA, M.D.

State University of New York Downstate Medical Center, Brooklyn, New York, USA

Summary: Atherosclerosis was relatively uncommon 100 years ago, when researchers first established its link to elevated cholesterol. As the twentieth century progressed, however, factors such as high-fat diets, sedentary lifestyles, cigarette smoking, and urbanization combined to increase the prevalence of both hypercholesterolemia and coronary heart disease (CHD) throughout the developed world. Atherogenesis begins at an early age and progresses throughout life, and cholesterol levels during young adulthood strongly predict the risk of CHD and related mortality during the ensuing decades. The total cholesterol level in youth also determines the actual age at which a critical level of atherosclerosis will be reached. Early studies on the primary and secondary prevention of CHD failed to identify a linear relationship between lipid lowering and risk reduction, primarily because older lipid-lowering agents lacked the potency to reduce cholesterol levels significantly enough to achieve lower cardiovascular event and mortality rates. The introduction of the statins, with their powerful lipid-lowering activity, overcame this limitation. Several large-scale trials of statins firmly established the efficacy of these agents in both primary and secondary CHD prevention. With the availability of statin therapy, we are now able to reduce the risk of major adverse CHD events by an average of 30%, regardless of patient age or gender.

Key words: atherosclerosis, hypercholesterolemia, statins

Address for reprints:

John C. LaRosa, M.D.
President, SUNY Downstate Medical Center
Health Science Center at Brooklyn
450 Clarkson Avenue, Box 1
Brooklyn, NY 11203, USA
e-mail: jclarosa@downstate.edu

Introduction

Atherogenesis has been the subject of investigation for more than 300 years, yet our understanding of cholesterol-deposition and plaque-formation processes continues to evolve. In 1695, Johann Conrad von Brunner illustrated autopsy-identified changes that he referred to as "hardening" of the aorta and major blood vessels. William Heberden penned a description of angina pectoris based on 20 cases in 1768, then expanded his observations to 100 cases in 1782.

The next milestone was Karl Freiherr von Rokitansky's 1852 description of atheroma pathology, which elucidated the "thrombogenic" or "encrustation" theory of atherosclerosis. A few years later, in 1856, Rudolf Virchow presented the "inflammatory" theory, which held that atherosclerosis is the result of intimal inflammation and subsequent fibrosis. Between 1909 and 1913, A. Ignatowsky, S. Saltykow, and N. N. Anitschkow developed the "lipid" theory of atherosclerosis, which linked dietary cholesterol to elevated circulating cholesterol and, in turn, to subintimal cholesterol deposits. In 1910, however, Sir William Osler contended that angina pectoris was a rare disease. "Indeed," he noted, "I had reached Fellowship before I saw a case in hospital or private practice."[1]

The theories of atherogenesis that occupy us today, then, have clearly been around for a while. Even so, as Osler noted, angina pectoris was an unusual finding in the early 1900s. As the twentieth century unfolded, this relatively rare condition[2] became the leading cause of mortality in the world.

Risk Factor Interactions

Studies carried out in recent decades have documented a clear relationship between serum cholesterol levels and the risk of coronary heart disease (CHD) in the developed world. As shown in Figure 1, curves depicting coronary artery disease (CAD) risk ratios from the landmark Multiple Risk Factor Intervention study (MRFIT) and a series of retrospective epidemiologic investigations in Japan are nearly identical.[3] These findings suggest that despite some degree of individual susceptibility, genetic predisposition plays only a minor role in

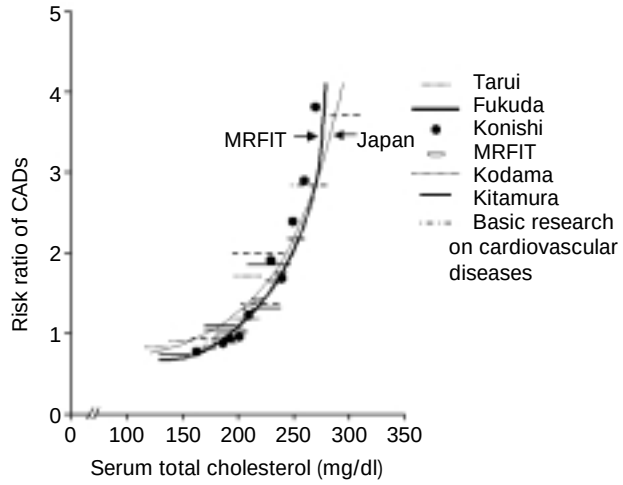


FIG. 1 Relationship between serum total cholesterol and risk ratio for coronary artery disease in the United States vs. Japan. Reprinted from Ref. No. 3 with permission. CAD = coronary artery disease, MRFIT = Multiple Risk Factor Intervention Trial.

determining the development of CAD as the result of elevated serum cholesterol. Rather, in the aggregate, this risk represents the influence of a constellation of factors, including high-fat diets, sedentary lifestyles, cigarette smoking, urbanization, and, most likely, others that have not yet been identified.

A study of Japanese patients—half living in Hiroshima, half living in Hawaii, and all having a 10- to 19-year history of type 2 diabetes—clearly illustrated the influence of diet, as opposed to genetics, on the development of CHD.[4] The incidence of retinopathy was similar in the two groups, affecting 57% of the Hiroshima residents and 50% of the Hawaiians. However, postmortem studies in individuals > 40 years old revealed that CHD was far more prevalent in Hawaii (33%) than in Hiroshima (14%). These data indicate that diabetes is an important risk factor for CHD in the presence of the factors that cause Western societies to have higher cholesterol levels—most prominently, high-fat diets.

Patterns of Atherogenesis

Pivotal data reported in the 1950s revealed that the process of atherogenesis begins early in life. Analyzing autopsy findings from 300 U.S. soldiers killed in action in the Korean conflict (mean age, 22 years), Enos *et al.* found that 35% had "fibrous" coronary arterial plaque with insignificant luminal narrowing, 12% had more than 50% occlusion of one or more vessels, and 3% had complete occlusion of one or more vessels.[5] Similar figures of 42, 12, and 0%, respectively, were reported by McNamara *et al.* in a 1971 analysis of data from 105 comparably aged casualties of the Vietnam War.[6]

For almost half a century, therefore, we have been aware that atherosclerosis is fairly well advanced by early adulthood. More recent confirmation of this pattern came from 1990s reports published by the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group.[7,8] Autopsy data from 2,876 individuals (15 to 34 years old) who had died of traumatic causes revealed the presence of raised lesions or fatty streaks even among teenagers; the percentage of intimal surface with such involvement increased with age. Fatty streaks were more extensive in black than in white subjects, but the prevalence of raised lesions did not differ by race. The extent of raised lesions in the aorta was similar in women and men, but raised lesions in the right coronary arteries were less common in women. Atherosclerotic damage to the intimal surface was positively associated with elevated serum levels of low-density lipoprotein (LDL) cholesterol and very-low-density lipoprotein (VLDL) cholesterol and negatively associated with high-density lipoprotein (HDL) cholesterol. Smoking was strongly associated with a greater prevalence of raised lesions—an effect that occurred independent of lipoprotein levels. Hypertension and diabetes also increased the risk of atherosclerotic changes. Assessing the clinical implications of this analysis, the investigators pointed out that the primary prevention of atherosclerosis, as opposed to the primary prevention of clinically manifest atherosclerotic disease, must begin in childhood or adolescence.

Other work showed that a single measurement of cholesterol in early adulthood does, in fact, predict which individuals will develop CHD as they grow older. In a prospective study of 1,017 men with a mean age of 22 years, Klag *et al.* found a strong relationship between the baseline serum cholesterol level and the occurrence of CHD, as well as CHD mortality and total mortality, during the subsequent 40 years (Fig. 2).[9]

Based on the strong association between cholesterol and CHD risk, one can reasonably conclude that consistently low cholesterol levels confer protection against heart disease. In Western societies with high-fat diets and sedentary habits, "low" indicates well below average. The median cholesterol level in the United States and Japan is 200 to 210 mg/dl (5.17 to 5.43 mmol/l),[10] which is probably 50 to 60 mg/dl (1.29 to 1.55 mmol/l) higher than the ideal in terms of preventing

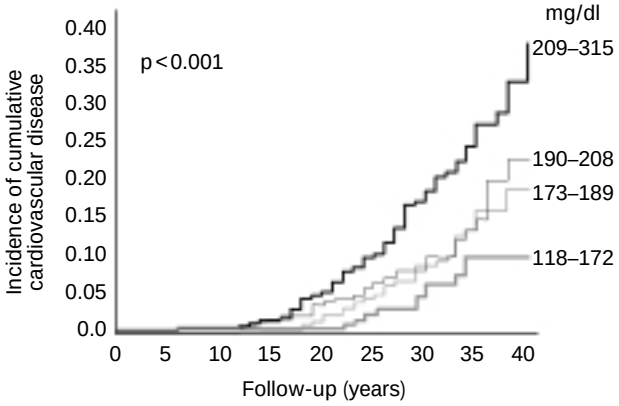


FIG. 2 Cumulative incidence of cardiovascular disease by cholesterol level at 22 years of age in men. Reprinted from Ref. No. 9 with permission.

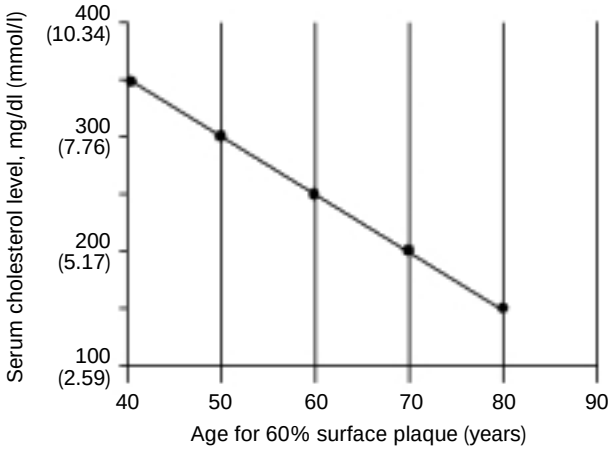


FIG. 3 Relationship of age to cholesterol level and extent of coronary artery plaque involvement. Reprinted from Ref. No. 11 with permission.

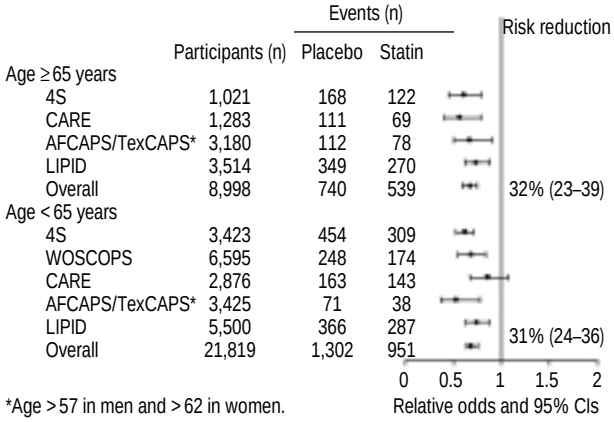


FIG. 4 Reduction in coronary heart disease risk by age in major statin trials. Reprinted from Ref. No. 18 with permission. 4S = Scandinavian Simvastatin Survival Study, CARE = Cholesterol and Recurrent Events Trial, AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study, LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease study, WOSCOPS = West of Scotland Coronary Prevention Study, CI = confidence interval.

atherosclerosis. A truly normal cholesterol level, from the standpoint of the process of atherogenesis, would be approximately 150 mg/dl (3.88 mmol/l).

The atherogenesis that begins at an early age progresses throughout life. The point at which an individual reaches a critical level of atherosclerosis depends on the cholesterol level. From a pathologic perspective, evidence of plaque formation on 60% of the coronary artery surface area could be considered significant atherosclerosis. An individual who maintains a total cholesterol level of 150 mg/dl (3.88 mmol/l) would reach the age of 80 before developing that degree of atherosclerosis (Fig. 3).[11] On the other hand, an individual with a steady total cholesterol level of 300 mg/dl (7.76 mmol/l) would reach this critical point at around the age of 50.

Primary and Secondary Prevention

Early studies of the primary and secondary prevention of CHD failed to identify a linear relationship between the degree of cholesterol reduction and the extent of CHD risk reduction.[12] In hindsight, it became apparent that the lipid-lowering agents used in the early trials (clofibrate, colestipol, cholestyramine, gemfibrozil, and niacin) simply lacked the cholesterol-lowering power needed to produce significant reductions in CHD risk.

Any doubt about the linear relationship between total cholesterol levels and CHD risk evaporated with the development of the statins, the most powerful agents for reducing cholesterol. Five pivotal, large-scale trials firmly established the efficacy of these agents in terms of both primary and secondary prevention of CHD morbidity and mortality.[13–17] A meta-analysis of data from these trials, representing a total of 30,817 participants, demonstrated that statin therapy reduces the risk of major adverse CHD events by approximately 30% regardless of patient age or gender (Figs. 4 and 5, respectively).

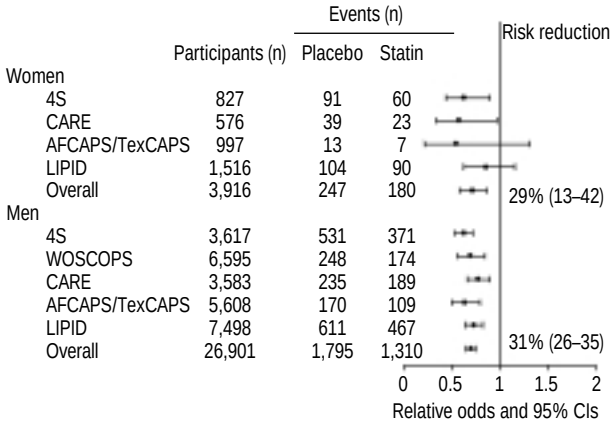


FIG. 5 Reduction in coronary heart disease risk by gender in major statin trials. Reprinted from Ref. No. 18 with permission. Definition of acronyms and abbreviations as in Figure 4.

Conclusion

Our understanding of the link between serum cholesterol and atherogenesis has been evolving for nearly 100 years. This association has become ever more striking during the past century as factors that raise atherogenic blood lipids—high-fat diets, sedentary lifestyles, cigarette smoking, and urbanization—have spread to affect every segment of society. With the understanding that atherogenesis begins early in life and that total cholesterol levels predict CHD risk, the goal of effective prevention through pharmacologic and behavioral interventions seems well within reach.

