Clin. Cardiol. 26, 509–514 (2003)

Differential Effects of Simvastatin and Atorvastatin on High-Density Lipoprotein Cholesterol and Apolipoprotein A-I Are Consistent across Hypercholesterolemic Patient Subgroups

MICHAEL H. DAVIDSON, M.D., LEIV OSE, M.D.,* JIRI FROHLICH, M.D.,† RUSSELL S. SCOTT, M.D.,‡ CARLOS A. DUJOVNE, M.D.,§ IVAN D. ESCOBAR, M.D.,|| MARCELO C. BERTOLAMI, M.D.,# FRANK CIHON, M.S.,** DARBIE L. MACCUBBIN, PH.D.,** MICHELE MERCURI, M.D., PH.D.**

Chicago Center for Clinical Research, Chicago, Illinois, USA; *Lipidklinikken, Oslo, Norway; †St. Paul Hospital, Vancouver, Canada; ‡Lipid and Diabetes Research Group, Christchurch Hospital, Christchurch, New Zealand; §Lipids, Heart Disease and Stroke Prevention Clinic, Radiant Research, Kansas City, Kansas, USA; ||Asociacian Colombiana de Diabetes, Bogota, Colombia; #Instituto Dante Pazzanese de Cardiologia, Sao Paulo, Brazil; **Merck Research Laboratories, Rahway, New Jersey, USA

Summary

Background: In addition to lowering plasma levels of low-density lipoprotein cholesterol (LDL-C), statins also raise high-density lipoprotein cholesterol (HDL-C).

Hypothesis: Recent studies have shown that treatment with simvastatin results in larger increases in HDL-C than those seen with atorvastatin. The results of three clinical studies are analyzed, comparing the effects of simvastatin and atorvastatin on HDL-C and apolipoprotein A-I (apo A-I) in the total cohort and in several subgroups of hypercholesterolemic patients. The three studies were all multicenter, randomized clinical trials that included simvastatin (20–80 mg) and atorvastatin (10–80 mg) treatment arms. The subgroup analyses performed were gender; age (< 65 and ≥ 65 years); baseline HDL-C (male: < 40 or ≥ 40 mg/dl; female: < 45 or ≥ 45 mg/dl), baseline LDL-C (< 160 or ≥ 160 mg/dl), and baseline triglycerides (< 200 or ≥ 200 mg/dl).

Results: Both drugs produced similar increases in HDL-C levels at low doses; however, at higher drug doses (40 and 80 mg), HDL-C showed a significantly greater increase with simvastatin than with atorvastatin ($p < 0.05$ to < 0.001). Therefore, while HDL-C remained consistently elevated across all doses of simvastatin, there appeared to be a pattern of decreasing HDL-C with an increasing dose of atorvastatin. A similar negative dose response pattern was also observed with apo A-I in atorvastatin-treated patients, suggesting a reduction in the number of circulating HDL particles at higher doses. Both drugs reduced LDL-C and triglycerides in a dose-dependent fashion, with atorvastatin showing slightly greater effects. The differential effects of atorvastatin and simvastatin on HDL-C and apo A-I were observed for both the whole study cohorts and all subgroups examined; thus, no consistent treatment-by-subgroup interactions were observed.

Conclusion: The data presented show that, across different hypercholesterolemic patient subgroups, simvastatin increases HDL-C and apo A-I more than atorvastatin at higher doses, with evidence of a negative dose response effect on HDL-C and apo A-I with atorvastatin, but not simvastatin.

Key words: statins, high-density lipoprotein, apolipoprotein A-I, simvastatin, atorvastatin

Introduction

The hydroxy-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) simvastatin, lovastatin, and pravastatin have been shown to reduce morbidity and mortality from coronary heart disease (CHD) in both primary and secondary prevention settings.[1–6] Although the primary goal of statin therapy is to reduce the plasma levels of low-density lipoprotein cholesterol (LDL-C), there is now considerable evidence that statins may exert their beneficial effects through a variety of mechanisms. Some involve modification of plasma lipids other than LDL-C (e.g., lowering triglycerides [TG] and raising high-density lipoprotein cholesterol [HDL-C]), and others are unrelated to lipids (e.g., anti-inflammatory and anti-thrombotic effects).[7–9] As these mechanisms are elucidated, it may be important to identify differences that may exist between the different marketed statins.

