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A New Statin: A New Standard

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Summary: Numerous studies have demonstrated that treatments designed to reduce low-density lipoprotein cholesterol (LDL-C) can reduce the risk of coronary heart disease (CHD) events in the setting of either primary or secondary prevention. The rationale for aggressive lowering of LDL-C, supported by large observational studies, is the concept that no threshold exists below which reductions fail to provide additional benefit. The statins are widely considered first-line therapy for preventing CHD events because these agents yield the greatest reductions in LDL-C. However, many patients do not achieve target LDL-C levels with the currently available statins. Newer, more effective statins may permit the benefits of aggressive LDL-C reduction to be extended to larger numbers of patients. A novel, highly efficacious statin, rosuvastatin (Crestor™, AstraZeneca group of companies), is currently undergoing clinical investigation. Dose-ranging studies in hypercholesterolemic patients have shown that rosuvastatin produces significant, dose-dependent decreases in LDL-C when compared with placebo. Reductions have ranged from 34% at a dose of 1 mg/day to 65% at 80 mg/day. This agent has been found to be well tolerated across the range of doses studied. Phase III studies indicate that rosuvastatin is more effective than atorvastatin, pravastatin, and simvastatin in improving the atherogenic lipid profiles of hypercholesterolemic patients, and more effective than atorvastatin in improving the atherogenic lipid profiles of patients with heterozygous familial hypercholesterolemia. Overall, these findings suggest that rosuvastatin is a promising new medication for the treatment of dyslipidemias.

Key words: low-density lipoprotein cholesterol, coronary heart disease, statins, rosuvastatin, dyslipidemia

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Introduction

Extensive clinical and epidemiologic data have attested to the value of cholesterol reduction as a means of modifying atherogenic risk. Low-density lipoprotein cholesterol (LDL-C) has been the primary target of efforts to prevent the adverse events of coronary heart disease (CHD).[1,2] Current knowledge supports the concept that aggressive LDL-C reduction, perhaps even below recommended levels, is a powerful tool for reducing the risk of CHD morbidity and mortality in the setting of either primary or secondary prevention.

Of the available lipid-lowering medications, the statins have the greatest potential for producing dramatic reductions in LDL-C and maintaining such levels over time. This class of agents is widely regarded as first-line therapy for patients at risk for atherosclerotic vascular disease. However, the different statins vary with regard to their pharmacologic properties, efficacy, and tolerability. Newer statins, with greater LDL-C-lowering effects, may increase our ability to extend the benefits of aggressive lipid lowering to larger numbers of patients.

Impact of Low-Density Lipoprotein-Cholesterol Reduction on Coronary Heart Disease Risk

Nearly two decades ago, the Lipid Research Clinics Coronary Primary Prevention Trial demonstrated a linear relationship between reductions in LDL-C and reductions in adverse CHD events.[3] The subsequent Helsinki Heart Study corroborated this observation.[4] However, these pioneering trials used agents such as bile acid sequestrants and fibric acid derivatives, which produced modest LDL-C reductions of approximately 8 to 13%.[5] Furthermore, the ability of lipid-lowering agents to reduce the risk of all-cause mortality, as well as CHD mortality, remained in doubt.

In the mid-1990s, the Scandinavian Simvastatin Survival Study (4S) found that statin therapy was associated with a 35% reduction in LDL-C, a 30% reduction in the risk of all-cause mortality ($p = 0.0003$), and a 42% reduction in CHD mortality (95% CI, 0.46–0.73) after a median of 5.4 years of follow-up.[6] Of importance is the fact that greater benefits were apparent among patients who had achieved the largest reduction in

LDL-C after 1 year of treatment. At follow-up, the incidence of major CHD events was 18.2% in patients who had achieved an LDL-C reduction of ≤34%, but was nearly halved—to 10.6%—in those who had attained a reduction of 45 to 70% (Fig. 1).[5]