References

1. Haust MD, More RH: Development of modern theories on the pathogenesis of atherosclerosis. In *The Pathogenesis of Atherosclerosis* (Eds. Wissler RW, Geer JC), p. 1–19. Baltimore, Md.: Williams and Wilkins, 1972
2. Murray CJ, Lopez AD: Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet* 1997;349: 1269–1276
3. Saito Y: Prevention of coronary heart diseases and lipid-lowering therapy in Japan. *Eur Heart* J 2000;2(suppl D):D49–D50
4. Kawate R, Yamakido M, Nishimoto Y, Bennett PH, Hamman RF, Knowler WC: Diabetes mellitus and its vascular complications in Japanese migrants on the island of Hawaii. *Diabetes Care* 1979;2: 161–170
5. Enos WF, Holmes RH, Beyer J: Coronary disease among United States soldiers killed in action in Korea. Preliminary report. *J Am Med Assoc* 1953;152:1090–1093
6. McNamara JJ, Molo MA, Stremple JF, Cutting RT: Coronary artery disease in combat casualties in Vietnam. *J Am Med Assoc* 1971;216:1185–1187
7. Strong JP, Malcom GT, McMahan CA, Tracy RE, Newman WP III, Herderick EE, Cornhill JF: Prevalence and extent of atherosclerosis in adolescents and young adults. Implications for prevention from the Pathobiological Determinants of Atherosclerosis in Youth Study. *J Am Med Assoc* 1999;281:727–735
8. Relationship of atherosclerosis in young men to serum lipoprotein cholesterol concentrations and smoking. A preliminary report from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *J Am Med Assoc* 1990;264;3018–3024
9. Klag MJ, Ford DE, Mead LA, He J, Whelton PK, Liang KY, Levine DM: Serum cholesterol in young men and subsequent cardiovascular disease. *N Engl J Med* 1993;328:313–318
10. Okayama A, Ueshima H, Marmot MG, Nakamura M, Kita Y, Yamakawa M: Changes in total serum cholesterol and other risk factors for cardiovascular disease in Japan, 1980–1989. *Int J Epidemiol* 1993;22:1038–1047
11. Grundy SM: Cholesterol and coronary heart disease. A new era. *J Am Med Assoc* 1986;256:2849–2858
12. Levine GN, Keaney JF Jr, Vita JA: Cholesterol reduction in cardiovascular disease. Clinical benefits and possible mechanisms. *N Engl J Med* 1995;332:512–521
13. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM Jr: Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/ TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *J Am Med Assoc* 1998;279:1615–1622
14. 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
15. Sacks FM, Pfeffer MA, Moyé LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JMO, Wun C, Davis B, Braunwald E, for the Cholesterol and Recurrent Events Trial Investigators: The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001–1009
16. Scandinavian Simvastatin Survival Study Group: Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–1389
17. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ: Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301–1307
18. LaRosa JC, He J, Vupputuri S: Effect of statins on risk of coronary disease: A meta-analysis of randomized controlled trials. *J Am Med Assoc* 1999;282:2340–2346

Clin. Cardiol. Vol. 26 (Suppl. I), I-7–I-10 (2003)

New Dimension of Statin Action on ApoB Atherogenicity

M. JOHN CHAPMAN, B.SC., PH.D., D.SC., MURIEL CASLAKE, B.SC., PH.D.,* CHRIS PACKARD, B.SC., PH.D., D.SC., *
FERGUS MCTAGGART, B.SC., PH.D.†

National Institute of Health and Medical Research (INSERM), Unit 551, Hôpital de la Pitié, Paris, France; *Glasgow Royal Infirmary, Glasgow, Scotland, Great Britain; †AstraZeneca, Alderley Park, Cheshire, Great Britain

Summary: Newer, more effective statins are powerful agents for reducing elevated levels of low-density lipoprotein (LDL) cholesterol and thereby lowering the risk of coronary heart disease (CHD) and related adverse events. Although LDL remains the primary target of therapy for reducing CHD risk, increased interest is focusing on apolipoprotein B (apoB)-containing lipoprotein subfractions—particularly very-low-density lipoprotein (VLDL), VLDL remnants, and intermediate-density lipoproteins (IDL)—as secondary targets of therapy. Elevated apoB is known to be an important risk factor for CHD, and dysregulation of the metabolism of apoB-containing lipoproteins is involved in the progression of atherosclerosis. Statins reduce circulating concentrations of atherogenic apoB-containing lipoproteins by decreasing the production of VLDL in the liver and, thus, the production of VLDL remnants and LDL. Statins also increase the clearance of these particles through upregulation of LDL receptors in the liver. Efforts to develop statins with enhanced lipid-modifying properties are ongoing. The optimal statin would offer a high degree of inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, a prolonged duration of action, hepatic selectivity for maximal upregulation of LDL receptors, and a low potential for drug–drug interactions. Recent studies have shown that rosuvastatin, a new agent in this class, demonstrates these qualities. Rosuvastatin is a highly effective inhibitor of HMG-CoA reductase, is relatively nonlipophilic, has a half-life of approximately 20 h, exhibits hepatic selectivity, has little systemic availability, and has a low potential for drug–drug interactions because of its limited degree of metabolism by the cytochrome P-450 system. A recent double-blind, crossover study revealed that treatment with rosuvastatin resulted in marked reductions in apoB-containing lipoproteins in patients with type IIa or IIb dyslipidemia. By reducing the number of atherogenic lipoprotein particles, rosuvastatin decreases the atherosclerotic burden in hyperlipidemic patients at high risk for CHD and related adverse outcomes.

Key words: apolipoprotein B, atherosclerosis, dyslipidemia, rosuvastatin, statins

Introduction

Since its inception in the 1980s, the National Cholesterol Education Program (NCEP) has focused on low-density lipoprotein (LDL) cholesterol as the principal target of therapy aimed at reducing the risk of coronary heart disease (CHD) and related adverse events in patients with dyslipidemia.[1–3] Statins have emerged as the most effective pharmacologic agents for reducing LDL levels, and numerous large-scale trials have confirmed that these effects translate into significant decreases in the risk of CHD events.[3–7] However, the most recent NCEP guidelines (NCEP ATP III), issued in May 2001, also recognize the importance of non–high-density lipoprotein (non-HDL) cholesterol as a secondary target of therapy in individuals with high triglyceride (TG) levels.[3] The term "non-HDL cholesterol" refers to the combined cholesterol content of LDL and other atherogenic apolipoprotein B (apoB)-containing lipoprotein subfractions—namely, very-low-density lipoprotein (VLDL), VLDL remnants, intermediate-density lipoproteins (IDL), and also lipoprotein(a) when present in significant quantities. High levels of serum apoB are important risk factors for ischemic heart disease, and dysregulation of apoB-containing lipoproteins is involved in atherosclerotic progression.[8,9]

Concentrations of apoB-containing, non-HDL particles are elevated in atherogenic lipoprotein phenotypes, of which type IIa and type IIb dyslipidemia are the most common. The type

These studies were supported by a grant from AstraZeneca.

Address for reprints:

M. John Chapman, B.Sc., Ph.D., D.Sc.
National Institute of Health and Medical Research (INSERM)
Unit 551
Pavillon Benjamin Delessert
Hôpital de la Pitié
83 Boulevard de l'hôpital
7561 Paris Cedex 13
Paris, France
e-mail: chapman@infobiogen.fr

IIa phenotype is characterized by elevated LDL and normal TG concentrations, whereas the type IIb phenotype (also known as mixed or combined dyslipidemia) is associated with hypercholesterolemia and elevated levels of TG-rich lipoproteins. Both phenotypes frequently give rise to premature cardiovascular morbidity and mortality.

Because of the growing attention to the role of non-HDL cholesterol in atherogenesis, it is of interest to consider whether the potent effects of statins on LDL cholesterol levels extend to other apoB-containing lipoproteins as well.

In Vivo Metabolism of Atherogenic Lipoproteins

An understanding of lipoprotein metabolism in normolipidemic and hyperlipidemic patients is essential in gaining a perspective on the actions of statins. The liver secretes VLDL particles that are precursors of VLDL remnants, which subsequently may be transformed into IDL and LDL.[10] This cascade occurs as the result of the actions of lipoprotein lipase and hepatic lipase. However, all apoB-containing particles are significantly enriched while circulating in the plasma by the action of the cholesteryl ester transfer protein, which transfers cholesterol, in the form of its ester, from HDL to these particles. Under normolipidemic conditions, this pathway can account for up to approximately 50% of the cholesterol taken up by the liver.[11] Hepatic uptake of these particles is primarily mediated by the LDL receptor, as identified in the work for which Brown and Goldstein were awarded the Nobel Prize.[12] The circulating concentrations of these particles are dependent on the rate of their production as well as their rates of intravascular remodeling and removal from the plasma compartment.

Certain alterations in lipoprotein metabolism result in elevated plasma concentrations of atherogenic lipoprotein particles in types IIa and IIb dyslipidemia (Fig. 1). These two forms of atherogenic dyslipidemia are often characterized by an overproduction of VLDL in the liver, or by delayed catabolism of VLDL, or both, leading to elevated concentrations of VLDL remnants and, ultimately, of LDL. The plasma pool of VLDL remnants is thereby increased, and their half-lives in plasma are extended. When these particles accumulate, their presence at high concentrations favors the accumulation and deposition of cholesterol in peripheral tissues and particularly in the arterial wall. Elevated levels of such particles set the stage for the development and progression of lipid-rich atherosclerotic plaque.

Effects of Statins on ApoB-Containing Lipoproteins

Statins act in two ways to reduce circulating concentrations of apoB-containing lipoproteins (Fig. 2). First, these agents reduce the production of VLDL particles in the liver by approximately 10 to 15%, resulting in decreased production of VLDL remnants and of LDL.[13] Of greater importance, however, is increased clearance via LDL receptors, which is responsible for the major reductions in levels of these particles in individuals receiving statin therapy.[14] Numbers of LDL receptors, especially in the liver, are increased, because statins inhibit the key enzyme in endogenous cholesterol synthesis: 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. A reduction in the cholesterol pool results in upregulation of LDL receptor expression, mediated by activation of the nuclear transcription factor, SREBP. This upregulation leads to enhanced clearance of atherogenic lipoproteins and, therefore, to reductions in the plasma pool of these particles. The atherosclerotic burden in individuals with type IIa or IIb dyslipidemia is consequently reduced on statin treatment.

The nature of the atherogenic particles that predominate in type IIa and type IIb dyslipidemia determines how statins normalize atherogenic lipoprotein phenotypes. The major atherogenic particles in type IIa dyslipidemia are large, buoyant LDLs (LDL-I and LDL-II subtypes), which are enriched in cholesteryl esters. In contrast, type IIb dyslipidemia is typified by increases in TG-rich VLDL, VLDL remnants, and small, dense LDL (LDL-III).[15, 16]

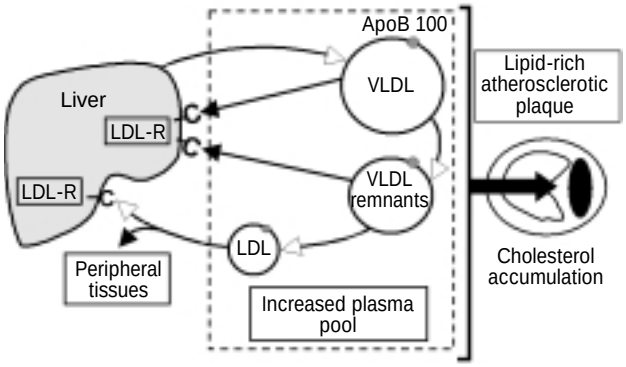


FIG. 1 In vivo metabolism of apoB-containing lipoproteins in types IIa and IIb dyslipidemia. ApoB = apolipoprotein B, LDL-R = low-density lipoprotein receptor, VLDL = very-low-density lipoprotein.

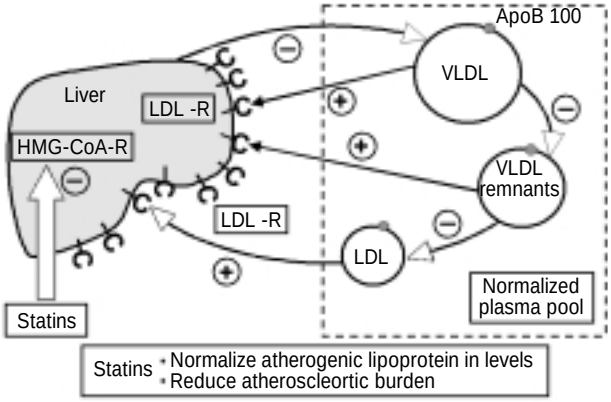


FIG. 2 Effects of statins on atherogenic apoB-containing lipoproteins in types IIa and IIb dyslipidemia. HMG-CoA-R = 3-hydroxy-3-methylglutaryl coenzyme A receptor, LDL = low-density lipoprotein. Other abbreviations as in Figure 1.

Characteristics of an Ideal Hypothetical Statin

The optimal statin would be one that produces a high degree of inhibition of HMG-CoA reductase, has a prolonged duration of action, is targeted to the liver for maximal upregulation of LDL receptors, and has a low potential for drug–drug interactions.[17] In addition, such an agent would offer pharmacologic properties designed to diminish the possibility of adverse effects in peripheral tissues. A favorable effect on the entire lipid profile is very important, as is lack of metabolism by the cytochrome P-450 system.

The ideal statin would produce significant reductions in coronary events and be cost-effective for both primary and secondary prevention.[18] Other desirable characteristics would include:

- Daily administration not affected by meals or time of day
- Tolerability and efficacy regardless of patient characteristics such as age or weight
- An accompanying educational program for physicians and patients to enhance understanding of treatment

Recent observations from studies of a new statin, rosuvastatin, provide insights into the prospects for achieving these objectives.

Pharmacologic Characteristics of Rosuvastatin

Like other agents in its class, the rosuvastatin molecule has a characteristic pharmacophore group that interacts with the binding site of HMG-CoA reductase (Fig. 3).[17] However, the other components of this molecule are distinct from those of other statins. In particular, rosuvastatin has a polar methane sulfonamide group that renders the molecule relatively hydrophilic.[17, 19] The log D value of rosuvastatin (−0.33 at pH 7.4) is considerably lower than the values for cerivastatin, simvastatin, fluvastatin, and atorvastatin (log D > 1.0 and < 2.0) and is closer to that of pravastatin (log D = −0.84).[20] This characteristic of relative hydrophilicity means that the molecule is relatively hepatoselective, with limited nonhepatic tissue uptake.

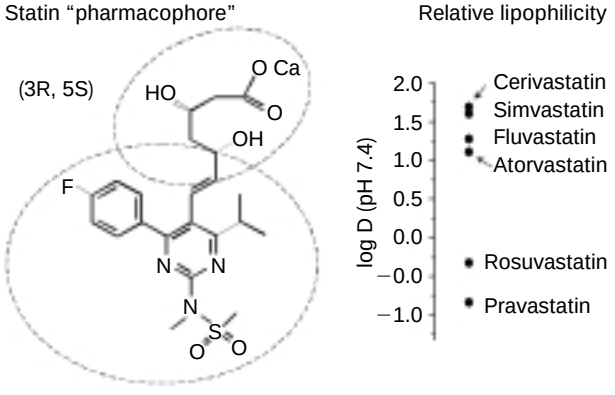


FIG. 3 Structure and relative lipophilicity of rosuvastatin. Reproduced from Ref. No. 16 with permission.

In a recently published study, Istvan and Deisenhofer cocrystallized the catalytic domain of human HMG-CoA reductase with each of the statins currently available or in late clinical development.[21] These researchers showed that all the statins interact with the binding site of HMG-CoA reductase, but rosuvastatin was distinguished by two factors. First, the total number of bonding interactions between the molecule and the active site of HMG-CoA reductase—that is, the catalytic portion—was higher than with any other statin. Second, a unique polar interaction was evident between the electronegative sulfone group of rosuvastatin and the Arg^{568} side chain of HMG-CoA, contributing to the potency with which the inhibitor binds to the enzyme. This degree of polarity confirms that rosuvastatin is relatively nonlipophilic and is also an excellent enzyme inhibitor.

Other work has helped elucidate the ways in which these structural features of rosuvastatin translate into pharmacologic properties, such as hepatic selectivity. A group studying the inhibition of cholesterol synthesis in primary rat hepatocytes found that the log mean IC_{50} was significantly lower with rosuvastatin than with the other available statins ($p < 0.001$).[19] This statistically significant difference reflects the enhanced potency of rosuvastatin with respect to HMG-CoA reductase inhibition and its ability to be actively taken up and concentrated by hepatic cells, with perhaps a low rate of efflux from hepatic cells, as well. The same researchers analyzed cell selectivity and found that simvastatin and cerivastatin were relatively nonspecific for hepatic uptake.[19] They also showed that the IC_{50} values for these agents were similar in primary rat hepatocytes and in cultured rat fibroblasts, and that cerivastatin probably has even greater selectivity for peripheral tissue than for the liver.

Given that rosuvastatin is relatively nonlipophilic, its metabolism by the cytochrome P-450 (CYP) system in the liver is relatively low.[17, 22] Studies have found minimal or no metabolism of the compound by CYP 3A4 and only minor metabolism by CYP 2C9 or 2C19.[22] Rosuvastatin has only limited systemic availability. Its absolute bioavailability is 20%.[17] Rosuvastatin is predominantly eliminated as the parent compound in bile.[17] The elimination half-life is approximately 20 h, which is among the longest for a statin and provides prolonged action on the target enzyme of cholesterol synthesis.