Results of previous studies in hypercholesterolemic patients showed that while atorvastatin and simvastatin both lower LDL-C and TG in a dose-dependent manner, they dif-

This work was sponsored by Merck Research Laboratories, Rahway, N.J.

Address for reprints:

Michael H. Davidson, M. D.
Chicago Center for Clinical Research
515 State St.
Chicago, IL 60610, USA
e-mail: mdavidson@protocare.com

Received: June 25, 2002
Accepted with revision: November 12, 2003

fer in their effects on HDL-C. At low doses, both drugs raise HDL-C to comparable levels, and while this HDL-C-raising effect is maintained across all doses of simvastatin, it appears to be attenuated with increasing doses of atorvastatin.[10, 11] Here we report the results of a post-hoc analysis of three comparative studies to determine whether this differential effect of atorvastatin and simvastatin on HDL-C is a generalized effect in hypercholesterolemic patients or is driven by a particular subset of patients.

Methods

Study Designs and Patient Characteristics

Post-hoc subgroup analyses were performed on data from three multicenter, randomized clinical trials originally designed to compare the lipid-modifying efficacy of various doses of simvastatin and atorvastatin in hypercholesterolemic patients. These three studies were selected because they were all comparative trials sponsored by Merck & Co., Inc.; therefore, data were available for performing retrospective analyses. A pooled analysis was not performed because of a lack of common, clinically equipotent doses across studies, and a large diversity in study designs and treatment durations. Key study design details and baseline patient characteristics are shown in Table I and have been described in detail in previous publications.[10–13] Treatment effects on the plasma levels of HDL-C, LDL-C, and TG were assessed in all three studies, and apo A-I was measured in Study #2 and Study #3. The following subgroups were investigated: gender; age (< 65 and ≥ 65 years); baseline HDL-C (male: < 40 or ≥ 40 mg/dl; female: < 45 or ≥ 45 mg/dl), baseline LDL-C (< 160 or ≥ 160 mg/dl), and baseline TG (< 200 or ≥ 200 mg/dl).

Statistical Analyses

Efficacy endpoints were analyzed for percent change from baseline in lipid levels. Analyses were based on the intention-

TABLE I Summary information for simvastatin versus atorvastatin multicenter, randomized trials

	Recto (Study #1) (n = 258)	Kastelein/Illingworth (Study #2) (n = 826)	Crouse (Study #3) (n = 846)
Study design	Open-label crossover split-plot study with two 6-week treatment periods and 1-week washout	Double-blind, parallel, 36-week study with dose escalation at 6 and 12 weeks	Open-label, parallel 12-week study
Patient eligibility	LDL-C ≥ 130 mg/dl TG ≤ 350 mg/dl	LDL-C ≥ 160 mg/dl TG ≤ 350 mg/dl	Eligible for pharmacologic therapy according to NCEP ATPII TG ≤ 350 mg/dl
Primary endpoint	LDL-C	HDL-C	LDL-C
Drug doses	Simvastatin 20 mg Atorvastatin 10 mg Simvastatin 40 mg Atorvastatin 20 mg	Weeks 1–6 Simvastatin 40 mg Atorvastatin 20 mg Weeks 6–12 Simvastatin 80 mg Atorvastatin 40 mg Weeks 12–36 Simvastatin 80 mg Atorvastatin 80 mg	Simvastatin 40 mg Atorvastatin 20 mg Simvastatin 80 mg Atorvastatin 40 mg
Patient demographics			
Mean age	53	54	53
Gender (% male)	51	53	58
Race (% white)	64	84	84
Baseline lipids: mean (SD); mg/dl			
LDL-C	193.4 ± 53.8	206.9 ± 49.6	213.8 ± 61.1
TG [a]	166.0 ± 79.6	165.5 ± 83.7	166.5 ± 92.1
HDL-C	47.2 ± 12.2	50.8 ± 11.8	47.8 ± 12.7
Apo A-I	[b]	152.0 ± 26.8	145.3 ± 27.7