In the third of patients whose levels of LDL-C were reduced to 127 to 266 mg/dl (3.3–6.9 mmol/l) at 1 year, the rate of major CHD events in the subsequent 4 years was 18.9%. The rate of CHD events at follow-up was substantially lower (13.3%) in patients who had LDL-C levels of 105 to 126 mg/dl (2.8–3.2 mmol/l) at 1 year and was even lower (11.0%) in those who had levels of 58 to 104 mg/dl (1.5–2.7 mmol/l) at 1 year. Indeed, each 1% reduction in LDL-C resulted in a 1.7% reduction in the risk of CHD events ($p < 0.00001$).[7]

During the past 10 years, numerous angiographic studies have shown that lowering LDL-C delays or arrests the progression of coronary atherosclerosis. In a meta-analysis of eight angiographic trials evaluating statins,[8–15] Thompson identified a linear relationship between LDL-C level and diameter of coronary artery stenosis (Fig. 2).[16] A ≥40% reduction in LDL-C was required to halt the progression of disease, which suggests that aggressive lipid lowering may be required to achieve a substantial impact on CHD risk. Notably, however, the degree of LDL-C reduction needed to arrest progression of atherosclerosis was achieved only in trials that used statins in combination with other lipid-lowering therapies, such as nicotinic acid, colestipol, cholestyramine, or gemfibrozil. Furthermore, many patients failed to achieve recommended levels of LDL-C in the major statin trials. For example, less than 30%

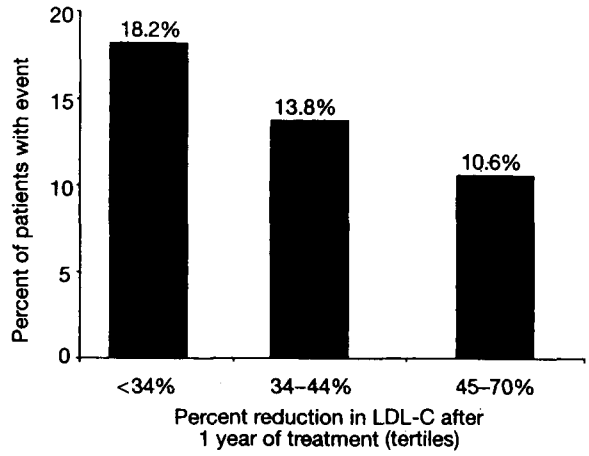

FIG. 1 Rate of major coronary events at a median of 5.4 years of follow-up according to percentage reduction in low-density lipoprotein cholesterol (LDL-C) achieved after 1 year of treatment with simvastatin in the 4S trial. Adapted from Ref. No. 5. Reprinted from the *Eur Heart J*, 19, (supp M), M15–M21 Fig. 3 with permission of Harcourt Publishers Ltd. ©1998 The European Society of Cardiology.

of patients receiving simvastatin in the 4S trial attained an LDL-C level <100 mg/dl (<2.6 mmol/l), as recommended by the National Cholesterol Education Program (NCEP) for individuals with established CHD.[1,5] Observations such as these have generated interest in developing statins with greater efficacy in lowering LDL-C.