Effects of Rosuvastatin on ApoB-Containing Lipoproteins

Rosuvastatin produces dose-related reductions in LDL cholesterol that meet or exceed the decreases achieved by any other statin monotherapy in patients with primary hypercholesterolemia.[23–27] The effects of rosuvastatin on levels of apoB-containing lipoproteins were examined in a double-blind, crossover study involving 14 patients with type IIa dyslipidemia (LDL 3.40–5.70 mmol/l, TG < 2.0 mmol/l) and 18 patients with type IIb dyslipidemia (LDL 2.75–5.55 mmol/l, TG > 2.0 mmol/l).[28] All patients received rosuvastatin 40 mg/day for 6 weeks. In patients with type IIa dyslipidemia, ro-

suvastatin reduced LDL by a mean of 43%, VLDL by 40% or more, IDL by 65%, and apoB by 51%. In patients with type IIb dyslipidemia, rosuvastatin reduced LDL by a mean of 62%, VLDL by 42 to 50%, IDL by 50%, and apoB by 51%. In the overall study population, the reduction in LDL was inversely related to baseline TG levels ($r = 0.33$, $p = 0.034$), whereas the reduction in TG was positively related to baseline TG levels ($r = 0.58$, $p < 0.001$). Clearly then, triglyceride lowering by rosuvastatin is intimately related to lipid phenotype.

Conclusion

The growing recognition of the importance of atherogenic apoB-containing lipoproteins in CHD is leading to a greater appreciation of the spectrum of potential therapeutic benefit associated with statin therapy. Along with the continuing focus on LDL reductions as the primary means of lowering CHD risk, there is a growing appreciation that other apoB-containing lipoproteins, not just LDL, possess atherogenic activity. Rosuvastatin is associated with marked reductions in all apoB-containing lipoproteins, including VLDL, IDL, and small, dense LDL, in the major atherogenic dyslipidemias—types IIa and IIb. By reducing the number of atherogenic lipoprotein particles, rosuvastatin decreases the atherosclerotic burden in these patients, who are at high risk of adverse cardiovascular outcomes. Clinical evaluations in type IIb dyslipidemia have shown that rosuvastatin reduces the number of atherogenic particles by more than half. These findings hold promise for more effective management of patients with atherogenic dyslipidemias.

References

1. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. The Expert Panel. *Arch Intern Med* 1988;148:36–69
2. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *J Am Med Assoc* 1993;269:3015–3023
3. 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). *J Am Med Assoc* 2001;235:2486–2497
4. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM Jr.: Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *J Am Med Assoc* 1998;279:1615–1622
5. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–1389
6. Sacks FM, Pfeffer MA, Moyé LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E: 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
7. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ: 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
8. Lamarche B, Moorjani S, Lupien PJ, Cantrin B, Bernard P-M, Dagenais GR, Després J-P: Apolipoprotein A-I and B levels and the risk of ischemic heart disease during a five-year follow-up of men in the Québec Cardiovascular Study. *Circulation* 1996;94:273–278
9. Tomkin GH, Owens D: Abnormalities in apo B-containing lipoproteins in diabetes and atherosclerosis. *Diabetes Metab Res Rev* 2001;17:27–43
10. Hahn SE, Goldberg DM: Factors affecting the regulation of apo B secretion by liver cells. *J Clin Lab Anal* 1995;9:431–449
11. Goldberg DI, Beltz WF, Pittman, RC: Evaluation of pathways for the cellular uptake of high-density lipoprotein cholesterol esters in rabbits. *J Clin Invest* 1991;87:331–346
12. Brown MS, Goldstein JL: A receptor-mediated pathway for cholesterol homeostasis. *Science* 1986;232:34–47
13. Vega GL, Grundy SM: Effect of statins on metabolism of apo-B-containing lipoproteins in hypertriglyceridemic men. *Am J Cardiol* 1998;81(suppl 4A):36B–42B
14. Forster RF, Stewart G, Bedford D, Stewart JP, Rogers E, Shepherd J, Packard CJ, Caslake MJ: Influence of atorvastatin and simvastatin on apolipoprotein B metabolism in moderate combined hyperlipidemic subjects with low VLDL and LDL fractional clearance rates. *Atherosclerosis* 2002;164:129–145
15. Milosavljevic D, Griglio S, Le Naour G, Chapman J: Preferential reduction of VLDL-1 particle number by fenofibrate in type IIB hyperlipidemia: Consequences for uptake by human monocyte-derived macrophages. *Atherosclerosis* 2001;155:251–260
16. Chapman JM: Atherogenicity of low-density lipoproteins: mechanisms. In *Plasma Lipids and Their Role in Disease* (Eds. Barter PJ, Rye KA), p. 69–84. Amsterdam, The Netherlands: Harwood Academic Publishers, 1999
17. McTaggart F, Buckett L, Davidson R, Holdgate G, McCormick A, Schneck D, Smith G, Warwick M: Preclinical and clinical pharmacology of rosuvastatin, a new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. *Am J Cardiol* 2001;87(suppl):28B–32B
18. Shephard J: The statin era: In search of the ideal lipid regulating agent. *Heart* 2001;85:259–264
19. Buckett L, Ballard P, Davidson R, Dunkley C, Martin L, Stafford J, McTaggart F: Selectivity of ZD4522 for inhibition of cholesterol synthesis in hepatic versus non-hepatic cells (abstract MoP29:W6). *Atherosclerosis* 2000;151:41
20. Smith G, Davidson R, Bloor S, Burns K, Calman C, McAulay P, Torr N, Ward W, McTaggart F: Pharmacological properties of ZD4522: A new HMG-CoA reductase inhibitor (abstract MoP20:W6). *Atherosclerosis* 2000;151:39
21. Istvan ES, Deisenhofer J: Structural mechanism for statin inhibition of HMG-CoA reductase. *Science* 2001;292:1160–1164
22. McCormick AD, McKillop D, Bulters CJ, Miles GS, Baba T, Touchi A, Yamaguchi Y: ZD4522: An HMG-CoA reductase inhibitor free of metabolically mediated drug interactions: Metabolic studies in human in vitro systems (abstract 46). *J Clin Pharmacol* 2000;40:1055
23. Olsson AG, Pears J, McKellar J, Mizan J, Raza A: Effect of rosuvastatin on low-density lipoprotein cholesterol in patients with hypercholesterolemia. *Am J Cardiol* 2001;88:504–508
24. Blumenthal RS: Statins: Effective antiatherosclerotic therapy. *Am Heart J* 2000;139:577–583
25. Knopp RH: Drug treatment of lipid disorders. *N Engl J Med* 1999; 341:498–511
26. Maron DJ, Fazio S, Linton MP: Current perspectives on statins. *Circulation* 2000;101:207–213
27. Nawrocki JW, Weiss SR, Davidson MH, Sprecher DL, Schwartz SL, Lupien PJ, Jones PH, Haber HE, Black DM: Reduction of LDL cholesterol by 25% to 60% in patients with primary hypercholesterolemia by atorvastatin, a new HMG-CoA reductase inhibitor. *Arterioscler Thromb Vasc Biol* 1995;15:678–682
28. Caslake MJ, Stewart G, Day S, Daly E, Nwose OM, Chapman MJ, Durrington P, Laggner P, Pears J, Packard CJ: Rosuvastatin normalises atherogenic levels of apo B-containing lipoprotein subfractions. *Int J Clin Pract* 2002;124(suppl):8

Clin. Cardiol. Vol. 26 (Suppl. I), I-11–I-14 (2003)

Effects of Statins in Reducing Thrombotic Risk and Modulating Plaque Vulnerability

PETER LIBBY, M.D. AND MASANORI AIKAWA, M.D., PH.D.

Harvard Medical School and Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA

Summary: A large body of evidence demonstrates that statin therapy reduces risk for coronary events. This benefit probably stems in large part from lipid lowering, but lipid-independent cellular effects may also contribute. Statin therapy may lower the risk of thrombosis by reducing tissue factor expression and increasing plasminogen activators while reducing plasminogen-activator inhibitor. The statins may also improve endothelial function and reduce inflammatory response by increasing nitric oxide activity; all statins tested can decrease levels of C-reactive protein, a systemic marker of inflammation. Indeed, limiting inflammation may prove an important mechanism of statins' clinical benefits due to both lipid lowering and direct cellular effects. For example, attenuation of inflammation probably promotes maintained integrity of the fibrous cap of the atherosclerotic lesion by inhibiting processes that degrade the collagenous structure of the cap. Rupture of the fibrous cap causes most fatal coronary thrombosis.

Key words: inflammation, thrombosis, statins

Introduction

Evidence from clinical trials demonstrates that lipid lowering with statin treatment reduces the incidence of coronary events and stroke in a broad spectrum of individuals. A number of mechanisms may account for or contribute to the protective effects of statins. Drugs in this class may reduce plaque thrombogenicity, lessen vasospasm, decrease inflammation, and stabilize the fibrous cap of the atherosclerotic lesion.[1]

Address for reprints:

Peter Libby, M.D.
Chief, Division of Cardiovascular Medicine
Brigham and Women's Hospital
Tower 3B, 75 Francis Street
Boston, MA 02115, USA

Reducing Thrombogenicity

Physical disruption of the atherosclerotic plaque precipitates most fatal cases of coronary thrombosis. Once a plaque ruptures and a thrombus begins to form, a robust endogenous fibrinolytic system may favor rapid clot dissolution, or if an unfavorable balance in local and systemic hemostatic factors prevails, an occlusive thrombus may result. The procoagulant, prothrombotic, and antifibrinolytic factors involved in determining the consequences of a given plaque disruption include tissue factor, plasminogen activator inhibitor-1 (PAI-1), fibrinogen, and platelet-activating factor; the anticoagulant, antithrombotic, and profibrinolytic factors include plasminogen activators, thrombomodulin, and prostacyclin. One potential mechanism for disruption of hemostatic balance, overexpression of the potent procoagulant tissue factor by macrophage foam cells in the atherosclerotic plaque lipid core, may result from inflammatory signals, namely the proinflammatory cytokine CD40 ligand.[2]

Statin drugs may lower thrombogenicity by exerting anticoagulant/profibrinolytic effects. Aikawa *et al.* have shown that dietary lipid lowering reduces tissue factor expression in rabbit atheroma.[3] In this study, rabbits with atheromas induced by balloon injury and high cholesterol diet (baseline group) were either switched to a purified-chow diet (low-cholesterol group) or maintained on a high-cholesterol diet (high-cholesterol group) for 16 months. Immunolocalization of tissue factor quantified by computer-assisted color image analysis showed strong expression of tissue factor in atheroma macrophages in the baseline and high-cholesterol groups and substantial reduction of tissue-factor protein expression in the low-cholesterol group (Fig. 1). This reduction corresponded to decreased activity of tissue factor assessed by in situ binding of tissue factor to factors VIIa and X; levels of tissue factor mRNA also decreased after dietary lipid lowering.

Other studies have found that statins can increase endothelial cell expression of an enzyme that favors fibribolysis, tissue plasminogen activator.[4] These in vitro studies demonstrated that endogenous tissue plasminogen activator levels increased in a lipid-independent manner, while levels of antifibrinolytic PAI-1 declined. Therefore, statins may act to reduce thrombus

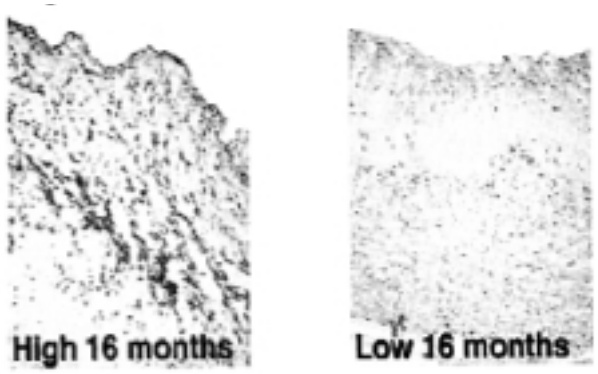


FIG. 1 Staining for tissue factor protein in rabbit atheromas after 16 months of high-cholesterol diet (A) and 16 months of low-cholesterol diet (B) following induction of the atheroma with balloon injury and 4 months of an atherogenic diet. Reproduced from Ref. No. 3 with permission.

accumulation in both a lipid-dependent manner (decreased tissue-factor activity) and a lipid-independent manner (decreased PAI-1 levels and enhanced plasminogen activator effect). Decreases in fibrinogen, an acute phase reactant, may also limit thrombus formation.

Opposing Vasospasm

A variety of studies indicate that lipid lowering (e.g., with statins and other drugs, plasmapheresis, or other means) can improve endothelial vasodilator function. Studies in vitro have shown that statins increase production of the potent vasodilator nitric oxide. Endres *et al.* showed that statin treatment significantly increased activity of endothelial nitric oxide synthase (eNOS), an enzyme responsible for nitric oxide production, in aortas of normocholesterolemic mice (Fig. 2).[5]

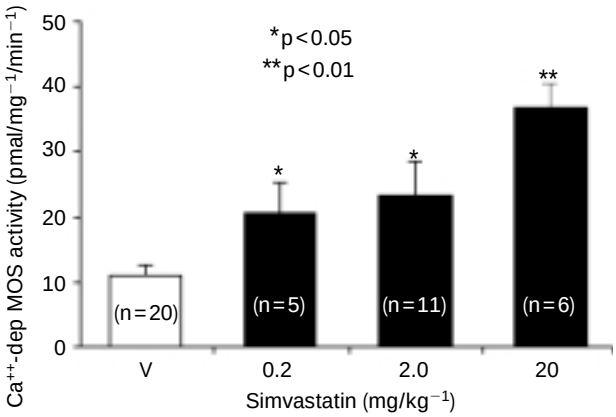


FIG. 2 Calcium-dependent nitric oxide synthase (Ca^{++}-dep NOS) catalytic activity in aortas from mice treated with simvastatin 0.2, 2, or 20 mg/kg for 14 days, compared with vehicle (V) treatment. Reproduced from Ref. No. 5 with permission.

In these animals, after ischemia and reperfusion of the middle cerebral artery territory, stroke size diminished, cerebral blood flow increased, and neurologic function improved as a result of statin pretreatment. Mice deficient in eNOS showed no improvement in cerebral blood flow or neuroprotective statin effect.

In addition to exerting a vasodilator effect, nitric oxide can impede platelet aggregation. It also limits activation of nuclear factor kappa B, a transcription factor involved in expression of genes encoding a number of proinflammatory functions of vascular wall cells and infiltrating leukocytes. Thus, nitric oxide has a direct anti-inflammatory effect.[1]

Decreasing Inflammation

C-reactive protein (CRP) sensitively indicates systemic inflammation. Apparently well individuals at risk for cardiovascular events tend to have levels of CRP in the upper end of the normal range. Treatment with statins may reduce CRP levels in a manner independent of the magnitude of low-density lipoprotein lowering in an individual. In an analysis of 472 patients who remained free of recurrent coronary heart disease (CHD) events at 5 years in the Cholesterol and Recurrent Events (CARE) trial, a secondary prevention study involving a patient population with average cholesterol levels, pravastatin recipients exhibited a median decrease of 17.4% in CRP, compared with a median increase of 4.2% in placebo recipients, during the 5-year trial period.[6]

Analysis of changes in CRP among 5,719 participants who remained event free at 1 year in the primary prevention Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS, which involved a population with average cholesterol and modestly reduced high-density lipoprotein cholesterol levels) showed a 14.8% decrease in CRP in the lovastatin group, compared with no change in the placebo group.[7] A study of the effects of cerivastatin over 8 weeks in 785 patients with primary hypercholesterolemia yielded similar findings.[8] Likewise, in the Pravastatin Inflammation/CRP Evaluation (PRINCE) study, which included a CHD-free cohort (n = 1,702) and a cohort of patients with a history of CHD (n = 1,182),[9] CRP levels fell a median of 14.7% from baseline in 12 weeks and 16.9% from baseline at 24 weeks among participants with no prior history of CHD. In patients with prior CHD, CRP levels were reduced 14.3% from baseline at 12 weeks and 13.1% from baseline at 24 weeks.[9]

Stabilizing the Fibrous Cap

Inflammation, particularly as it affects the stability of the atherosclerotic plaque, appears to link atherosclerosis to coronary events. Indeed, the finding that lipid-lowering treatment generally produces only slight improvements in the fixed stenoses in coronary arteries suggests that the reduced rates of myocardial infarction observed with lipid reduction involve qualitative changes in plaque biology rather than regression

per se. We have hypothesized that lipid lowering acts as an anti-inflammatory intervention to improve plaque stability.