[a] Values are medians.
[b] Not measured.
Abbreviations: LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, TG = triglycerides, NCEP = National Cholesterol Education Program, ATP II = Adult Treatment Panel II, Apo A-I = apoliproprotein A-I, SD = standard deviation.

to-treat populations, which included all randomized patients with baseline and at least one post-treatment measurement. All statistical tests were two-tailed with $\alpha = 0.050$. Subgroup analyses were performed on data measured at consistent time points across the three studies. Analyses were based on patients who completed 6 weeks of treatment. However, if patients received a common dose for 12 consecutive weeks or longer, the average of the 6-week intervals was used. For Studies #1 and #3, analyses were based on the 6-week and average of 6- and 12-week measurements, respectively. Study #2 analyses were performed for each dose schedule—that is, based on measurements at Week 6, Week 12, and the average of Weeks 18, 24, 30, and 36. The consistency of the between-treatment differences over time (Weeks 18 to 36) was assessed by the treatment-by-week interaction and was nonsignificant for the lipid endpoints. Table I shows drug doses examined across all three studies. Subgroups were analyzed using a parametric analysis of variance model that included factors for treatment, subgroup and treatment-by-subgroup interaction (Studies #2 and #3), and for center, dose, period, treatment, subgroup, treatment-by-dose interaction, and treatment-by-subgroup interaction (Study #1). Additional factors were included in the above model (Study #1) due to the complexity of the study design. Between-treatment inferential testing was performed only when the treatment-by-subgroup interaction was significant. Inferential subgroup results were cautiously interpreted, recognizing the possible effect of repeated testing on the type 1 error rate.

Results

Cohort Analyses

The comparative effects of simvastatin and atorvastatin on HDL-C, apo A-I, LDL-C, and TG for each study cohort have been reported previously.[10–13] These overall results are shown here (Fig. 1), but for the purposes of this presentation, the data from all three studies for a given lipid endpoint (e.g., HDL-C) are provided together and summarized by statin and dose. For HDL-C (Fig. 1A) and apo A-I (Fig. 1B), a pattern of decreasing mean percent changes from baseline with increasing doses of atorvastatin was seen, but with simvastatin, the percent changes from baseline for both lipid components were consistently increased across all doses. In contrast to their effects on HDL-C and apo A-I, both drugs reduced LDL-C (Fig. 1C) and TG (Fig. 1D) in a dose-dependent fashion, with the LDL-C- and TG-lowering effect of 10, 20, or 40 mg of atorvastatin greater than that seen with 20, 40, and 80 mg simvastatin, respectively.

Subgroup Analyses

Comparative effects of simvastatin and atorvastatin on HDL-C in the five subgroups examined are shown in Figure 2 (A–E). Across all subgroups, the pattern of HDL-C response to atorvastatin and simvastatin was similar to that observed for the study cohorts. Thus, while HDL-C was, in general, consistently increased by all doses of simvastatin, the HDL-C re-