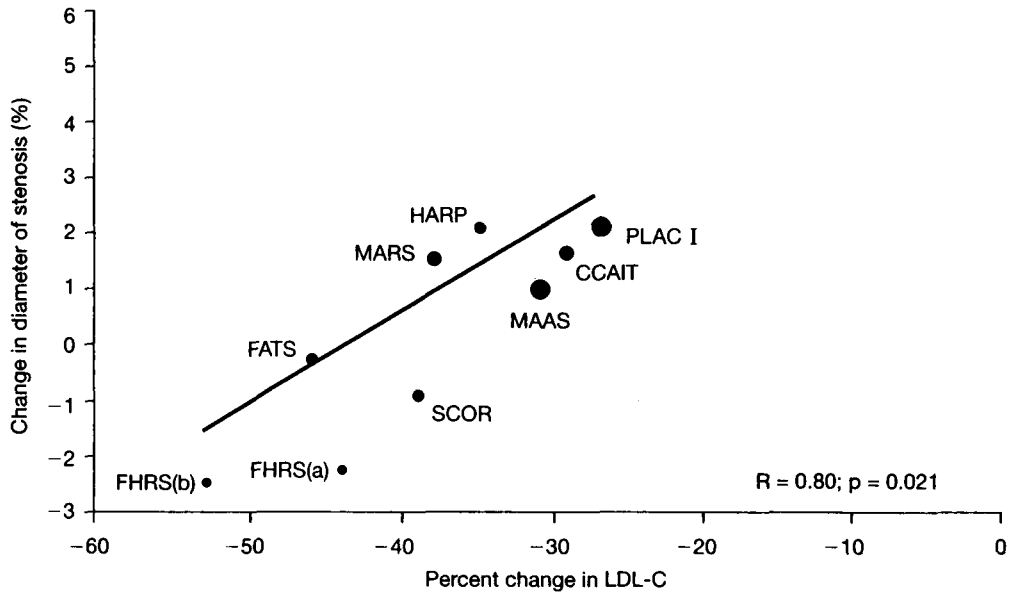

FIG. 2 Correlation between angiographic change in stenosis diameter and reduction in low-density lipoprotein cholesterol (LDL-C) in patients treated with statins in major trials. CCAIT = Canadian Coronary Atherosclerosis Intervention Trial[13]; FATS = Familial Atherosclerosis Treatment Study[8]; FHRS = Familial Hypercholesterolemia Regression Study, (a) colestipol plus simvastatin, (b) apheresis plus simvastatin[15]; HARP = Harvard Atherosclerosis Reversibility Project[12]; MAAS = Multicentre Anti-Atheroma Study[11]; MARS = Monitored Atherosclerosis Regression Study[10]; PLAC I = Pravastatin Limitation of Atherosclerosis in the Coronary Arteries Study[14]; SCOR = San Francisco Specialized Center of Research trial.[9] Adapted from Ref. No. 16.

Relative Efficacy of Available Statins

The available statins vary with regard to their pharmacologic properties and relative efficacy in reducing LDL-C.[17] Atorvastatin produces the greatest documented reductions in LDL-C in patients at risk for CHD or with confirmed atherosclerosis.[18–22] For instance, in a trial of 662 patients, the proportion who achieved target LDL-C levels (as defined by the NCEP) after 12 weeks at starting doses was significantly higher in those receiving atorvastatin than lovastatin, simvastatin, or fluvastatin.[18,19,21] The superiority of atorvastatin was apparent in 344 patients at risk for CHD as well as in 318 with documented atherosclerosis. Treatment doses were then titrated from Week 12 to Week 54, at which time the proportion of patients achieving target LDL-C levels was significantly greater with atorvastatin than with the other statins in patients at risk for CHD, and significantly greater than fluvastatin in those with documented atherosclerosis. In addition, an 8-week trial of patients with hypercholesterolemia demonstrated that atorvastatin was significantly more effective in lowering LDL-C than milligram-equivalent doses of pravastatin, lovastatin, simvastatin, and fluvastatin.[20]

New Statin in Development

Other statins with increased efficacy are currently in development. One such agent is rosuvastatin (Crestor™), a highly efficacious, orally active, hepatoselective, hydrophilic synthetic statin that appears to have a reduced potential for drug–drug interactions via the cytochrome P450 3A4 system.[23] The pharmacologic properties of rosuvastatin have been established in preclinical studies and evaluations in healthy volunteers.[24–27] Recently, the effects of rosuvastatin on LDL-C and other lipid parameters were examined in a dose-ranging program involving patients (men 18–70 years old and postmenopausal women 50–70 years old) with primary hypercholesterolemia.[28] The program was conducted in two stages at 14 northern European centers. First, patients were randomized to receive double-blind placebo or rosuvastatin (1, 2.5, 5, 10, 20, or 40 mg/day) or open-label atorvastatin (10 or 80 mg/day, as a benchmark for responses) for 6 weeks. In a second, follow-up trial, patients were randomized to receive double-blind placebo or rosuvastatin 40 or 80 mg/day in a 1:1:2 ratio for 6 weeks. The second trial was prospectively designed to be analyzed in combination with the first.

