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]

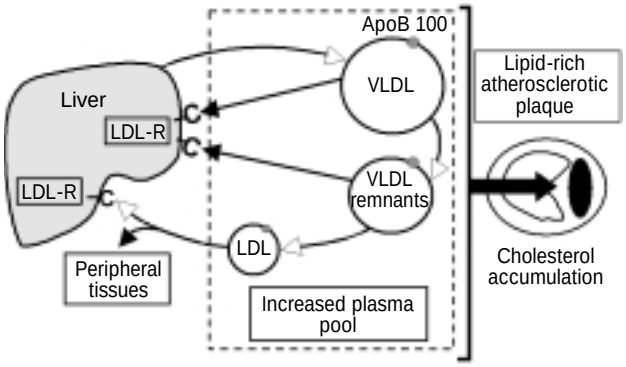

FIG. 1 In vivo metabolism of apoB-containing lipoproteins in types IIa and IIb dyslipidemia. ApoB = apolipoprotein B, LDL-R = low-density lipoprotein receptor, VLDL = very-low-density lipoprotein.

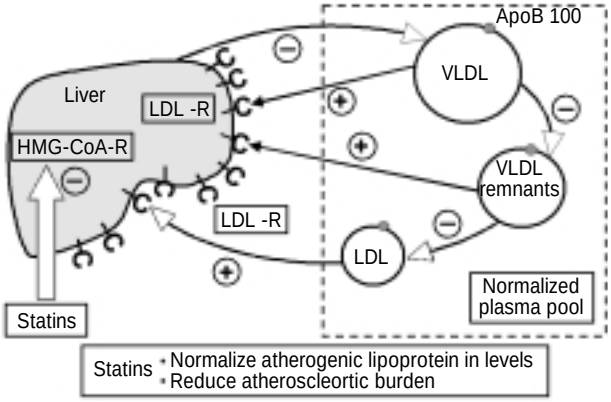

FIG. 2 Effects of statins on atherogenic apoB-containing lipoproteins in types IIa and IIb dyslipidemia. HMG-CoA-R = 3-hydroxy-3-methylglutaryl coenzyme A receptor, LDL = low-density lipoprotein. Other abbreviations as in Figure 1.

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.

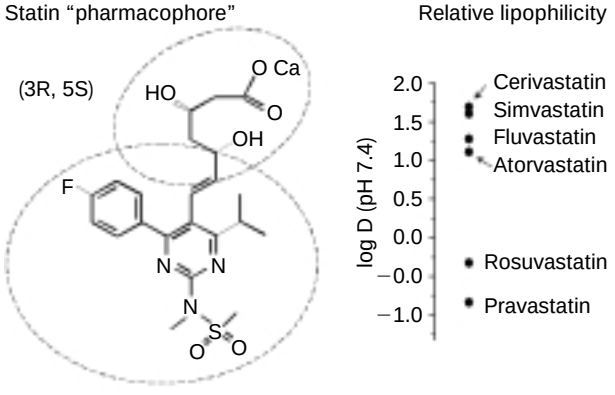

FIG. 3 Structure and relative lipophilicity of rosuvastatin. Reproduced from Ref. No. 16 with permission.

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