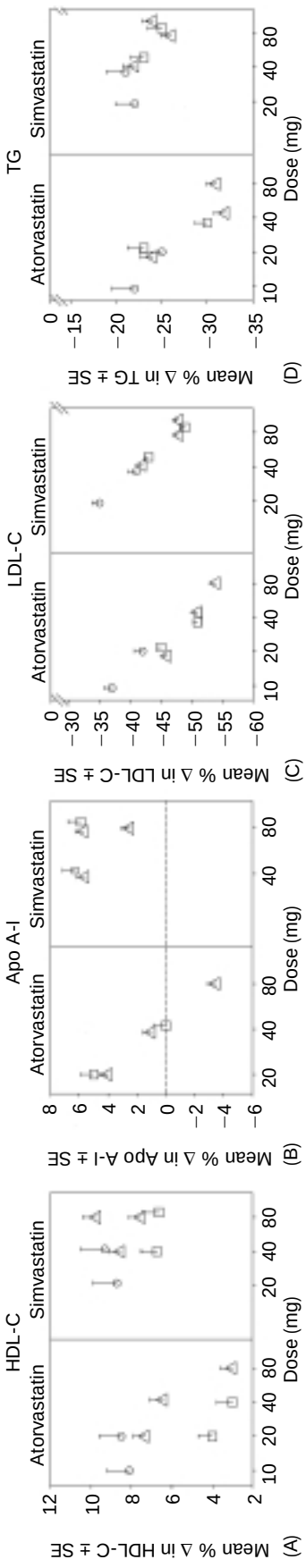
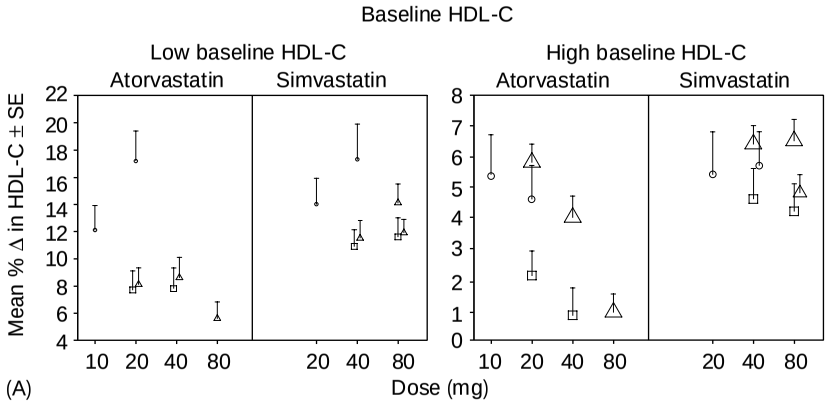
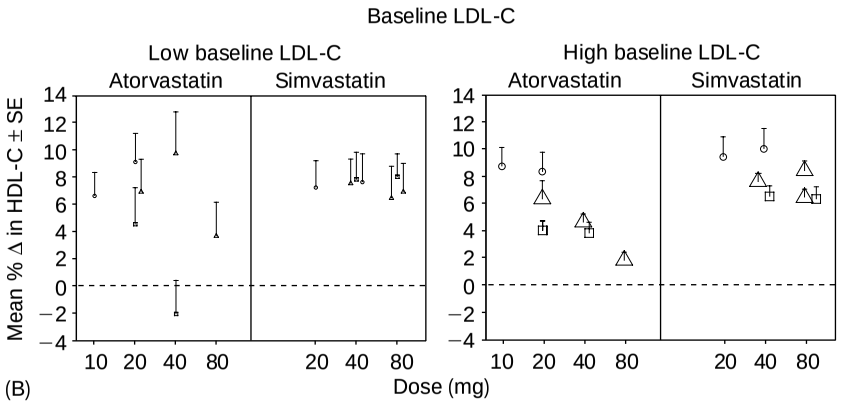
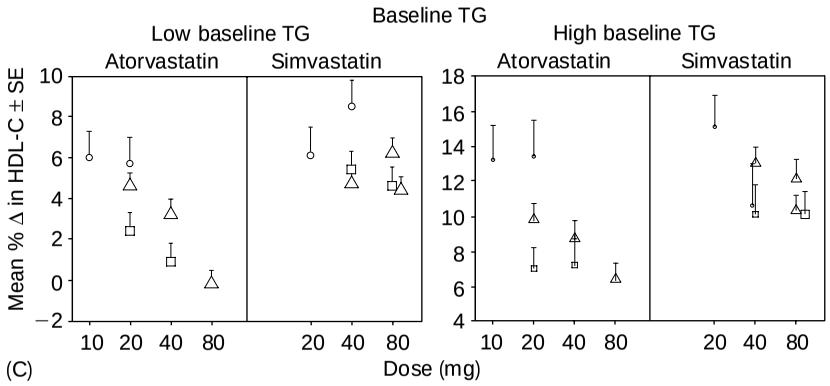
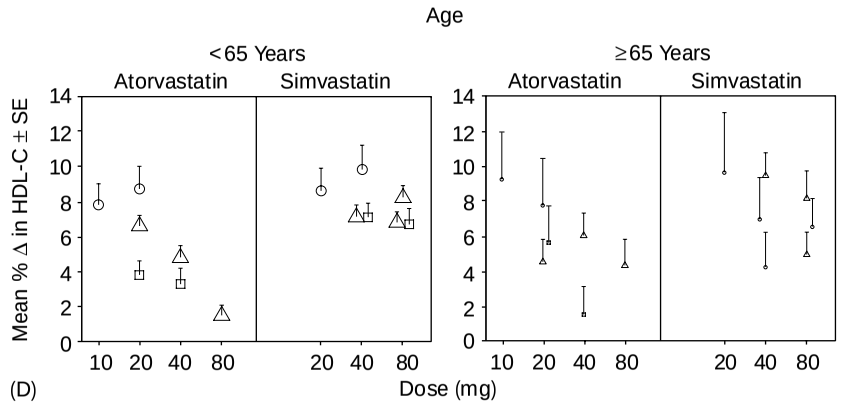