All doses of rosuvastatin significantly reduced levels of LDL-C in the 189 patients included in the per-protocol analysis when compared with placebo ($p < 0.001$) (Fig. 3). A linear dose–response relationship was apparent, with LDL-C reductions ranging from 34% with the 1 mg dose of rosuvastatin to 65% with the 80 mg dose. According to linear regression analysis, each doubling of the rosuvastatin dose produced an additional 4.5% decrease in the level of LDL-C. Furthermore, reductions in LDL-C occurred rapidly, with 90% of the effect evident by Week 2 across the dose range. Atorvastatin produced similar reductions (a decrease of 44% at 10 mg and 59% at 80 mg). Compared with placebo, all doses of rosuvastatin significantly reduced total cholesterol and apolipoprotein B ($p < 0.001$) in a linear fashion (no statistical comparisons with atorvastatin were performed, since it was included as a clinical benchmark only). Furthermore, all rosuvastatin doses increased levels of high-density lipoprotein cholesterol (HDL-C) (range, 9–14%) and decreased levels of triglycerides, albeit not in a dose-dependent manner (a dose-dependent response would not be expected in this patient population, since they were not recruited on the basis of low HDL-C or elevated triglyceride levels). The safety profile of rosuvastatin compared favorably with those of atorvastatin and placebo.

Preliminary findings of three phase III studies have also confirmed the positive effects of rosuvastatin on LDL-C and other lipid parameters, suggesting that rosuvastatin is more effective than atorvastatin, pravastatin, and simvastatin in improving the atherogenic lipid profiles of hypercholesterolemic patients, and more effective than atorvastatin in improving the atherogenic lipid profiles of patients with heterozygous familial hypercholesterolemia. In all of these trials, active treatment was well tolerated and the occurrence of adverse events was similar among all treatment groups.

In one phase III study, 516 patients with primary hypercholesterolemia were randomized to receive placebo, 10 mg atorvastatin, 5 mg rosuvastatin, or 10 mg rosuvastatin once daily for 12 weeks.[29] Both doses of rosuvastatin produced greater reductions in LDL-C than did atorvastatin at Week 12; these differences were statistically significant (Fig. 4). In addition, more rosuvastatin patients achieved NCEP target LDL-C levels than did patients treated with atorvastatin. For example, at 12 weeks, 84% of patients treated with either dose of rosu-

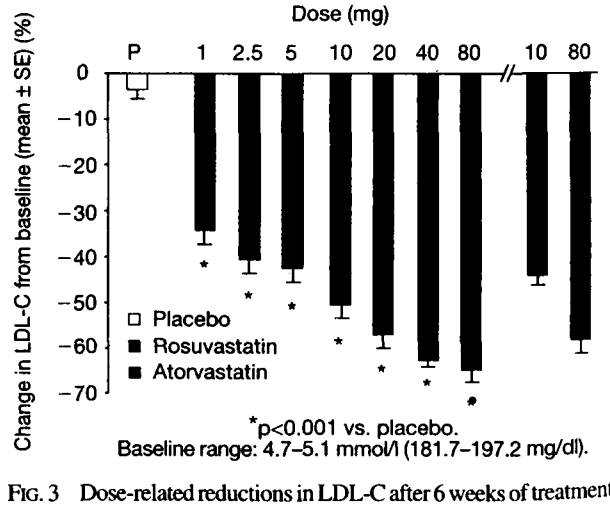

FIG. 3 Dose-related reductions in LDL-C after 6 weeks of treatment with rosuvastatin and atorvastatin. No statistical comparisons were made with atorvastatin. LDL-C = low-density lipoprotein cholesterol, SE = standard error. Adapted from Ref. No. 28. Reprinted from *Amer J Cardiol*, Olsson AG, Pears JS, McKellar J, Caplan RJ, Raza A, Pharmacodynamics of new HMG-CoA reductase inhibitor ZD4522 in patients with primary hypercholesterolaemia, 2000, with permission from Excerpta Medica Inc.