We have proposed the hypothesis that the fibrous cap of the atherosclerotic lesion undergoes dynamic remodeling and exhibits considerable metabolic activity.[1, 10] Interstitial collagen fibrils strengthen the fibrous cap and render it resistant to rupture. The balance among inflammatory mediators controls the level of collagen in the arterial extracellular matrix. Inflammation in the matrix, which may in part reflect effects of hyperlipidemia, results in reduced synthesis of collagen. The proinflammatory cytokine gamma interferon, for example, inhibits interstitial collagen synthesis by smooth muscle cells, the primary source of this extracellular matrix protein in the arterial wall. Other proinflammatory cytokines induce enzymes that can degrade collagen—e.g., matrix metalloproteinases, including collagenases and gelatinases. Inflammation reduces the ability of smooth muscle cells to repair and maintain the collagen component of the fibrous cap as well, since inflammatory factors overexpressed in plaques can trigger apoptosis; sites of fatal thrombosis where plaques have ruptured typically feature few smooth muscle cells. In summary, these inflammatory processes can weaken the ordinarily stable fibrous cap, rendering it prone to disruption and hence thrombosis.

Statin or other lipid-lowering therapy can stabilize the fibrous cap by reducing inflammation. In one experimental study, atheromas were induced in rabbits by balloon injury and atherogenic diet for 4 months, at which time one group (baseline) was sacrificed, while another group consumed a high-cholesterol diet for 16 months and another group consumed a low-cholesterol diet for 8 or 16 months. Measurement of macrophage and collagenase content by quantitative image analysis of standardized sections of immunostained aortas showed that atheromas in the baseline and hyperlipemic groups featured high macrophage content and high levels of collagenase; in contrast, atheromas in the lipid-lowering group showed reduction in both macrophage and collagenase content (Fig. 3).[11] Measurement of the amount of interstitial collagen content by Sirius red staining showed that most of the intact fibrillar collagen in the aortas of hyperlipemic animals resided in the vessel adventitia, with only a filamentous network in the intima. In contrast, animals receiving the low-cholesterol diet had a marked reinforcement of the collagenous structure of the atheroma fibrous cap (Fig. 4). If applicable to humans, these findings suggest that lipid lowering stabilizes vulnerable plaques by reducing expression of the enzymes that degrade the arterial extracellular matrix and may reduce susceptibility of atheromas to disruption and thrombosis by promoting collagen accumulation in the fibrous cap. The recent observations of Crisby *et al.* indeed suggest similar changes in carotid atheroma of patients treated with pravastatin in a nonrandomized series.[12]

Conclusion

Statins may improve outcomes and limit complications of atherosclerosis by a variety of mechanisms, including reducing thrombogenicity, opposing vasospasm, decreasing inflammation, and stabilizing the atherosclerotic lesion fibrous cap. Recent experimental investigations have shown that lipid lowering reduces other markers of endothelial activation, including expression of the leukocyte-receptor vascular cell adhesion molecule-1.[13]

A decrease in inflammatory responses as a result of lipid lowering may underlie many of the beneficial effects of statins in atherosclerotic disease. However, statins may also exert effects independent of systemic lipid lowering, including the increased levels of eNOS and expression of plasminogen activator and decreased expression of PAI-1. Inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase

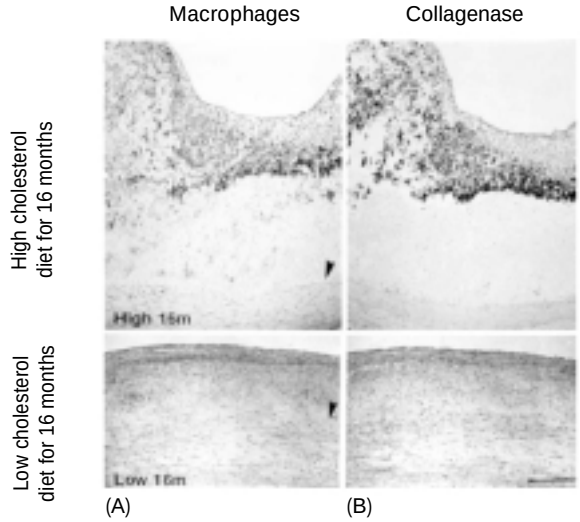


FIG. 3 Macrophage (A) and collagenase (B) content of rabbit atheromas were induced by balloon injury and 4 months of a high-cholesterol diet. After 16 additional months of high-cholesterol diet (top), macrophages continue to exhibit strong expression of collagenase. After a switch to and maintenance of low-cholesterol diet for 16 months (bottom), only scant macrophages and collagenase remain. Arrows indicate the internal elastic lamina. Reproduced from Ref. No. 11 with permission.

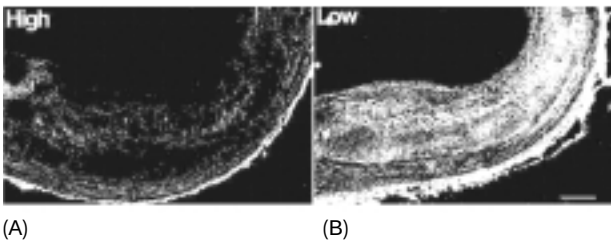


FIG. 4 Interstitial collagen content in the rabbit aortic intima is shown by Sirius red staining. A typical lesion in the high-cholesterol group (A) shows little intimal collagen, whereas a representative lesion in the low-cholesterol group (B) shows an abundance of interstitial collagen in the intima. Reproduced from Ref. No. 11 with permission.

by statins reduces formation of the polyisoprenoids farnesyl pyrophosphate and geranyl pyrophosphate, intermediates in the pathway of cholesterol synthesis. These polyisoprenoids can derivatize proteins and alter their functions. Inhibition by statins of the prenylation of the polyisoprenoids with intracellular signaling molecules including small G proteins may in this manner produce direct effects on cell function independent of lipid lowering. In summary, the well-characterized reduction in cardiovascular risk associated with statin therapy may arise from both direct effects on lipid lowering and lipid-independent effects.

References

1. Libby P: Current concepts of the pathogenesis of the acute coronary syndromes. *Circulation* 2001;104:365–372
2. Mach, F, Schonbeck U, Bonnefoy JY, Pober JS, Libby P: Activation of monocyte/macrophage functions related to acute atheroma complication by ligation of CD40: Induction of collagenase, stromelysin, and tissue factor. *Circulation* 1997;96:396–399
3. Aikawa M, Voglic SJ, Sugiyama S, Rabkin E, Taubman MB, Fallon JT, Libby P: Dietary lipid lowering reduces tissue factor expression in rabbit atheroma. *Circulation* 1999;100:1215–1222
4. Bourcier T, Libby P: HMG CoA reductase inhibitors reduce plasminogen activator inhibitor-1 expression by human vascular smooth muscle and endothelial cells. *Arterioscler Thromb Vasc Biol* 2000; 20:556–562
5. Endres M, Laufs U, Huang Z, Makamura T, Huang P, Moskowitz MA, Liao JK: Stroke protection by 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors mediated by endothelial nitric oxide synthase. *Proc Natl Acad Sci USA* 1998;95:8880–8885
6. Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwald E: Long-term effects of pravastatin on plasma concentration of C-reactive protein. The Cholesterol and Recurrent Events (CARE) Investigators. *Circulation* 1999;100:230–235
7. Ridker PM, Rifai N, Clearfield M, Downs JR, Weis SE, Miles JS, Gotto AM Jr, for the Air Force/Texas Coronary Atherosclerosis Prevention Study Investigators: Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med* 2001;344:1959–1965
8. Ridker PM, Rifai N, Lowenthal SP: Rapid reduction in C-reactive protein with cerivastatin among 785 patients with primary hypercholesterolemia. *Circulation* 2001;103:1191–1193
9. Albert MA, Danielson E, Rifai N, Ridker PM, for the PRINCE Investigators: Effect of statin therapy on C-reactive protein levels: The pravastatin inflammation/CRP evaluation (PRINCE): A randomized trial and cohort study. *J Am Med Assoc* 2001;286:64–70
10. Libby P: Molecular bases of the acute coronary syndromes. *Circulation* 1995;91:2844–2850
11. Aikawa M, Rabkin E, Okada Y, Voglic SJ, ClintonSK, Brickerhoff CE, Sukhova GK, Libby P: Lipid lowering by diet reduces matrix metalloproteinase activity and increases collagen content of rabbit atheroma: A potential mechanism of lesion stabilization. *Circulation* 1998;97:2433–2444
12. Crisby M, Nordin-Fredriksson G, Shah PK, Yano J, Zhu J, Nilsson J: Pravastatin treatment increases collagen content and decreases lipid content, inflammation, metalloproteinases, and cell death in human carotid plaques: Implications for plaque stabilization. *Circulation* 2001;103:926–933
13. Aikawa M, Sugiyama S, Voglic SJ, Rabkin E, Fukumoto Y, Hill CC, Schoen FJ, Witztum JL, Libby P: Lipid lowering reduces oxidative stress and endothelial cell activation in rabbit atheroma. *Circulation* 2002;106:1390–1396

Clin. Cardiol. Vol. 26 (Suppl. I), I-15–I-20 (2003)

Comparing HMG-CoA Reductase Inhibitors

PETER H. JONES, M.D.

Baylor College of Medicine, Houston, Texas, USA

Summary: The statins have proved to be some of the most potent therapies for reducing elevated low-density lipoprotein (LDL) cholesterol and lessening the risk of coronary heart disease (CHD) and related events. Nonetheless, there are still questions about the clinical relevance of individual drug characteristics, such as chemical derivation, solubility properties, and metabolic route, in terms of tolerability or therapeutic benefit. At the same time, no clear explanation has emerged for the significantly steeper reductions in LDL cholesterol levels achieved with atorvastatin versus lovastatin, simvastatin, pravastatin, or fluvastatin, or, more recently, with rosuvastatin versus atorvastatin, although possible mechanisms have been suggested. More studies are needed to characterize the effects of statins on high-density lipoprotein (HDL) in different patient groups. Clearly, though, several statins have yielded significant reductions in CHD risk and have shown to be well tolerated in both primary and secondary prevention trials. The possibility that statins exert pronounced effects beyond lowering blood lipids is opening other avenues of research into the benefits of these drugs.

Key words: coronary heart disease, dyslipidemia, statins

Introduction

A large body of evidence demonstrates that reducing the levels of low-density lipoprotein (LDL) cholesterol lessens the risk of coronary heart disease (CHD) and related events.[1] The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) lower LDL more consistently and dramatically than other lipid-lowering agents, thus exerting a significant impact on CHD risk.[1–6]

While these drugs have similar lipid-lowering effects, they vary in their derivation, pharmacology, and pharmacokinetics. The older statins (lovastatin, pravastatin, and simvastatin) are naturally derived, while the newer ones (atorvastatin, rosuvastatin, and itavastatin) are synthetic. In addition, several statin drugs are metabolized via the cytochrome P-450 (CYP) 3A4 enzyme system, a characteristic with potential clinical importance for drug interactions.[7]

As data from different statin trials continue to accumulate, more distinct features of the class and of the individual drugs within it will emerge. A review of observations to date about statin pharmacology, effects on lipid and nonlipid (pleiotropic) parameters, impact on clinical end points, and tolerability (in mono- and combination therapy) will lay the groundwork for future studies that may demonstrate more striking clinical differences among these drugs.

Pharmacology

Introduced in 1987, lovastatin was the first HMG-CoA reductase inhibitor—a natural product isolated from fungal metabolites. A similar agent, pravastatin, followed in 1991, along with simvastatin, a semisynthetic compound consisting of lovastatin plus an extra methyl group. Fluvastatin, cerivastatin, and atorvastatin are synthetic enantiomers, as is the investigational HMG-CoA reductase inhibitor rosuvastatin.[8,9]

Both lovastatin and simvastatin have a closed lactone ring, which makes them prodrugs; these compounds must be converted in the liver to the open lactone form. All the other statins are open lactone forms. Each of the agents in this class has a characteristic pharmacophore group that interacts with the binding site of HMG-CoA reductase.[10]

The pharmacokinetic and pharmacodynamic characteristics of the various statins are summarized in Table I. Lovastatin, simvastatin, fluvastatin, atorvastatin, and cerivastatin are lipophilic agents, whereas pravastatin and rosuvastatin are hydrophilic, with negative values on a log-dose scale at pH 7.4, compared with >1 for the other drugs.[9] Half-lives are generally in the range of 1 to 3 h, with the exception of atorvastatin (14 h) and rosuvastatin (20 h).[7,11] Lovastatin, simvastatin, and atorvastatin are metabolized by the most common isoform of the

Address for reprints:

Peter H. Jones, M.D.
Associate Professor
Baylor College of Medicine
Alkek Tower, ALKT A656
Houston, TX 77030, USA
e-mail: jones@bcm.tmc.edu

TABLE I Pharmacokinetic/pharmacodynamic comparison of statins

Statin	Lipophilic/ hydrophilic	T½ (h)	Active metabolites	Metabolism
Lovastatin	Lipophilic	2–3	Yes	CYP 3A4
Simvastatin	Lipophilic	2	Yes	CYP 3A4
Pravastatin	Hydrophilic	1.5–2	No	No CYP
Fluvastatin	Lipophilic	1	No	CYP 2C9
Atorvastatin	Lipophilic	14	Yes	CYP 3A4
Rosuvastatin	Hydrophilic	20	Yes	CYP 2C9, CYP 2C19

cytochrome P-450 system, namely CYP 3A4. Fluvastatin and rosuvastatin are primarily metabolized by CYP2C9 and also, in the case of the latter agent, by CYP 2C19. Rosuvastatin does not undergo any appreciable metabolism by cytochrome P-450 3A4; thus, this agent presents less potential for drug–drug interactions than some other statins.[7,12]

Effects on Lipids

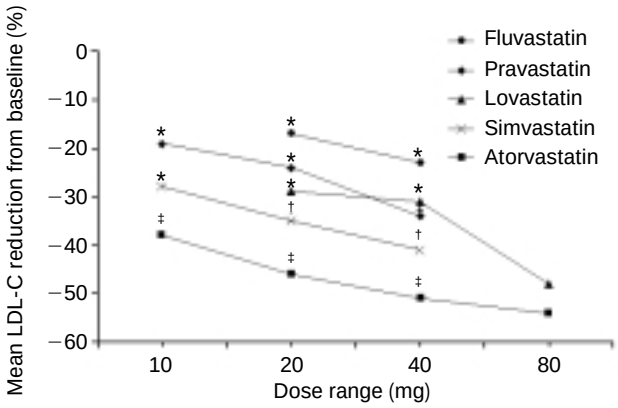
The multicenter, randomized, open-label CURVES study compared the effects of five different statins on LDL cholesterol levels in 534 patients.[13] Dose-dependent reductions in LDL cholesterol were significantly greater with atorvastatin than with milligram-equivalent doses of lovastatin, simvastatin, pravastatin, or fluvastatin (Fig. 1). Over the dose range of 10 to 80 mg, atorvastatin reduced LDL cholesterol by 38 to 54%. Agents with even greater lipid-lowering effects have been under investigation. In a two-phase investigation involving 206 patients with hypercholesterolemia, rosuvastatin produced highly significant, dose-dependent reductions in LDL cholesterol when compared with placebo; atorvastatin was used as a benchmark comparator.[14]

A more recent 12-week, multicenter, randomized, double-blind, placebo-controlled trial found that reductions in LDL were significantly greater with rosuvastatin than with atorvastatin (Fig. 2).[15] This comparison of the two agents in 516 patients with hypercholesterolemia revealed LDL reductions of 40 and 43% with rosuvastatin 5 mg and 10 mg, respectively, as opposed to 35% with atorvastatin 10 mg ($p < 0.01$ vs. rosuvastatin 5 mg, $p < 0.05$ vs. rosuvastatin 10 mg).

Another recent randomized, double-blind trial in 502 patients found significantly greater reductions in LDL cholesterol with rosuvastatin as opposed to pravastatin or simvastatin.[16] At 12 weeks, rosuvastatin 5 and 10 mg had reduced LDL cholesterol by 42 and 49%, respectively, compared with 28% for pravastatin 20 mg ($p < 0.01$ vs. both rosuvastatin doses) and 37% for simvastatin ($p < 0.01$ vs. rosuvastatin 5 mg, $p < 0.001$ vs. rosuvastatin 10 mg).