FIG. 1 Effect of increasing doses of atorvastatin (left) and simvastatin (right) on high-density lipoprotein cholesterol (HDL-C) (A), apolipoprotein A-I (apo A-I) (B), low-density lipoprotein cholesterol (LDL-C) (C), and triglycerides (TG) (D). Individual studies are represented by symbol shape: Recto (○), Kastelein/Illingworth (△), Crouse (□). Symbol sizes from smallest to largest reflect treatment group sizes of ≤ 50, 51–100, 101–200, 201–300, and > 300, respectively. The two graph points from the Kastelein/Illingworth study for 80 mg simvastatin represent two different treatment time points: 12 weeks (simvastatin 80 vs. atorvastatin 40 mg), and an average of 18, 24, 30, and 36 weeks (simvastatin 80 vs. atorvastatin 80 mg). SE = standard error.









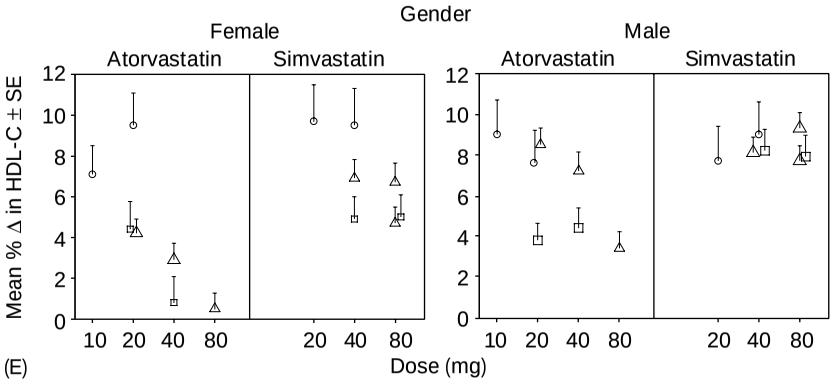


FIG. 2 Effect of increasing doses of atorvastatin and simvastatin on HDL-C in patients with low (< 40 [men], < 45 [women] mg/dl), or high (≥ 40 [men], ≥ 45 [women] mg/dl) baseline HDL-C levels (A); patients with low (< 160 mg/dl) or high ≥ 160 mg/dl) baseline LDL-C levels (B); patients with low (< 200 mg/dl) or high (≥ 200 mg/dl) baseline TG levels (C); patients < 65 or ≥ 65 years of age (D); and female and male patients (E). Individual studies are represented by symbol shape: Recto (○), Kastelein/Illingworth (△), Crouse (□). Symbol sizes from smallest to largest reflect treatment group sizes of (≤ 50, 51–100, 101–200, 201–300, and > 300, respectively. The two graph points from the Kastelein/Illingworth study for 80 mg simvastatin represent two different treatment time points: 12 weeks (simvastatin 80 vs. atorvastatin 40 mg), and an average of 18, 24, 30, and 36 weeks (simvastatin 80 vs. atorvastatin 80 mg). Abbreviations as in Figure 1.

sponse to atorvastatin generally decreased with increasing atorvastatin dose. No consistent treatment by subgroup interactions was observed, indicating similar treatment effects on HDL-C across the subgroups. However, across all studies and for both drugs, high baseline TG and low baseline HDL-C were strong predictors of a higher HDL-C-raising effect ($p < 0.001$).

The differential effects of atorvastatin and simvastatin on apo A-I were also maintained across the five subgroups (data not shown). Similarly, no consistent subgroup effect was observed on the dose-dependent reduction of LDL-C and TG observed with either drug (data not shown).

Discussion