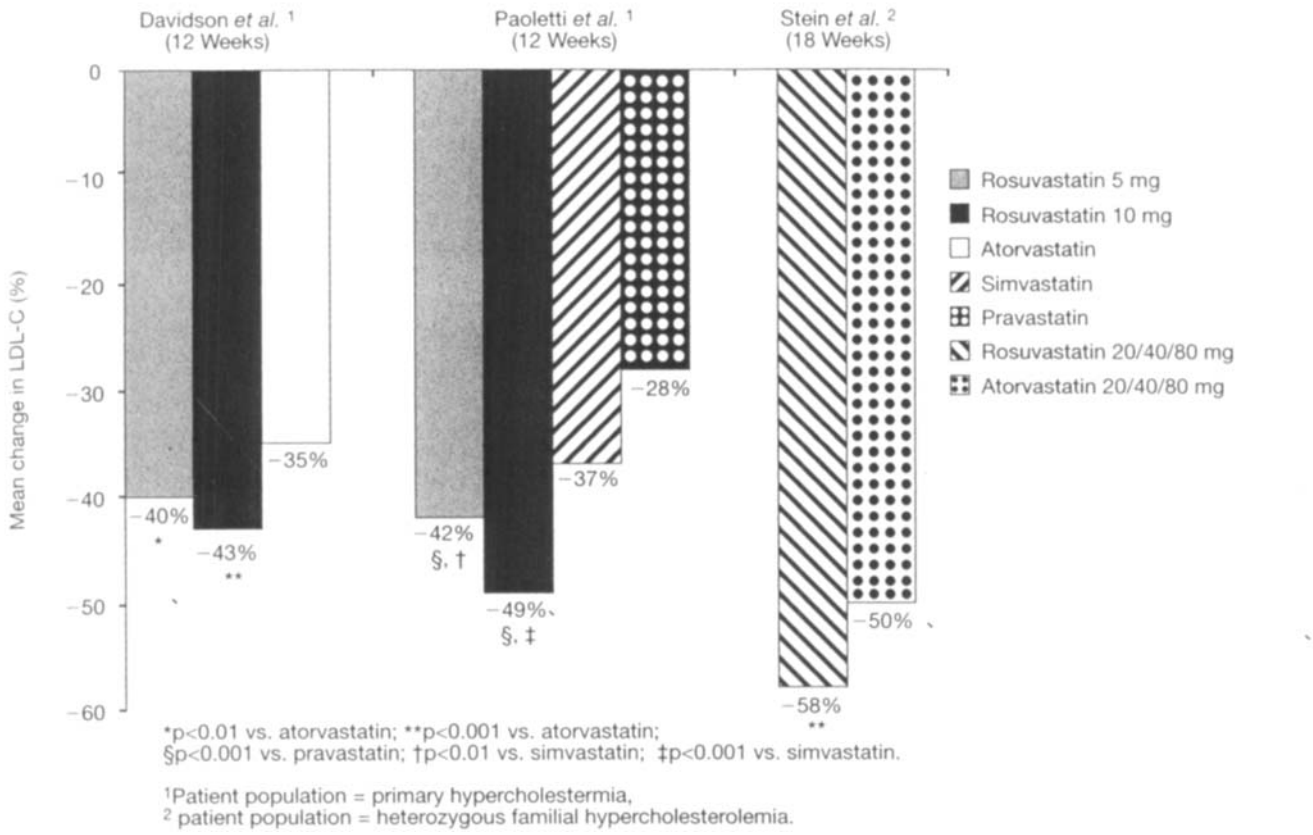

FIG. 4 Rosuvastatin phase III trials: Mean changes from baseline in low-density lipoprotein cholesterol (LDL-C) at 12 weeks[29, 30] and 18 weeks.[31]

vastatin met the LDL-C target, compared with 73% of patients receiving atorvastatin. The treatment difference was evident in all risk categories and more marked in the high-risk patients (target LDL-C ≤ 100 mg/dl). Compared with atorvastatin or placebo, treatment with 5 or 10 mg rosuvastatin also produced significantly greater decreases in total cholesterol and apolipoprotein B levels ($p<0.05$) and significantly greater increases in HDL-C and apolipoprotein A-I levels ($p<0.05$).