In the CURVES study, the 40-mg dose of atorvastatin produced a greater reduction in triglyceride levels than did the 40-mg dose of fluvastatin, lovastatin, pravastatin, and simvastatin; other doses did not produce different effects among the statins for triglycerides.[13] Elsewhere, rosuvastatin also has been shown to produce significant reductions in triglyceride levels, albeit not in a dose-related manner.[14]

A large body of data gathered over the past decade has confirmed the significant inverse relationship between high-density lipoprotein (HDL) cholesterol levels and the risk of CHD events,[17,18] but the potential impact of statins on HDL remains only partially understood. In a recent review, researchers suggested several possible mechanisms for this effect.[19] Statins might bring about an increase in the messenger RNA (mRNA) for apolipoprotein A-I (apoA-I) at the promoter site. The elevation in mRNA for apoA-I appears to be reversed by adding mevalonate, suggesting an underlying process related to prenylated proteins or isoprenoids. Alternatively, statins may increase apoA-I expression by inhibiting Rho activation. Reduced Rho stimulates peroxisome proliferator activated receptor-α (PPARα), which in turn is known to increase apoA-I expression, as shown in studies of fibrates. Furthermore,



*Significantly less than atorvastatin 10 mg ($p<0.02$).
†Significantly less than atorvastatin 20 mg ($p<0.01$).
‡Significantly greater than mg-equivalent dose of compatative agents ($p\leq0.01$).

FIG. 1 Reductions in low-density lipoprotein cholesterol (LDL-C) with statins in the CURVES study. Reproduced from Ref. No. 13 with permission.

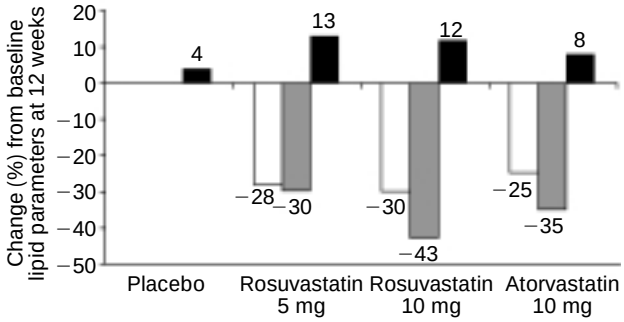


FIG. 2 Reductions in low-density lipoprotein cholesterol (LDL-C) and increases in high-density lipoprotein cholesterol (HDL-C) with rosuvastatin versus atorvastatin. □ = Total cholesteral, ▒ = LDL-C, ■ = HDL-C. Data from Ref. No. 15.

statins may reduce the activity of cholesterol ester transfer protein (CETP) to varying degrees, depending on the agent. Higher doses of atorvastatin may not inhibit CETP activity as strongly as some of the other statins, although data on CETP inhibition are contradictory.[20] The extent to which any or all of these mechanisms contribute to increases in HDL cholesterol levels is far from clear, but all the statins could potentially display such actions.

Increases in HDL cholesterol levels ranged from 3.0 to 9.9% with the statins evaluated in the CURVES study.[13] The amount of the increase did not differ significantly between atorvastatin and the other agents except at a dose of 40 mg, when elevations in HDL cholesterol were significantly greater with simvastatin than with atorvastatin ($p \leq 0.05$). In a recent study of rosuvastatin, HDL cholesterol levels increased by 10.0 to 14.4% over baseline in the same dosage range used in the CURVES study.[14] Levels of HDL cholesterol also increased more with rosuvastatin at a dosage of 5 mg or 10 mg than with atorvastatin 10 mg in a recent 12-week trial. With rosuvastatin 5 mg and 10 mg, HDL levels rose 13% ($p < 0.01$) and 12% ($p < 0.05$) over baseline, respectively, vs. 8% with atorvastatin.[15]

The CURVES investigators are planning to repeat the protocol, using a larger number of patients and including rosuvastatin as one of the treatment arms in the Statin Therapies for Elevated Lipid Levels Compared Across Dose Ranges to Rosuvastatin (STELLAR) study. More than 2,000 patients will be randomized to 6 weeks of treatment with either rosuvastatin, simvastatin, or atorvastatin (each in doses of 10, 20, 40, or 80 mg) or pravastatin (10, 20, or 40 mg). The primary end point will be the percentage reduction in LDL cholesterol levels, secondary end points will include changes in other lipoprotein levels, and safety will be assessed with careful attention to adverse events. In a trial extension, all patients who are not initially randomized to rosuvastatin will receive rosuvastatin 10 mg for at least 12 weeks.

Effects on Clinical End Points

Five major trials[2–6] have confirmed that therapy with lovastatin, simvastatin, or pravastatin has beneficial effects on hard clinical end points in the primary and secondary prevention of CHD events. Pravastatin reduced rates of major coronary events (CHD death or nonfatal myocardial infarction) in high-risk patients with no evidence of CHD by 33%, compared with placebo.[6] Hypercholesterolemic patients with no history of CHD had 37% fewer CHD events (fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death) with lovastatin therapy than with placebo.[2] Among patients with established CHD, pravastatin and simvastatin reduced major coronary events by 23 to 34%.[3–5]

More recently, data from the Heart Protection Study[21] suggested that statin therapy lowers CHD death rates among patients with average or below-average lipid levels who are still at increased risk because of previous myocardial infarction, noncardiac occlusive arterial disease, treated hypertension, or diabetes. Across all these patient groups, the rate of CHD events was 24% lower among patients taking simvastatin 40 mg/day over the 5.5-year study period than among similar patients taking placebo. A benefit was seen regardless of baseline LDL level.

Other studies have suggested beneficial effects of statin therapy on surrogate end points, including markers of atherosclerotic regression or progression as assessed by quantitative coronary angiography[22, 23] or high-resolution ultrasound.[24] As evidence mounts that other surrogate end points correlate with CHD events, it is likely that lipid-lowering therapy will be found to affect them.

For example, statin therapy is showing promise in patients with acute coronary syndrome (ACS). In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, recurrent ischemic events in the first 16 weeks were reduced significantly in patients with ACS treated with atorvastatin 80 mg/day.[25] In a recent study using data from the Swedish Register of Cardiac Intensive Care (RIKS-HIA), early initiation of statin treatment was associated with reduced 1-year mortality in patients with acute myocardial infarction.[26]

Pleiotropic Effects

The Heart Protection Study has added weight to the intriguing theory that the antiatherogenic effects of statin therapy extend beyond lipid lowering—that they are, in fact, pleiotropic. Basic research suggests that the statins may exert such nonlipid effects as modifying endothelial function, mediating inflammatory responses, promoting plaque stability, and inhibiting thrombus formation.[20] Statins stabilize endothelial nitric oxide synthase (eNOS) mRNA and increase the release of nitric oxide from the endothelium.[27] Notably, reduced stability of eNOS is the major factor contributing to endothelial dysfunction in cardiovascular disease states (including CHD, myocardial ischemia, cerebral ischemia, and diabetes). Statins also increase the number of endothelial progenitor cells and promote their function, resulting in angiogenesis through the protein kinase AKT/eNOS pathway.[27] In addition, they arrest the creation of vascular cell adhesion molecules in endothelial cells and limit the formation of CD11b and CD18 on leukocytes.[28, 29] Other work has shown that statins reduce levels of plasminogen activator inhibitor-1 while increasing the production of tissue plasminogen activator in endothelial cells and lowering the expression of tissue factor.[30, 31]

Several studies have examined the effect of statins on inflammation. The Cholesterol and Recurrent Events (CARE) trial involving patients who had suffered acute myocardial infarction found a significant association between levels of high-sensitive C-reactive protein (hs-CRP, a marker of inflammation and predictor of CHD risk) and subsequent risk in a placebo group.[32] The Pravastatin Inflammation/CRP Evaluation, a large-scale, prospective, randomized trial, revealed that pravastatin reduced CRP levels significantly, by 17% at 24 weeks ($p < 0.001$).[33] An analysis of data from 5,742 patients

in the Air Force/Texas Coronary Atherosclerosis Prevention Study recently demonstrated a significant 15% reduction of CRP levels by lovastatin.[34] Another study of hypercholesterolemic patients without CHD showed that rates of coronary events increased significantly with increases in baseline levels of CRP, and that lovastatin significantly reduced CRP levels.[35] In addition, a recent short-term study found that hs-CRP levels were reduced by 15 to 25% when hyperlipidemic patients were treated with simvastatin, pravastatin, or atorvastatin.[36]

The statins also decrease levels of isoprenoid proteins (GGPP and FPP), which are important in cellular signaling, and they may reduce osteoclastic activity, with possible relevance in osteoporosis. Furthermore, the statins may reduce the formation of beta-amyloid deposits, thereby possibly decreasing the risk of dementia. In addition, these agents may reduce levels of reactive oxygen species (i.e., superoxide and hydroxyl radicals), exert anti-inflammatory activities that could reduce the risk of diabetes, and produce antithrombotic effects that could reduce the risk of deep vein thrombosis.[37, 38] More research is needed to clarify whether such effects may translate into additional clinical benefit beyond LDL reduction in patients treated with statins.

Tolerability

More than 25,000 patients received lovastatin, simvastatin, or pravastatin in the six major, large-scale clinical trials involving more than 50,000 patients with hypercholesterolemia.[2–6, 39, 40] No serious morbidity or mortality was observed during these trials, and there were few drug interactions. Subsequent work has also found no appreciable tolerability issues among patients taking atorvastatin or rosuvastatin.[13, 41]

The withdrawal of cerivastatin from the U.S. market in 2001, however, because of reports of serious myopathy and rhabdomyolysis, prompted concerns regarding the statins as a drug class. Investigators first noted a possible increase in the risk of myotoxicity with combined statin-fibrate therapy in a 1990 report of 12 cases of myopathy or rhabdomyolysis among patients taking lovastatin plus gemfibrozil.[42] Since then, reports of 52 deaths from rhabdomyolysis worldwide in patients taking cerivastatin led to its withdrawal.[43] The increased risk of myotoxicity appears to be greater with cerivastatin rather than generally present with all statins; among the 416 U.S. cases of fatal or nonfatal statin-related rhabdomyolysis, 10 times as many were associated with cerivastatin as with other statins.[44]

A 1995 analysis of data from 516 patients yielded evidence that combined statin-fibrate therapy poses no excess risk of adverse effects on skeletal muscle. Only 1% of these patients had significant, drug-related increases in creatine kinase (CK), and only 1% had significant muscle pain requiring drug discontinuation.[45] No cases of rhabdomyolysis were observed. More recently, a review of 36 clinical trials involving a total of 1,674 patients treated with statins plus fibrates found CK levels greater than 10 times the upper limit of normal in only 0.12% of patients and no cases of rhabdomyolysis.[46] Most of the studies in this analysis, however, excluded patients with renal or hepatic impairment, both of which are suspected risk factors for statin-fibrate–associated myopathy. Other risk factors include advanced age, female gender, increased serum creatinine, high-dose statin therapy, use of gemfibrozil rather than another fibrate, hypothyroidism, and concomitant use of CYP3A4-inhibiting medications such as erythromycin and azole antifungal agents.[46, 47]

Although postmarketing reports of adverse events have been very limited compared with the large number of persons taking approved statins, a clinical advisory was recently issued by the American College of Cardiology/American Heart Association/National Heart, Lung, and Blood Institute to provide updated recommendations for the appropriate use of statins, including cautions, contraindications, and monitoring.[48]

The main points made in the statement are:

- There are no clinically important differences in the rate of fatal complications among patients taking atorvastatin, fluvastatin, lovastatin, pravastatin, or simvastatin
- Statin therapy appears to carry a small risk of myopathy. Since most cases occur in patients who are at risk for the condition, if statins are used with appropriate caution, the likelihood of developing clinically important myopathy is substantially reduced
- The combination of a statin plus nicotinic acid seems to carry a lower risk for myopathy than does a statin plus a fibrate
- Myopathy is more likely to occur at higher statin doses; thus, doses should not exceed those required to attain the ATP III goal of therapy
- All persons starting statin therapy should be instructed to report muscle discomfort or weakness or brown urine immediately, which should then prompt a CK measurement.

Early trials suggested a possible increase in cancer risk with statin therapy, but subsequent analyses have proved that concern unfounded. Data from 6,721 cancer-free patients (> 65 years old) who were taking lipid-lowering drugs showed that patients treated with statins had a 28% lower risk of cancer after 2.7 years of follow-up than those treated with bile acid resins.[49] Likewise, the five major statin trials (involving 30,817 patients followed for 5 to 6 years),[2–6] analyzed together, showed no increased risk of all cancers or site-specific cancers with the use of statin therapy over a 5-year period.[50]

Conclusion

Clinical trials to date indicate that the derivation of a statin (i.e., natural or synthetic) has no bearing on clinical pharmacologic effects. More work is required to determine whether the relative hydrophilicity or lipophilicity of a compound may have a bearing on efficacy or tolerability. Metabolism through the CYP system may be important, as there appear to be rele-

vant clinical differences in drug interactions with statins that are not metabolized by this cytochrome system.

The various statins differ somewhat with regard to their LDL cholesterol–lowering effects. Clinical trials show greater decreases in LDL cholesterol with atorvastatin or rosuvastatin than with other agents in this class. Notably, recent data suggest that the LDL cholesterol–lowering ability of rosuvastatin may be even greater than that of atorvastatin. To date, not all statins have been evaluated with regard to their effects on hard clinical end points (e.g., CHD event rates), but the body of evidence accumulated thus far suggests that all agents in this class will eventually prove to have significant benefits. With the exception of cerivastatin, the statins do not appear to differ with regard to overall tolerability or incidence of adverse effects. Pleiotropic effects are most likely a class effect, and future research promises to shed more light on the extent of these effects.

References

1. 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). *J Am Med Assoc* 2001;235:2486–2497
2. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM Jr: Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *J Am Med Assoc* 1998;279:1615–1622
3. Scandinavian Simvastatin Survival Study Group: Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–1389
4. 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
5. Sacks FM, Pfeffer MA, Moyé LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JMO, Wun C, Davis BR, Braunwald E, for the Cholesterol and Recurrent Events Trial Investigators: The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001–1009
6. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ: Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301–1307
7. Knopp RH: Drug treatment of lipid disorders. *N Engl J Med* 1999; 341:498–511
8. Blumenthal RS: Statins: Effective antiatherosclerotic therapy. *Am Heart J* 2000;139:577–583
9. McTaggart F, Buckett L, Davidson R, Holdgate G, McCormick A, Schneck D, Smith G, Warwick M: Preclinical and clinical pharmacology of rosuvastatin, a new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. *Am J Cardiol* 2001;87(suppl):28B–32B
10. Istvan ES, Deisenhofer J: Structural mechanism for statin inhibition of HMG-CoA reductase. *Science* 2001;292:1160–1164
11. Hanefeld M: Clinical rationale for rosuvastatin, a potent new HMG-CoA reductase inhibitor. *Int J Clin Pract* 2001;55:399–405
12. McCormick AD, McKillop D, Bulters CJ, Miles GS, Baba T, Touchi A, Yamaguchi Y: ZD4522: An HMG-CoA reductase inhibitor free of metabolically mediated drug interactions: Metabolic studies in human in vitro systems (abstr 46). *J Clin Pharmacol* 2000;40:1055
13. Jones P, Kafonek S, Laurora I, Hunninghake D: Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). *Am J Cardiol* 1998;81:582–587
14. Olsson AG, Pears J, McKellar J, Mizan J, Raza A: Effect of rosuvastatin on low-density lipoprotein cholesterol in patients with hypercholesterolemia. *Am J Cardiol* 2001;88:504–508
15. Davidson M, Ma P, Stein EA, Gotto AM Jr, Raza A, Chitra R, Hutchinson H: Comparison of effects on low-density lipoprotein cholesterol and high-density lipoprotein cholesterol with rosuvastatin versus atorvastatin in patients with type IIa or IIb hypercholesterolemia. *Am J Cardiol* 2002;89:268–275
16. Paoletti R, Fahmy M, Mahla G, Mizan J, Southworth H: Rosuvastatin demonstrates greater reduction of low-density lipoprotein cholesterol compared with pravastatin and simvastatin in hypercholesterolaemic patients: A randomized, double-blind study. *J Cardiovasc Risk* 2001;8:383–390
17. Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, Jacobs DR Jr, Bangdiwala S, Tyroler HA: High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation* 1989;79:8–15
18. Jacobs DR, Mebane IL, Bangdiwala SI, Criqui MH, Tyroler HA: High-density lipoprotein cholesterol as a predictor of cardiovascular disease mortality in men and women: The follow-up study of the Lipid Research Clinics Prevalence Study. *Am J Epidemiol* 1990; 131:32–47
19. Yamamoto Y, Gaynor RB: Therapeutic potential of inhibition of the NF-κB pathway in the treatment of inflammation and cancer. *J Clin Invest* 2001;107:135–142
20. Rosenson RS, Tangney CC: Antiatherothrombotic properties of statins: Implications for cardiovascular event reduction. *J Am Med Assoc* 1998;279:1643–1650
21. 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. Brown G, Albers JJ, Fisher LD, Schaefer SM, Lin JT, Kaplan C, Zhao XQ, Bisson BD, Fitzpatrick VF, Dodge HT: Regression of coronary artery disease as a result of intensive lipid lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med* 1990;323:1289–1298
23. Effect of simvastatin on coronary atheroma: The Multicentre Anti-Atheroma Study (MAAS). *Lancet* 1994;344:633–638
24. Smilde TJ, van den Berkmortel FW, Wollersheim H, van Langem H, Kastelein JJ, Stalenhoef AF: The effect of cholesterol lowering on carotid and femoral artery wall stiffness and thickness in patients with familial hypercholesterolaemia. *Eur J Clin Invest* 2000;30: 473–480
25. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, Zeiher A, Chaitman BR, Leslie S, Stern T: Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: The MIRACL study: A randomized controlled trial. *J Am Med Assoc* 2001;285:1711–1718
26. Stenestrand U, Wallentin L: Early statin treatment following acute myocardial infarction and 1-year survival. *J Am Med Assoc* 2001;285:430–436
27. Lefer AM, Scalia R, Lefer DJ: Vascular effects of HMG CoA-reductase inhibitors (statins) unrelated to cholesterol lowering: New concepts for cardiovascular disease. *Cardiovasc Res* 2001;49: 281–287
28. Kwak BR, Mach F: Statins inhibit leukocyte recruitment. New evidence for their anti-inflammatory properties. *Arterioscler Thromb Vasc Biol* 2001;21:1712–1719
29. Takemoto M, Liao JK: Pleitropic effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Arterioscler Thromb Vasc Biol* 2001;161:1405–1410
30. Bellosta S, Bernini F, Ferri N, Quarato P, Canavesi M, Arnaboldi L, Fumagalli R, Paoletti R, Corsini A: Direct vascular effects of