Low plasma HDL-C has been identified as an important CHD risk factor. Follow-up of the Framingham Heart Study revealed that HDL-C levels were inversely related to the incidence of myocardial infarction,[14] and in the Helsinki Heart Study, HDL-C levels were predictive of future coronary artery disease risk in patients with Type IIa hyperlipoproteinemia.[15] Based on an analysis of four major trials, Gordon *et al.* found that the risk of CHD was reduced by 2 to 3% for every 1 mg/dl increase in HDL-C.[16] More recently, the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) provided evidence that raising HDL-C and lowering TG in patients with low levels of HDL-C and normal or near normal LDL-C levels can substantially reduce the risk of nonfatal myocardial infarction and CHD-related death.[17]

All statins produce dose-dependent reductions in the plasma levels of LDL-C and TG. The HDL-C levels are only modestly increased by statin therapy, and differences have been shown between simvastatin and atorvastatin.[10, 11, 18, 19] In the present analysis, data from three previously published comparative trials were summarized to illustrate the differential effects of atorvastatin and simvastatin across their dosage ranges on HDL-C and apo A-I. In general, HDL-C and apo A-I were comparably increased across the simvastatin dosage range; however, there appeared to be a dose-related attenuation of these responses with increasing doses of atorvastatin. Furthermore, subgroup analyses demonstrated that this differential effect was maintained in patient subgroups characterized by gender, age, and baseline levels of HDL-C, TG, and LDL-C. The LDL-C and TG reductions by atorvastatin and simvastatin observed in the present analysis were typical of what has been reported by others.[20–22] Atorvastatin produced slightly greater reductions in LDL-C (-37 to -54% for atorvastatin vs. -35 to -49% for simvastatin) and TG (-22 to -31% for atorvastatin vs. -22 to -26% for simvastatin). However, the overall pattern of response (dose-dependent reductions) was the same for both drugs and was maintained across all of the subgroups examined.

The subgroup analysis reported here was conducted before the recent release of the National Cholesterol Education Program (NCEP) Adult Treatment Plan III (ATP III) guidelines.[23] Nevertheless, the age and lipid cutoffs selected are generally consistent with the new recommendations. The cutoff values used for LDL-C (160 mg/dl) and TG (200 mg/dl) coincide with the ATP III-defined lower limit of the "high" category for both lipid parameters. For HDL-C, ATP III designates levels < 40 mg/dl as categorically low for both men and women. However, because women typically have higher HDL-C levels than men, the guidelines also recommend that an HDL-C level < 50 mg/dl be defined as a marginal risk factor for women. In the present analysis, the HDL-C cut points were < 40 mg/dl for men and < 45 mg/dl for women.