In a similar study, 502 patients with hypercholesterolemia were randomized to receive 20 mg simvastatin, 20 mg pravastatin, 5 mg rosuvastatin, or 10 mg rosuvastatin once daily for 12 weeks.[30] Compared with simvastatin and pravastatin, both doses of rosuvastatin produced significantly greater reductions in LDL-C at 12 weeks (Fig. 4). Moreover, a higher percentage of patients receiving rosuvastatin achieved NCEP target LDL-C levels than did patients treated with simvastatin and pravastatin. At Week 12, 87% of patients receiving rosuvastatin 10 mg and 71% of those receiving rosuvastatin 5 mg achieved the treatment target, compared with only 53 and 64% of patients receiving pravastatin and simvastatin, respectively. Again, the advantage of rosuvastatin treatment was most marked in the NCEP high-risk group. Statistically significant improvements in favor of rosuvastatin were also seen for total cholesterol and apolipoprotein B levels ($p<0.05$) and lipid ratios ($p<0.01$). A third phase III study demonstrated the benefits of rosuvastatin in patients with heterozygous familial hypercholesterolemia.[31] This 18-week study involved weighted randomization of all patients to once-daily treatment with either rosuvastatin (n = 435) or atorvastatin (n = 187). After receiving an initial dosage of 20 mg rosuvastatin or atorvastatin, patients were force-titrated to 40 and 80 mg at 6-week intervals. Compared with atorvastatin, rosuvastatin produced significantly greater decreases in LDL-C ($p<0.001$) (Fig. 4) and total cholesterol ($p<0.001$) and greater increases in HDL-C ($p<0.001$) at 18 weeks; similar statistical benefits were seen at Weeks 2, 6, and 12. After 18 weeks, rosuvastatin also significantly increased apolipoprotein A-I levels ($p<0.001$), significantly decreased apolipoprotein B levels ($p<0.001$), and significantly improved lipid ratios ($p<0.001$). Moreover, rosuvastatin enabled 61% of these severe, difficult-to-treat patients to meet the NCEP target LDL-C level, compared with 46% in the atorvastatin group (24%, rosuvastatin vs. 3%, atorvastatin for NCEP high-risk patients).

Conclusion

Epidemiologic observations and data from clinical intervention studies support the strategy of lowering LDL-C to modify atherogenic risk. Because of the superiority of statins

in reducing LDL-C, they are widely regarded as first-line therapy for patients at risk for atherosclerotic vascular disease and its adverse sequelae. It is important to note, however, that many patients do not achieve recommended levels of LDL-C in major trials of statins. The development of statins with greater LDL-C-lowering effects may permit more aggressive management of hypercholesterolemic patients.

The new, highly efficacious statin rosuvastatin has been shown to produce significant, dose-dependent reductions in LDL-C levels across a wide range of doses. In addition, data from recent phase III studies suggest that rosuvastatin is more effective than atorvastatin, pravastatin, and simvastatin in improving the atherogenic lipid profiles of hypercholesterolemic patients, and more effective than atorvastatin in improving the atherogenic lipid profiles of patients with heterozygous familial hypercholesterolemia. Overall, these trials suggest that the introduction of such new "superstatins" in coming years may allow clinicians to extend the benefits of lipid-lowering therapy to a greater number of patients and to make even greater inroads with respect to cardiovascular risk reduction.