HMG-CoA reductase inhibitors. *Atherosclerosis* 1998;137(suppl): S101–S109
31. Miller SJ: Emerging mechanisms for secondary cardioprotective effects of statins. *Cardiovasc Res* 2001;52:5–7
32. Ridker PM, Rifai N, Pfeffer MA, Sacks FM, Moyé LA, Goldman S, Flaker GC, Braunwald E: Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. *Circulation* 1998;98:839–844
33. Albert MA, Danielson E, Rifai N, Ridker PM, for the PRINCE Investigators: Effect of statin therapy on C-reactive protein levels. The Pravastatin Inflammation/CRP Evaluation (PRINCE): A randomized trial and cohort study. *J Am Med Assoc* 2001;286:64–70
34. Ridker PM, Rifai N, Clearfield M, Downs JR, Weis SE, Miles JS, Gotto AM Jr, for the Air Force/Texas Coronary Atherosclerosis Prevention Study Investigators: Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med* 2001;344:1959–1965
35. Ridker PM: High-sensitivity C-reactive protein: Potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. *Circulation* 2001;103:1813–1818
36. Jialal I, Stein D, Balis D, Grundy SM, Adams-Huet B, Devarag S: Effect of hydroxymethyl glutaryl coenzyme A reductase inhibitor therapy on high sensitive C-reactive protein levels. *Circulation* 2001;103:1933–1935
37. Ray JG, Mamdani M, Tsuyuki RT, Anderson DR, Yeo EL, Laupacis A: Use of statins and the subsequent development of deep vein thrombosis. *Arch Intern Med* 2001;161:1405–1410
38. Freeman DJ, Norrie J, Sattar N, Neely RD, Cobbe SM, Ford I, Isles C, Lorimer AR, Macfarlane PW, McKillop JH, Packard CJ, Shepherd J, Gaw A: Pravastatin and the development of diabetes mellitus: Evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. *Circulation* 2001;103:357–362
39. Bradford RH, Shear CL, Chremos AN, Dujovne C, Downton M, Franklin FA, Gould AL, Heeney M, Higgins J, Hurley DP, Langendorfer A, Nash DT, Pool JL, Schnaper H: Expanded clinical evaluation of lovastatin (EXCEL) study results: I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8,245 patients with moderate hypercholesterolemia. *Ann Intern Med* 1991;151:43–49
40. Collins R, Peto R, Armitage J: The MRC/BHF Heart Protection Study: Preliminary results. *Int J Clin Pract* 2002;56(1):53–56
41. Shepherd J, Hunninghake D, Harris S, Hutchinson H, Pears J: A review of the safety profile of rosuvastatin in an international phase II/III clinical trial programme. *Int J Clin Pract* 2002;124(suppl):15
42. Pierce LR, Wysowski DK, Gross TP: Myopathy and rhabdomyolysis associated with lovastatin-gemfibrozil combination therapy. *J Am Med Assoc* 1990;264:71–75
43. Wooltorton E: Bayer pulls cerivastatin (Baycol) from market. *Can Med Assoc J* 2001;165:632
44. Furberg CD, Pitt B: Withdrawal of cerivastatin from the world market. *Curr Control Trials Cardiovasc Med* 2001;2:205–207
45. Shepherd J: Fibrates and statins in the treatment of hyperlipidaemia: An appraisal of their efficacy and safety. *Eur Heart J* 1995;16:5-13
46. Shek A, Ferrill MJ: Statin-fibrate combination therapy. *Ann Pharmacother* 2001;35:908–917
47. Milionis HJ, Tsapoga TG, Elisaf MS: Another report of acute rhabdomyolysis following cerivastatin monotherapy. *Arch Intern Med* 2001;161:2629–2930
48. Pasternak RC, Smith SC Jr, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C: ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567–572
49. Blais L, Desgagne A, LeLorier J: 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and the risk of cancer: A nested case-control study. *Arch Intern Med* 2000;160:2363–2368
50. Bjerre LM , LeLorier J: Do statins cause cancer? A meta-analysis of large randomized clinical trials. *Am J Med* 2001;110:716–723

Clin. Cardiol. Vol. 26 (Suppl. I), I-21–I-28 (2003)

Treating Hypercholesterolemia: Looking Forward

ANTONIO M. GOTTO, JR., M.D., D.PHIL.

The Joan and Sanford I. Weill Medical College of Cornell University, New York, New York, USA

Summary: Despite important advances in the management of hypercholesterolemia in recent decades, many patients with lipid disorders remain unidentified or undertreated and so continue to have unfavorable levels of low-density lipoprotein (LDL) cholesterol and an increased risk for coronary events. The statins—which inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis—have proved to be the most powerful pharmacologic agents for lowering serum lipids, and newer statins offer even greater efficacy than the agents introduced 10 to 15 years ago. Studies have shown that rosuvastatin, in late-stage development, is a very potent agent for the treatment of primary hypercholesterolemia, and that relatively low doses decrease LDL cholesterol levels to a greater extent than do similar doses of pravastatin, simvastatin, or atorvastatin as evaluated in separate clinical trials. Pitavastatin, in phase II trials, also has promise as a more potent drug than currently available statins. Because neither of these drugs has been approved for use in the United States, clinical trial results should be considered preliminary. In the future, agents that combine the actions of statins and nicotinic acid may achieve still greater LDL cholesterol reductions. Drugs that lower lipids via mechanisms other than inhibition of HMG-CoA reductase also offer promise. The newest addition to the roster of lipid-regulating agents is ezetimibe, a cholesterol absorption inhibitor that has been approved for use either alone or in combination with a statin. Agents in development include bile acid transport inhibitors and inhibitors of acyl CoA:cholesterol acyltransferase. More research will be needed to determine the full clinical potential of such approaches to the management of hypercholesterolemia.

Corresponding author:

Antonio M. Gotto, Jr., M.D., D.Phil.
The Joan and Sanford I. Weill Medical College of Cornell University
Olin Hall, Room 205
445 East 69th Street
New York, NY 10021, USA
e-mail: pat2004@med.cornell.edu

Key words: hypercholesterolemia, lipoprotein, low-density lipoprotein cholesterol, coronary disease, hydroxymethylglutaryl-CoA reductase inhibitors, investigational drugs

Introduction

In the past 20 years, public and professional education initiatives such as the National Cholesterol Education Program (NCEP) have increased awareness of hypercholesterolemia as a risk factor for cardiovascular disease. At the same time, treatment advances have placed the goal of significant serum-cholesterol reduction within reach for a large proportion of the at-risk population. Nevertheless, clinical practice lags behind therapeutic progress: improvement in the identification, treatment, and follow-up of individuals with hypercholesterolemia is needed if the nation is to realize the full potential of newer, more potent lipid-lowering agents, particularly as drugs that act through novel mechanisms move through the clinical development process.

Hypercholesterolemia: Defining the Challenge

Guidelines for detecting, evaluating, and treating high cholesterol, from both the NCEP Adult Treatment Panel II (ATP II) and Adult Treatment Panel III (ATP III), call for periodic cholesterol screening.[1, 2] Elevated levels of low-density lipoprotein (LDL) cholesterol are the primary indication for initiating therapy aimed at reducing the risk for coronary heart disease (CHD). Evidence suggests, however, that many patients who are clearly at risk for CHD are not undergoing periodic cholesterol screening. An observational study examining 10-year data on the measurement of cholesterol levels among patients hospitalized for acute myocardial infarction (MI) in the Worcester, Massachusetts, area found a marked increase in rates of cholesterol measurement between 1986 (< 60% screened) and 1991 (approximately 90% screened).[3] Thereafter, however, the trend was reversed, with serum cholesterol measurements reported for less than 25% of hospitalized patients with MI, and complete lipid profiles (LDL and high-density lipoprotein [HDL] cholesterol and triglycerides) reported for only 15%, in 1997 (Fig. 1). A multivariate analysis showed

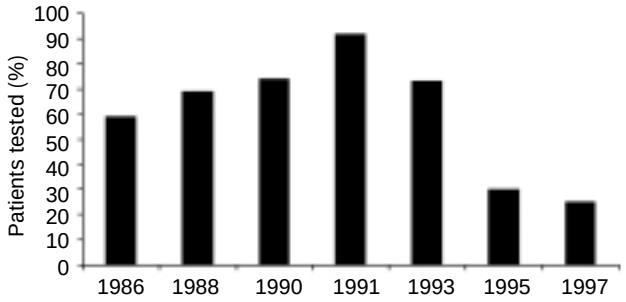


FIG. 1 Annual percentage of patients hospitalized with myocardial infarction and undergoing total cholesterol screening, 1986–1997, in the Worcester, Mass., Heart Attack Study. Reprinted from Ref. No. 3 with permission.

that men and patients with an initial Q-wave MI were more likely to have their cholesterol levels measured during the index hospitalization. The likelihood of cholesterol screening declined with older age (1986–1988) and was significantly reduced in patients with a history of diabetes or hypertension.

In the same observational study, 0.4% of post-MI patients received prescriptions for lipid-lowering drugs in 1986. The rate remained relatively low until 1997, when it rose to 10.7%. Data from 1997 showed that patients who had their cholesterol levels measured were four times more likely to receive prescriptions for lipid-lowering therapy than patients whose lipid levels were not checked. Nonetheless, only 36.6% of patients found to have total cholesterol levels ≥ 6.2 mmol/l (≥ 240 mg/dl) received lipid-lowering therapy in 1997.

Studies examining physician practice and prescribing patterns for patients with varying degrees of risk document the undertreatment of hyperlipidemia and the need to improve physician adherence to evaluation and treatment guidelines in community-based and hospital settings. For example, in the Merck-funded Quality Assurance Program, a retrospective chart audit of 48,586 adult outpatients with coronary artery disease (CAD), found that only 44% had LDL cholesterol testing within 1 year of their last visit, only 39% were taking lipid-lowering medications, and only 25% were able to attain an LDL cholesterol level of ≤ 2.6 mmol/l (≤ 100 mg/dl), the goal for high-risk patients as established by NCEP ATP II[4] (the goal established by NCEP ATP III is < 2.6 mmol/l [< 100 mg/dl]).[2] The chart audit also revealed that patients between the ages of 55 and 64 were more likely to receive a prescription for lipid-lowering therapy than patients > 65, and that women < 65 years of age were less likely to receive a prescription than men < 65 years.

The Lipid Treatment Assessment Project (L-TAP), which studied 4,888 adult patients with dyslipidemia who had been receiving the same lipid-lowering therapy for at least 3 months, found that 38% of patients achieved ATP II target levels for LDL cholesterol.[5] However, the study also found that achievement of goal was higher in the low-risk patients and lower in the high-risk patients: 68% in patients at low risk (fewer than two major risk factors for CHD and no evidence of CHD), 37% in patients at high risk (two or more major risk factors but no evidence of CHD), and 18% in patients with CHD.

Practice and prescribing data from the National Registry of Myocardial Infarction 3 have shown that only 31.7% of 138,001 patients discharged from the hospital after an acute MI received a prescription for lipid-lowering medication as part of the discharge regimen.[6] In this large prospective observational study, patients between 65 and 74 years of age were less likely to receive a prescription for lipid-lowering therapy than those younger than 55. Patients with a history of hypertension and those undergoing coronary artery bypass graft surgery were also less likely to receive a prescription.

Further evidence of the inadequate control of hypercholesterolemia even in high-risk patients comes from a recent analysis of data from the Third National Health and Nutrition Examination Survey. Of 417 survivors of MI, stroke, or both, whose LDL cholesterol levels were measured, fewer than half met the target levels established by the NCEP ATP III (Fig. 2).[2,7] A total of 57% of these patients had levels > 3.36 mmol/l (> 130 mg/dl).

Meeting the Challenge

Current Efficacy of Statins

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, are the most potent pharmacologic agents available for reducing elevated levels of LDL cholesterol.[2] By inhibiting the activity of HMG-CoA reductase, the statins limit cholesterol biosynthesis in the liver and extrahepatic cells. This also leads to upregulation of LDL receptors, which promotes the clearance of LDL cholesterol from plasma. The net result is a substantial reduction in LDL cholesterol levels.