The differential effects of simvastatin and atorvastatin on HDL-C were consistent across all subgroups defined by baseline levels of LDL-C, TG, or HDL-C. Thus, the pattern of response that was observed across the dosage range in the whole study cohorts (sustained with simvastatin and attenuated with atorvastatin) appeared to be unrelated to baseline lipid levels. With both drugs, however, the magnitude of the HDL-C response was significantly higher ($p < 0.001$) in all groups with low HDL-C or high TG levels at baseline. These two lipid abnormalities constitute the lipid components of the metabolic syndrome[24, 25] and, as such, often occur together. In the present analysis, baseline HDL-C levels of patients in the high TG subgroups were generally 5–10% lower than those of patients with low TG. As a result, it is difficult to distinguish the relative importance of these two baseline effects on the HDL-C response to statin treatment. The studies used for this analysis were not placebo controlled; therefore, these and other baseline effects observed (e.g., LDL-C and TG were reduced significantly more in the high LDL-C and TG subgroups, respectively) may be due to regression to the mean. Nevertheless, this analysis provides evidence that simvastatin and atorvastatin may differ in their capacity to provide multifactorial benefit to hypercholesterolemic patients who are at particularly high risk of CHD because of abnormal levels of HDL-C or TG. Ballantyne *et al.*[26] conducted a post-hoc analysis on data from the Scandinavian Simvastatin Survival Study (4S) to assess the added CHD risk of low HDL-C and high TG in patients with elevated LDL-C (210–310 mg/dl) and a history of myocardial infarction and/or angina. They found that patients in the lowest HDL-C quartile (< 39 mg/dl) and highest TG quartile (> 159 mg/dl) had a greater risk of CHD events on placebo and benefited more from simvastatin treatment than did patients in the highest HDL-C quartile (HDL-C > 52 mg/dl) and lowest TG quartile (< 98 mg/dl).[26]

The risk of CHD increases with increasing age in both men and women; however, women tend to develop CHD 10–15 years later than men.[27] Thus, male gender as a CHD risk must be qualified with age range designations. The ATP III guidelines classify older adults as ≥ 65 for men and ≥ 75 for women. The upper age limit for patient eligibility for all three studies used in the present analysis was 70; therefore, a cutoff of 65 for both men and women was used for the subgroup analysis. The overall pattern of HDL-C response in simvastatin-versus atorvastatin-treated patients was consistent across the age and gender subgroups. In two of the three studies, however, HDL-C responses were significantly lower (regardless of drug) in women, due possibly to the slightly higher baseline HDL-C levels of women in these two studies (53 and 55 mg/dl in women vs. 44 and 47 in men, respectively).

The effects of simvastatin and atorvastatin on apo A-I were similar to those observed for HDL-C in the total cohort and in all subgroups. While the apo A-I increase was generally consistent with simvastatin, it decreased with increasing doses of atorvastatin and was decreased below baseline in the 80 mg group. These results suggest that the effect of atorvastatin on HDL-C may be due, at least in part, to a reduced number of circulating HDL particles. The overall apo A-I response, regardless of drug, was significantly higher in patients with low baseline HDL-C, but was not influenced by gender or baseline TG levels, as was observed for the HDL-C response. Thus, the lower HDL-C responses in women and patients with low baseline TG are more likely due to a reduced concentration of HDL-associated cholesterol rather than to a reduced number of HDL particles.

Little is known about the HDL-C- and apo A-I-raising effects of statins in general or why there are dose-related differences between atorvastatin and simvastatin. Careful consideration of the differences in the structure, metabolism, pharmacokinetics, or interaction with HMG CoA reductase have failed to reveal factors that could account for the difference between atorvastatin and simvastatin on HDL-C and apo A-I. Since the unfavorable response to atorvastatin is seen most clearly at the highest dose, it seems possible that it may be due to an off-target activity.