References

1. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: 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
2. Second Joint Task Force of European and Other Societies on Coronary Prevention: Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and Other Societies on Coronary Prevention. *Eur Heart J* 1998;19:1434–1503
3. Lipid Research Clinics Program: The Lipid Research Clinics Coronary Primary Prevention Trial results II: The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *J Am Med Assoc* 1984;251:365–374
4. Manninen V, Elo MO, Frick MH, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Mäenpää H, Mälkönen M, Mänttäri M, Norola S, Pasternack A, Pikkareinen J, Romo M, Sjöblom T, Nikkilä EA: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *J Am Med Assoc* 1988;260:641–651
5. Pedersen TR: Aggressive lipid-lowering therapy: A clinical imperative. *Eur Heart J* 1998;19(suppl M):M15–M21
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;334:1383–1389
7. Pedersen TR, Olsson AG, Færgeman O, Kjekshus J, Wedel H, Berg K, Wilhelmsen L, Haghfelt T, Thorgeirrson G, Pyörälä K, Miettinen T, Christophersen B, Tobert JA, Musliner TA, Cook TJ, for the Scandinavian Simvastatin Survival Study Group: Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). *Circulation* 1998;97:1453–1460
8. Brown G, Albers JJ, Fisher LD, Schaefer SM, Lin J-T, Kaplan C, Zhao X-Q, 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
9. Kane JP, Malloy MJ, Ports TA, Phillips NR, Diehl JC, Havel RJ: Regression of coronary atherosclerosis during treatment of familial hypercholesterolemia with combined drug regimens. *J Am Med Assoc* 1990;264:3007–3012
10. Blankenhorn DH, Azen SP, Kramsch DM, Mack WJ, Cashin-Hemphill L, Hodis HN, DeBoes LWV, Mahrer PR, Masteller MJ, Vailas LI, Alaupovic P, Hirsch LJ, and the MARS Research Group: Coronary angiographic changes with lovastatin therapy: The Monitored Atherosclerosis Regression Study (MARS). *Ann Intern Med* 1993;119:969–976
11. MAAS Investigators: Effect of simvastatin on coronary atheroma: The Multicentre Anti-Atheroma Study (MAAS). *Lancet* 1994;344: 633–638
12. Sacks FM, Pasternak RC, Gibson CM, Rosner B, Stone PH, for the Harvard Atherosclerosis Reversibility Project (HARP) Group: Effect on coronary atherosclerosis of decrease in plasma cholesterol concentrations in normocholesterolaemic patients. *Lancet* 1994;344:1182–1186
13. Waters D, Higginson L, Gladstone P, Kimball B, Le May M, Boccuzzi SJ, Lespérance J, for the CCAIT Study Group: Effects of monotherapy with an HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography. The Canadian Coronary Atherosclerosis Intervention Trial. *Circulation* 1994;89:959–968
14. Pitt B, Mancini GB, Ellis SG, Rosman HS, Park J-S, McGovern ME, for the PLAC I Investigators: Pravastatin limitation of atherosclerosis in the coronary arteries (PLAC I): Reduction in atherosclerosis progression and clinical events. *J Am Coll Cardiol* 1995; 26:1133–1139
15. Thompson GR, Maher VM, Matthews S, Kitano Y, Neuwirth C, Schrott MB, Davies G, Rees A, Mir A, Prescott RJ, Feyter PD, Henderson A: Familial Hypercholesterolaemia Regression Study: A randomised trial of low-density-lipoprotein apheresis. *Lancet* 1995;345:811–816
16. Thompson GR: What targets should lipid-modulating therapy achieve to optimise the prevention of coronary heart disease? *Atherosclerosis* 1997;131:1–5
17. Knopp RH: Drug treatment of lipid disorders. *N Engl J Med* 1999; 341:498–511
18. Brown AS, Bakker-Arkema RG, Yellen L, Henley RW, Guthrie R, Campbell CF, Koren M, Woo W, McLain R, Black DM: Treating patients with documented atherosclerosis to National Cholesterol Education Program-recommended low-density-lipoprotein cholesterol goals with atorvastatin, fluvastatin, lovastatin and simvastatin. *J Am Coll Cardiol* 1998;32:665–672
19. Hunninghake D, Bakker-Arkema RG, Wigand JP, Drehobl M, Schrott H, Early JL, Abdallah P, McBride S, Black DM: Treating to meet NCEP-recommended LDL cholesterol concentrations with atorvastatin, fluvastatin, lovastatin, or simvastatin in patients with risk factors for coronary heart disease. *J Fam Pract* 1998;47: 349–356
20. Jones P, Kafonek S, Laurora I, Hunninghake D, for the CURVES Investigators: 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
21. Koren MJ, Smith DG, Hunninghake DB, Davidson MH, McKenney JM, Weiss SR, Schrott HG, Henley RW Jr, Tresh P, McLain RW, Bakker-Arkema RG, Black DM: The cost of reaching National Cholesterol Education Program (NCEP) goals in hypercholesterolaemic patients. A comparison of atorvastatin, simvastatin, lovastatin, and fluvastatin. *Pharmacoeconomics* 1998;14:59–70
22. März W, Wollschläger H, Klein G, Neiss A, Wehling M: Safety of low-density lipoprotein cholesterol reduction with atorvastatin versus simvastatin in a coronary heart disease population (the TARGET TANGIBLE trial). *Am J Cardiol* 1999;84:7–13
23. McCormick AD, McKillop D, Bulters CJ, Miles GS, Baba T, Touchi A, Yamaguchi Y. ZD4522—an HMG-CoA reductase in-