Six major studies of simvastatin, lovastatin, and pravastatin have confirmed that statin therapy significantly reduces CHD-

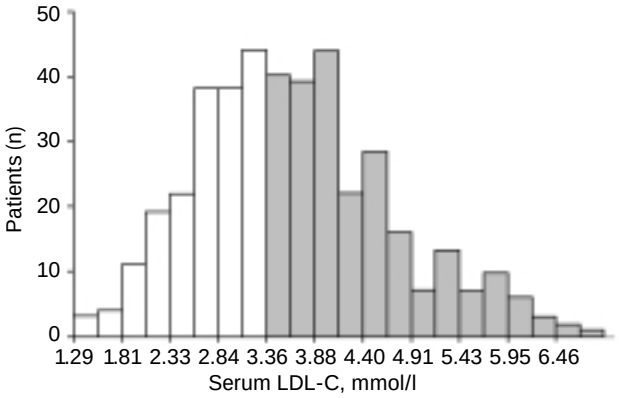


FIG. 2 Low-density lipoprotein cholesterol (LDL-C) levels in 417 survivors of myocardial infarction, stroke, or both in the Third National Health and Nutrition Examination Survey. The white and gray bars signify levels below and above the cut-point that defines adequate control. Reprinted from Ref. No. 7 with permission.

associated risk in both primary and secondary prevention.[8–13] These studies have shown that statins can lower LDL levels by 20 to 36%, decrease the incidence of nonfatal MI or CHD death by 27 to 34%, and reduce the need for interventional coronary procedures (angioplasty or coronary artery bypass graft surgery) by 20 to 37%. The risk for stroke may also be lowered by up to 31%. The most recent of these six trials, the Heart Protection Study (HPS), examined the effect of cholesterol-lowering therapy with simvastatin in the largest number (n = 20,536) and the widest range of high-risk individuals studied to date. The trial, which focused on groups for whom sufficient data had been lacking, included patients with diabetes or noncoronary occlusive arterial disease, but without CAD; women; the elderly; and those with below-average LDL cholesterol concentrations for Western societies. Results indicate that lowering LDL cholesterol by 39 mg/dl produced a proportional risk reduction of about 25% in patients with baseline levels < 116 mg/dl and in those with higher baseline levels. This supports the hypothesis that current guidelines may inadvertently result in undertreatment of high-risk patients who present with LDL cholesterol levels that are below or close to recommended targets.[13]

The HPS also found a significant decrease in the primary end point of all-cause mortality, based chiefly on a highly significant 18% reduction in the coronary death rate (also a primary end point) and a marginally significant reduction of 16% in other vascular deaths. There were highly significant reductions in the secondary end points of nonfatal MI or coronary death (−27%), nonfatal or fatal stroke (−25%), and coronary or noncoronary revascularization (−24%), with an overall 24% reduction in the occurrence of any major vascular event. Risk reductions were similar in each major subcategory of participant studied. Overall, results of the HPS demonstrate the importance of treating high risk, not just high cholesterol. The recently published Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), which enrolled 5,804 men and women aged 70 to 82 years, found that pravastatin 40 mg/d significantly reduced the risk for a composite primary end point event (CHD death, nonfatal MI, or fatal/nonfatal stroke) by 15% and for CHD death or nonfatal MI by 19%, compared with placebo. However, there was no significant treatment effect on the incidence of stroke. Because only 266 patients suffered a stroke, one possible explanation for this outcome may be a lack of statistical power.[14, 15]

The statins also produce moderate increases (5 to 15%) in HDL cholesterol.[2] Although the mechanisms responsible for this effect remain uncertain, they may involve apolipoprotein (apo)A-I, the major apolipoprotein of HDL. Researchers have suggested that statins may induce apoA-I messenger RNA by activating peroxisome proliferator-activated receptor-α, a nuclear transcription factor that binds to a peroxisome proliferator response element mapped to the apoA-I promoter A site.[16] Because the addition of mevalonate can reverse this mechanism, it is thought that the effects of statins on apoA-I gene expression are a downstream effect of HMG-CoA reductase inhibition.[16]

Safety of Statins

The major safety concerns with statins have involved skeletal muscle function and liver toxicity. However, large-scale analyses attest to the highly favorable safety profiles of these drugs. In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) of 6,605 participants randomized to lovastatin or placebo, serious drug-related adverse events and treatment discontinuations were similar for both treatment groups.[8] Patients receiving lovastatin and placebo showed no significant differences in the incidence of creatine kinase elevations (> 10 times ULN), rhabdomyolysis, or treatment discontinuation because of myalgia. There were no cases of myopathy (i.e., muscle symptoms plus creatine kinase > 10 times ULN). Although any increase in alanine aminotransferase levels occurred significantly more often with lovastatin than with placebo (3.3 vs. 2.1%; p = 0.003), the incidence of consecutive liver enzyme elevations > 3 times ULN was rare and similar for both treatment groups. Mortality and incidence of fatal and nonfatal cancer were similar with lovastatin and placebo.

In the HPS, there was no significant excess in the number of simvastatin-treated patients with elevated alanine aminotransferase concentrations (> 4 times ULN) compared with those receiving placebo, and no significant difference between the groups in the number of patients who discontinued treatment because of elevated liver enzymes (48 [0.5%] in the simvastatin group vs. 35 [0.3%] in the placebo group).[13] In addition, there was no significant difference between the treatment groups with regard to reports of unexplained muscle pain or weakness (32.9% among those receiving simvastatin, 33.2% among those receiving placebo on at least one occasion) and no significant difference in the number of patients who discontinued treatment because of muscle symptoms (49 in the simvastatin group vs. 50 in the placebo group). Rhabdomyolysis (creatine kinase > 40 times ULN) developed in five patients in the simvastatin group and three in the placebo group, but none died.

The Prospective Pravastatin Pooling (PPP) Project, which analyzed data from three large-scale trials involving > 19,000 patients and > 112,000 patient-years, likewise found no significant differences in the occurrence of side effects with pravastatin therapy versus placebo.[17, 18] Included in the PPP Project were one primary-prevention trial (West of Scotland Coronary Prevention Study) and two secondary-prevention trials (Cholesterol and Recurrent Events, Long-Term Intervention with Pravastatin in Ischemic Disease). In this combined analysis, the pravastatin and placebo groups did not differ in the proportion of noncardiovascular deaths and in the number of noncardiovascular serious adverse events, including musculoskeletal and hepatobiliary events, over an average of 5 to 6 years. The reduction in total mortality with pravastatin occurred largely because of the significant decrease in cardiovascular events. Similarly, pooled data from 44 studies involving 4,271 patients have shown that atorvastatin was safe and well tolerated, with less than 2% of statin patients withdrawing from the studies because of drug-attributable adverse

events. In addition, only 0.7% of patients had confirmed liver transaminase elevations > 3 times ULN, and no patients had proven drug-induced myopathy.[19]

Recently, four patients enrolled in a clinical trial were able to identify blinded statin therapy based on reproducible muscle symptoms.[20] Despite normal creatine kinase levels, the patients were found to have biopsy-confirmed myopathy. Pathologists reading the biopsies were not blinded to the patients' treatment status. Three of the subjects also had 3-methylglutaconic aciduria. These data suggest that creatine kinase levels may not be an adequate test for statin-associated myopathy. Therefore, physicians should closely monitor patients reporting muscle pain, decreased exercise tolerance, weakness, or other symptoms compatible with myopathy and determine whether the symptoms resolve when therapy is discontinued. In PROSPER, the incidence of skeletal muscle and hepatic adverse events was similar with pravastatin and placebo, with no reported cases of rhabdomyolysis. Although the rate of new cancers was 25% higher in the pravastatin group, the authors interpret this in the context of meta-analyses of prior statin trials, which showed no increased risk for cancer with long-term statin use. Moreover, the HPS, which enrolled a large number of elderly subjects, found no excess incidence of cancer with statin treatment. The investigators attribute the PROSPER result to chance, perhaps driven in part by the enrollment of individuals with occult cancers .[14, 15, 21]

Because some epidemiologic studies have found an inverse association between serum cholesterol levels and hemorrhagic stroke, there has been concern that reducing cholesterol concentrations with drug therapy may increase the risk for intracranial hemorrhage.[22, 23] However, neither the PPP Project nor the HPS found that pravastatin had any effect on the incidence of hemorrhagic stroke.[13, 24]

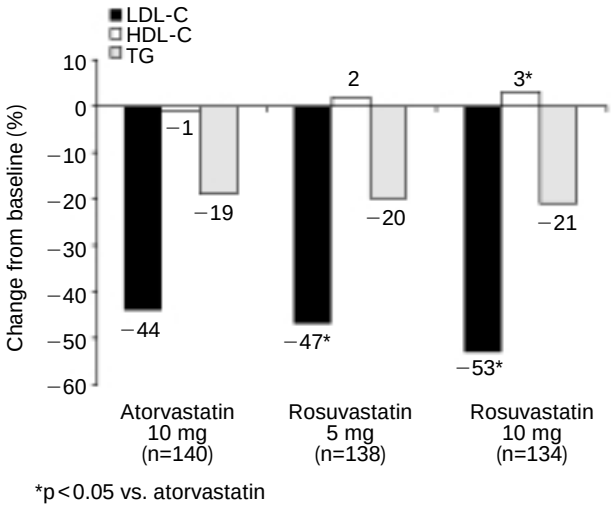


FIG. 3 Changes from baseline in lipid fractions after 52 weeks of therapy with rosuvastatin versus atorvastatin. Reprinted from Ref. No. 28 with permission.

Statins in Development

Rosuvastatin and pitavastatin are two HMG-CoA reductase inhibitors now in development. Rosuvastatin has been submitted to the Food and Drug Administration, but it is not approved at this time.

Six double-blind studies of 6 to 52 weeks' duration have shown that rosuvastatin at relatively low doses is a very potent agent for the treatment of primary hypercholesterolemia. Four of the studies, each one involving approximately 400 to 500 subjects, compared rosuvastatin with atorvastatin, simvastatin, or pravastatin. In the six studies, rosuvastatin at doses of 5 mg and 10 mg reduced LDL cholesterol levels by 39 to 53%, with one of the studies reporting a reduction of 47% with 5 mg at 52 weeks (Fig. 3). All but one of the reductions, an outcome achieved with rosuvastatin 5 mg, were statistically significant versus either placebo or the comparator drug.[25–29] Based on the results of separate clinical trials, atorvastatin reduces LDL cholesterol levels by 39 to 60%, simvastatin produces reductions of 26 to 47%, and pravastatin reduces LDL cholesterol by 22 to 37%, when administered at approved doses ranging from low (5 mg or 10 mg) to high (80 mg).[30–32] In two of the comparative studies cited above, the proportion of rosuvastatin patients who achieved ATP II goals for LDL cholesterol ranged from 71 to 87%, compared with 53 to 73% of patients taking pravastatin, simvastatin, or atorvastatin. Post hoc analyses following release of the ATP III guidelines show that target levels were reached by 64 to 84% of patients treated with rosuvastatin, compared with 48 to 72% in the pravastatin, simvastatin, and atorvastatin groups.[25, 26] In the other two comparative studies, ATP II goals were achieved by 62 to 97% of rosuvastatin-treated patients with CHD, peripheral vascular disease, or diabetes versus 6 to 61% of patients taking pravastatin, simvastatin, or atorvastatin.[27, 28]

Because rosuvastatin has not been approved, the starting dose is unknown. Therefore, the results of studies at different doses must be considered very preliminary.

Pitavastatin (NK-104), an investigational agent now in phase II trials, has been evaluated for periods of 8 to 104 weeks in two small studies conducted in patients with heterozygous familial hypercholesterolemia (HeFH). Results indicate that doses of 2 mg to 4 mg significantly reduced LDL cholesterol levels by 40 to 48% from baseline.[33, 34] In a 12-week double-blind dose-finding study, pitavastatin 1 mg to 4 mg produced significant LDL cholesterol reductions of 34 to 47% in 273 patients with hyperlipidemia.[35] A comparative study of the same duration in 240 subjects with primary hypercholesterolemia found that pitavastatin 2 mg decreased LDL cholesterol levels by 38%, which was significantly greater than the reduction with pravastatin, the comparator drug.[36] As with rosuvastatin, the results of these studies should be considered preliminary, because pitavastatin is not approved and the starting dose is unknown.

Future statin-based agents may employ a dual mechanism to regulate serum cholesterol levels. Recent structural analyses indicate that statins leave the nicotinamide-binding site of HMG-CoA reductase unoccupied.[37] Conceivably, therefore,

the covalent attachment of a nicotinamide-like moiety to a statin might result in even greater potency.

On the Horizon: New Approaches to Lipid Lowering

Lipid metabolism involves many complex processes that may be potential targets for pharmacologic intervention aimed at regulating various dyslipidemias. At present, several novel agents for the reduction of LDL cholesterol are being investigated (Table I). With all investigational agents, the results of clinical trials must be considered preliminary, because the starting doses are unknown.

Recently, ezetimibe became the first agent in a new class of cholesterol absorption inhibitors to receive approval in the United States. As an adjunct to diet, ezetimibe was approved for use either alone or in combination with a statin to reduce total cholesterol, LDL cholesterol, and apoB in patients with primary hypercholesterolemia. Other indications include the lowering of total and LDL cholesterol levels in homozygous familial hypercholesterolemia (HoFH) and the treatment of homozygous sitosterolemia. For all indications, the recommended dose is 10 mg/day.[38]

Ezetimibe selectively inhibits the absorption of dietary and biliary cholesterol at the brush border of the intestine.[39, 40] Both ezetimibe and its pharmacologically active glucuronide conjugate undergo enterohepatic recycling, which repeatedly delivers drug back to the intestine. No significant effect on major drug-metabolizing enzymes has been identified. Therefore, the potential for interaction with substrates of cytochrome P-450 enzymes is low.[39]

Two phase III studies published as abstracts indicate that combination therapy with ezetimibe and a statin improves cholesterol lowering, with a safety profile similar to that of statin therapy alone. In 628 patients with primary hypercholesterolemia, a 12-week study compared ezetimibe 10 mg; atorvastatin 10, 20, 40, or 80 mg either alone or with ezetimibe 10 mg; and placebo. For the primary endpoint, ezetimibe plus atorvastatin (pooled doses) significantly reduced LDL cholesterol by 54.5% from baseline, compared with −42.4% for atorvastatin alone (pooled doses).[41] Ezetimibe alone reduced LDL cholesterol levels by 18.4%. A similarly designed study (n = 668) found that ezetimibe plus simvastatin (pooled doses) produced a 49.9% decrease in LDL cholesterol, which exceeded the reductions with simvastatin alone (−36.1%, pooled doses) ($p < 0.01$). Ezetimibe 10 mg decreased LDL cholesterol levels by 18.1%.[42]

In 50 patients with HoFH, ezetimibe 10 mg plus a statin (atorvastatin or simvastatin) 40 or 80 mg reduced LDL cholesterol levels by 20.7% from baseline after 12 weeks of treatment following a lead-in period with open-label statin therapy (40 mg), versus a reduction of 6.7% with statin 80 mg alone. Ezetimibe plus statin 80 mg decreased LDL cholesterol by 27.5% from baseline following open-label statin therapy, compared with −7.0% in patients randomized to statin 80 mg alone. Figure 4 depicts mean percentage reductions in LDL cholesterol over time in the ezetimibe plus statin 80 patients. All between-group treatment effects were statistically significant, with no clinically meaningful differences in adverse effects.[40]

In a small (n = 32) randomized evaluator-blind study, published as a poster abstract, ezetimibe 10 mg administered with fenofibrate 200 mg was found to reduce levels of LDL cholesterol by 36.3% from baseline, compared with −22.3, −13.5, and −10.1% for ezetimibe, fenofibrate, and placebo, respectively ($p \leq 0.03$ for either drug alone or placebo).[43] Ezetimibe plus fenofibrate also reduced levels of LDL-III (small dense LDL) by 37%, a significantly greater decrease ($p \leq 0.05$) than the results seen either with fenofibrate (+8%), ezetimibe (−8%), or placebo (+6%).

Another class of agents, the bile acid transport inhibitors, specifically inhibits the intestinal epithelial uptake of bile acids, which may affect cholesterol metabolism. These agents

TABLE I Agents in development for reducing low-density lipoprotein cholesterol

Mechanism of action/agent	Developmental phase	Results to date
Bile acid transport inhibition		
S-8921	Phase I	↓ Serum cholesterol and ↓ appearance of severe stenosis (preclinical)[45, 46]
ACAT inhibition		
Avasimibe	Phase III	↓ Triglycerides, ↓ VLDL-C, ↓ cholesterol and ↓ atherosclerotic lesion progression[48, 49]
TS-962	Preclinical	Possible suppression of arterial foam cell formation in early atherosclerosis[50]
F-12511	Phase I	Used with atorvastatin, ↓ cholesterol and ↓ apoB-100 greater than with each agent alone; potential plaque-stabilizing effects[51]
HMG-CoA reductase inhibition		
Rosuvastatin	Phase III	↓ LDL-C 34–65%[29]
Pitavastatin	Phase II	↓ LDL-C 38–49%[34, 35]

Abbreviations: ACAT = acyl CoA:cholesterol acyltransferase; apo = apolipoprotein; HMG-CoA = 3-hydroxy-3-methylgutaryl coenzyme A; LDL-C = low-density lipoprotein cholesterol; VLDL-C = very-low-density lipoprotein cholesterol.