hibitor free of metabolically mediated drug interactions: Metabolic studies in human in vitro systems (abstr). *J Clin Pharmacol* 2000;40:1055

24. Buckett L, Ballard P, Davidson R, Dunkley C, Stafford MJ, McTaggart F: Selectivity of ZD4522 for inhibition of cholesterol synthesis in hepatic versus non-hepatic cells (abstr). *Atherosclerosis* 2000;151(suppl):MoP29:W6
25. Nezasa K, Higaki K, Hasegawa H, Inazawa K, Takeuchi M, Yukawa T, McTaggart F, Nakano M: Uptake of HMG-CoA reductase inhibitor ZD4522 into hepatocytes and distribution into liver and other tissues of the rat (abstr). *Atherosclerosis* 2000;151(suppl): MoP21:W6
26. Smith G, Davidson R, Bloor S, Burns K, Calnan C, McAulay P, Torr N, Ward D, McTaggart F: Pharmacological properties of ZD4522—a new HMG-CoA reductase inhibitor (abstr). *Atherosclerosis* 2000; 151(suppl):MoP20:W6
27. Warwick MJ, Dane AL, Raza A, Schneck DW: Single- and multiple-dose pharmacokinetics and safety of the new HMG-CoA reductase inhibitor ZD4522 (abstr). *Atherosclerosis* 2000;151(suppl): MoP16:W6
28. Olsson AG, Pears JS, McKellar J, Caplan RJ, Raza A: Pharmacodynamics of new HMG-CoA reductase inhibitor ZD4522 in patients with primary hypercholesterolaemia. Paper presented at the XIIth International Symposium on Atherosclerosis; June 28, 2000; Stockholm, Sweden
29. Davidson MH, Ma P, Stein E, Hutchinson HG, Chitra R, Raza A, Gotto AM: ZD4522 is superior to atorvastatin in decreasing low-density lipoprotein cholesterol and increasing high-density lipoprotein cholesterol in patients with type IIa or IIb hypercholesterolemia (abstr). *J Am Coll Cardiol* 2001:37(suppl A):Abstr 1261-175
30. Paoletti R, Fahmy M, Mahla G, Mizan J, Southworth H: ZD4522 is superior to pravastatin and simvastatin in reducing low-density lipoprotein cholesterol, enabling more hypercholesterolemic patients to achieve target low-density lipoprotein cholesterol guidelines. *J Am Coll Cardiol* 2001(suppl A):Abstr 1261-174
31. Stein E, Strutt KL, Miller E, Southworth H: ZD455 is superior to atorvastatin in the treatment of patients with heterozygous familial hypercholesterolemia (abstr). *J Am Coll Cardiol* 2001(suppl A): Abstr 1261-176