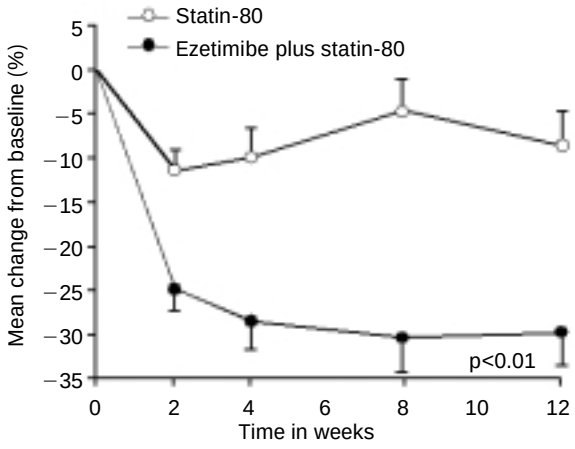


Fig. 4 Mean percentage reduction in low-density lipoprotein cholesterol over time for 50 patients with homozygous familial hypercholesterolemia receiving ezetimibe 10 mg/day plus statin (atorvastatin or simvastatin) 80 mg/day versus statin 80 mg/day alone. Reprinted from Ref. No. 40 with permission.

are likely to be more effective in lowering cholesterol levels than older bile acid–absorbing resins, which work through competitive, rather than specific, inhibition.[44] S-8921, a bile acid transport inhibitor that entered phase I clinical trials in 2000, has been shown in preclinical studies to reduce serum cholesterol levels via mechanisms that may involve increased fecal excretion of bile acids and increased hepatic LDL receptor expression.[45,46] Animal data also indicate a decrease in the appearance of severe stenosis with S-8921.[46] Like cholesterol absorption inhibitors such as ezetimibe, the bile acid transport inhibitors could potentially be used with statin therapy to improve cholesterol lowering.[44]

Three more experimental agents are members of a class known as acyl CoA:cholesterol acyltransferase (ACAT) inhibitors.[44] ACAT is an enzyme that esterifies cholesterol in the arterial wall and appears to be largely responsible for the generation of monocyte-macrophage foam cells in the presence of excess cholesterol. Inhibition of arterial wall ACAT may limit macrophage accumulation and reduce the expression of matrix metalloproteinases, the matrix-degrading enzymes that contribute to plaque rupture.[47] One ACAT inhibitor, avasimibe, has been found to reduce intracellular cholesteryl ester levels and to decrease atherosclerotic lesion area in rabbits.[47] Avasimibe is now in phase III clinical trials.

In an 8-week double-blind placebo-controlled trial (n = 130), avasimibe at doses of 50, 125, 250, and 500 mg/day significantly decreased triglyceride and very-low-density lipoprotein (VLDL) cholesterol levels in patients with combined hyperlipidemia and low levels of HDL cholesterol. The reductions in triglycerides and VLDL cholesterol ranged from 16 to 23% and from 20 to 30%, respectively; however, these results appear to be independent of dose, which suggests that hepatic ACAT may be maximally inhibited with 50 mg avasimibe. Alternatively, ACAT inhibition may increase with higher doses of the drug, but further decreases in lipid levels may be blunted by a compensatory response. There were no statistically significant changes from baseline in total cholesterol, LDL cholesterol, or HDL cholesterol. The incidence of adverse events was similar with avasimibe and placebo (11 vs. 8%), with no clinically significant changes in laboratory values among patients receiving avasimibe.[48]

Although clinical trials have consistently shown that statins can decrease the incidence of coronary events by up to one third, there is a need for pharmacologic interventions able to provide additional cardiovascular protection in patients with coronary atherosclerosis. By inhibiting ACAT in the arterial wall, avasimibe may slow the development of atherosclerosis by several possible mechanisms.[49] The Avasimibe and Progression of Coronary Lesions Assessed by Intravascular UltraSound (A-PLUS) trial, now in progress, is designed to test the hypothesis that avasimibe 50, 250, or 750 mg will inhibit the progression of atherosclerosis when administered with lipid-lowering therapy as needed to reach a target LDL cholesterol level ≤ 125 mg/dl.[49] Participants in this 2-year, 28-center study must have at least one lesion with stenosis of 20 to 50% diameter in a coronary artery of ≥ 2.5 mm. The primary end point is the change in plaque volume in a 30-mm segment of the coronary artery assessed by three-dimensional intravascular ultrasound.

Another ACAT inhibitor, TS-962, was shown to suppress the formation of arterial foam cells in hamsters fed a high-fat diet.[50] A third compound, F-12511, has potential lipid-lowering effects; F-12511 and atorvastatin appear to have synergistic hypocholesterolemic effects in rabbits.[51]

Conclusion

Despite clinical evidence that the statins significantly reduce LDL cholesterol and CHD-related risk, hyperlipidemia is still undertreated. The problem of undertreatment has two components: insufficient adherence to current guidelines and the inadequate response of some patients to currently available agents. The former issue requires the development of new compliance strategies for patients and physicians. Regarding the latter, although statins—which inhibit HMG-CoA reductase—are highly effective in reducing cardiovascular risk by up to one third, interventions are needed to prevent the remaining two thirds of events that still occur. Advances in statin therapy and the development of new agents aimed at modifying other mechanisms involved in lipid metabolism may help close the treatment gap and extend CHD risk reduction to a larger segment of the population.

References

1. Summary of the second report of the National Cholesterol Education Program (NECP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *J Am Med Assoc* 1993;269:3015–3023
2. 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). *J Am Med Assoc* 2001;285:2486–2457

3. Yarzebski J, Spencer F, Goldberg RJ, Lessard D, Gore JM: Temporal trends (1986–1997) in cholesterol level assessment and management practices in patients with acute myocardial infarction. A population-based perspective. *Arch Intern Med* 2001;161: 1521–1528
4. Sueta CA, Chowdhury M, Boccuzzi SJ, Smith SC Jr, Alexander CM, Londhe A, Lulla A, Simpson RJ Jr: Analysis of the degree of undertreatment of hyperlipidemia and congestive heart failure secondary to coronary artery disease. *Am J Cardiol* 1999;83: 1303–1307
5. 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
6. Fonarow GC, French WJ, Parsons LS, Sun H, Malmgren JA: Use of lipid-lowering medications at discharge in patients with acute myocardial infarction: Data from the National Registry of Myocardial Infarction 3. *Circulation* 2001;103:38–44
7. Qureshi AI, Suri FK, Guterman LR, Hopkins LN: Ineffective secondary prevention in survivors of cardiovascular events in the US population: Report from the Third National Health and Nutrition Examination Survey. *Arch Intern Med* 2001;161:1621–1628
8. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM Jr: Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/ TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *J Am Med Assoc* 1998;279:1615–1622
9. Scandinavian Simvastatin Survival Study Group: Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–1389
10. 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
11. Sacks FM, Pfeffer MA, Moyé LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JMO, Wun CC, Davis BR, Braunwald E: 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
12. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ: 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
13. 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
14. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG: Pravastatin in elderly individuals at risk of vascular disease (PROSPER): A randomized controlled trial. *Lancet* 2002;360:1623–1630
15. Collins R, Armitage J: High-risk elderly patients PROSPER from cholesterol-lowering therapy (commentary). *Lancet* 2002;360: 1618–1619
16. Martin G, Duez H, Blanquart C, Berezowski V, Poulain P, Fruchart JC, Najib-Fruchart J, Glineur C, Staels B: Statin-induced inhibition of the Rho-signaling pathway activates PPARalpha and induces HDL apoA-I. *J Clin Invest* 2001;107:1423–1432
17. Simes J, Furberg CD, Braunwald E, Davis BR, Ford I, Tonkin A, Shepherd J: Effects of pravastatin on mortality in patients with and without coronary heart disease across a broad range of cholesterol levels. The Prospective Pravastatin Pooling Project. *Eur Heart J* 2002;23:207–215
18. Pfeffer MA, Keech A, Sacks FM, Cobbe SM, Tonkin A, Byington RP, Davis BR, Friedman CP, Braunwald E: Safety and tolerability of pravastatin in long-term clinical trials: Prospective Pravastatin Pooling (PPP) Project. *Circulation* 2002;105:2341–2346
19. Black DM, Bakker-Arkema R, Nawrocki JW: An overview of the clinical safety profile of atorvastatin (Lipitor), a new HMG-CoA reductase inhibitor. *Arch Intern Med* 1998;158:577–584
20. Phillips PS, Haas RH, Bannykh S, Hathaway S, Gray NL, Kimura BJ, Vladutiu GD, England JD: Statin-associated myopathy with normal creatine kinase levels. *Ann Intern Med* 2002;137:581–585
21. Extending benefits of pravastatin to the elderly: Results of the PROSPER study. Available at: http://www.forhealthyaging.com/ results. Accessed December 5, 2002
22. Yano K, Reed D, MacLean CJ: Serum cholesterol and hemorrhagic stroke in the Honolulu Heart Program. *Stroke* 1989;20:1460–1465
23. Iso H, Jacobs DR Jr, Wentworth D, Neaton JD, Cohen JD: Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the Multiple Risk Factor Intervention Trial. *N Engl J Med* 1989;320:904–910
24. Byington RP, Davis BR, Plehn JF, White HD, Baker J, Cobbe SM, Shepherd J:. Reduction of stroke events with pravastatin. The Prospective Pravastatin Pooling (PPP) Project. *Circulation* 2001;103: 387–392
25. Paoletti R, Fahmy M, Mahla G, Mizan J, Southworth H: Rosuvastatin demonstrates greater reduction of low-density lipoprotein cholesterol compared with pravastatin and simvastatin in hypercholesterolaemic patients: A randomized, double-blind study. *J Cardiovasc Risk* 2001;8:383–390
26. Davidson M, Ma P, Stein EA, Gotto AM Jr, Raza A, Chitra R, Hutchinson H: Comparison of effects on low-density lipoprotein cholesterol and high-density lipoprotein cholesterol with rosuvastatin versus atorvastatin in patients with type IIa or IIb hypercholesterolemia. *Am J Cardiol* 2002;89:268–275
27. Brown WV, Chitra RR, Zedler BK, Bays HE, Hassman HA: Long-term efficacy and safety of rosuvastatin: Results of a 52-week comparator-controlled trial versus pravastatin and simvastatin (abstr P1526). *Eur Heart J* 2001;22(suppl):270
28. Olsson A, Southworth H, Wilpshaar JW: Long-term efficacy and safety of rosuvastatin: Results of a 52-week comparator-controlled trial versus atorvastatin (abstr 1410). *Eur Heart J* 2001;22 (suppl):253
29. Olsson AG, Pears J, McKellar J, Mizan J, Raza A: Effect of rosuvastatin on low-density lipoprotein cholesterol in patients with hypercholesterolemia. *Am J Cardiol* 2001;88:504–508
30. Lipitor® (atorvastatin calcium) tablets. Prescribing information. Parke-Davis, division of Pfizer Inc. Revised April 2002
31. Pravachol® (pravastatin sodium) tablets. Prescribing information. Bristol-Myers Squibb Company. Revised May 2002
32. Zocor® (simvastatin) tablets. Prescribing information. Merck & Co., Inc. Issued May 2002
33. Kajinami K, Koizumi J, Ueda K, Miyamoto S, Takegoshi T, Mabuchi H: Effects of NK-104, a new hydroxymethylglutaryl-coenzyme reductase inhibitor, on low-density lipoprotein cholesterol in heterozygous familial hypercholesterolemia. Hokuriku NK-104 Study Group. *Am J Cardiol* 2000;85:178–183
34. Noji Y, Higashikata T, Inazu A, Nohara A, Ueda K, Miyamoto S, Kajinami K, Takegoshi T, Koizumi J, Mabuchi H: Long-term treatment with pitavastatin (NK-104), a new HMG-CoA reductase inhibitor, of patients with heterozygous familial hypercholesterolemia. *Atherosclerosis* 2002;163:157–164

35. Saito Y, Yamada N, Teramoto T, Itakura H, Hata Y, Nakaya N, Mabuchi H, Tushima M, Sasaki J, Goto Y, Ogawa N: Clinical efficacy of pitavastatin, a new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, in patients with hyperlipidemia. *Arzneim-Forsch/Drug Res* 2002;52:251–255
36. Saito Y, Yamada N, Teramoto T, Itakura H, Hata Y, Nakaya N, Mabuchi H, Tushima M, Sasaki J, Ogawa N, Goto Y: A randomized, double-blind trial comparing the efficacy and safety of pitavastatin versus pravastatin in patients with primary hypercholesterolemia. *Atherosclerosis* 2002;162:373–379
37. Istvan ES, Deisenhofer J: Structural mechanism for statin inhibition of HMG-CoA reductase. *Science* 2001;292:1160–1164
38. Zetia™ (ezetimibe) tablets. Prescribing information. Copyright© Merck/Schering-Plough Pharmaceuticals, 2001, 2002
39. Bays HE, Moore PB, Drehobl MA, Rosenblatt S, Toth PD, Dujovne CA, Knopp RH, Lipka LJ, Lebeaut AP, Yang B, Mellars LE, Cuffie-Jackson C, Veltri EP: Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: Pooled analysis of two phase II studies. *Clin Ther* 2001;23:1209–1230
40. Gagné C, Gaudet D, Bruckert E, for the Ezetimibe Study Group: Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. *Circulation* 2002;105:2469–2475
41. Ballantyne C, Houri J, Notarbartolo A, Melani L, Lipka L, LeBeaut A, Suresh R, Sun S, Veltri E, for the Ezetimibe Study Group: Ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia (abstr 1084–91). American College of Cardiology 51st Annual Scientific Session. *J Am Coll Cardiol* 2002;39(5 suppl A):227A
42. Davidson M, McGarry T, Bettis R, Melani L, Lipka L, LeBeaut A, Suresh R, Sun S, Veltri E, for the Ezetimibe Study Group: Ezetimibe coadministered with simvastatin in 668 patients with primary hypercholesterolemia (abstr 1084–90). American College of Cardiology 51st Annual Scientific Session. *J Am Coll Cardiol* 2002b;39 (5 suppl A):226A–227A (in press)
43. Kosoglou T, Fruchart J-C, Guillaume M, Pember LJC, Sun S, Picard G, Affrime MB, Veltri EP: Coadministration of ezetimibe and fenofibrate leads to favorable effects on apo CIII and LDL subfractions (poster 172). 72nd European Atherosclerosis Society Congress. *Atherosclerosis* 2001; (suppl)2:89
44. Brown WV: Novel approaches to lipid lowering: What is on the horizon? *Am J Cardiol* 2001;87(suppl):23B–27B
45. Booker ML: S-8921 (Shionogi). *Curr Opin Investig Drugs* 2001; 2:393–395
46. Higaki J, Hara S, Takasu N, Tonda K, Miyata K, Shike T, Nagata K, Misui T: Inhibition of ileal Na+/bile acid cotransporter by S-8291 reduces serum cholesterol and prevents atherosclerosis in rabbits. *Arterioscler Thromb Vasc Biol* 1998;18:1304–1311
47. Bocan TM, Krause BR, Rosebury WS, Mueller SB, Lu X, Dagle C, Major T, Lathia C, Lee H: The ACAT inhibitor avasimibe reduces macrophages and matrix metalloproteinase expression in atherosclerotic lesions of hypercholesterolemic rabbits. *Arterioscler Thromb Vasc Biol* 2000;20:70–79
48. Insull W Jr, Koren M, Davignon J, Sprecher D, Schrott H, Keilson LM, Brown AS, Dujovne CA, Davidson MH, McLain R, Heinonen T: Efficacy and short-term safety of a new ACAT inhibitor, avasimibe, on lipids, lipoproteins, and apolipoproteins, in patients with combined hyperlipidemia. *Atherosclerosis* 2001;157:137–144
49. Tardif J-C, Grégoire J, Lespérance J, Lambert J, L'Allier PL, Rodés J, Anderson T, Blue JW, Imus J, Heinonen T: Design features of the Avasimibe and Progression of coronary Lesions assessed by intravascular UltraSound (A-PLUS) clinical trial. *Am Heart J* 2002; 144:589–596
50. Asami Y, Yamagishi I, Akiyoshi K, Tomoike H, Tsuchida K, Higuchi S: Inhibitory effect of TS-962 on the formation of early atherosclerotic lesions in high fat-fed hyperlipidemic hamsters. *Atherosclerosis* 1999;146:237–242
51. Junquero D, Bruniquel F, N'Guyen X, Autin JM, Patoiseau JF, Degryse AD, Colpaert FC, Delhon A: F 12511, a novel ACAT inhibitor, and atorvastatin regulate endogenous hypercholesterolemia in a synergistic manner in New Zealand rabbits fed a casein-enriched diet. *Atherosclerosis* 2001;155:131–142