Conclusion

In the present analysis, simvastatin and atorvastatin produced large dose-dependent reductions in LDL-C and TG, but differed in their capacity to increase HDL-C and apo A-I, particularly at higher doses. Whereas HDL-C and apo A-I were generally increased by all doses of simvastatin, the responses of both lipid parameters were attenuated with increasing doses of atorvastatin. The negative dose-response effect of atorvastatin on HDL-C appeared to be due, in part, to a reduction in the number of circulating HDL particles; however, an additional effect on cholesterol metabolism cannot be ruled out. Regardless of mechanism, the differential effects of simvastatin and atorvastatin on HDL-C and apo A-I were observed in all subgroups of hypercholesterolemic patients examined, including those with the added CHD risk of low HDL-C or high TG plasma levels.

References

1. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, Macfarlane PW, McKillop JH, Packard CJ, for the West of Scotland Coronary Prevention Study Group: Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301–1307
2. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendörfer A, Stein EA, Kruyer W, Gotto AM Jr, for the AFCAPS/TexCAPS Research Group: Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. *J Am Med Assoc* 1998;279:1615–1622
3. Scandinavian Simvastatin Survival Study Group: Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–1389
4. 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 participants with average cholesterol levels. *N Engl J Med* 1996;335:1001–1009
5. Hunt D, Young P, Simes J, Hague W, Mann S, Owensby D, Lane G, Tonkin A: Benefits of pravastatin on cardiovascular events and mortality in older patients with coronary heart disease are equal to or exceed those seen in younger patients: Results of the LIPID trial. *Ann Intern Med* 2001;134:931–940
6. Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: A randomized placebo-controlled trial. *Lancet* 2002;360:7–22.
7. Rosenson RS, Tangney CC: Antiatherothrombic properties of statins: Implications for cardiovascular event reduction. *J Am Med Assoc* 1998;279: 1643–1650
8. White MC: Pharmacological effects of HMG CoA reductase inhibitors other than lipoprotein modulation. *J Clin Pharmacol* 1999;39:111–118
9. Ferro D, Parrotto S, Basili S, Alessandri C, Violi F: Simvastatin inhibits the monocyte expression of proinflammatory cytokines in patients with hypercholesterolemia. *J Am Coll Cardiol* 2000;36:427–431
10. Crouse JR, Frohlich J, Ose L, Mercuri M, Tobert JA: Effects of high doses of simvastatin and atorvastatin on high-density lipoprotein cholesterol and apolipoprotein A-I. *Am J Cardiol* 1999;83:1476–1477
11. Illingworth DR, Crouse JR III, Hunninghake DB, Davidson MH, Escobar ID, Stalenhoef AF, Paragh G, Ma PT, Liu M, Melino MR, O'Grady L, Mercuri M, Mitchel YB, for the Simvastatin Atorvastatin HDL Study Group: A comparison of simvastatin and atorvastatin up to maximal recommended doses in a large multicenter randomized clinical trial. *Curr Med Res Opin* 2001;17:43–50
12. Kastelein JJP, Isaacsohn JL, Ose L, Hunninghake DB, Frohlich J, Davidson MH, Habib R, Dujovne CA, Crouse JR, Liu M, Melino MR, O'Grady L, Mercuri M, Mitchel YB: Comparison of effects of simvastatin versus atorvastatin on high-density lipoprotein cholesterol and apolipoprotein A-I levels. *Am J Cardiol* 2000;86:221–223
13. Recto CS, Acosta S, Dobs A: Comparison of the efficacy and tolerability of simvastatin and atorvastatin in the treatment of hypercholesterolemia. *Clin Cardiol* 2000;23:682–688
14. Wilson PWF: High-density lipoprotein, low-density lipoprotein and coronary artery disease. *Am J Cardiol* 1990;66:7A–10A
15. Manninen V, Kostinen P, Manttari M, Huttunen JK, Canter D, Frick HM: Predictive value for coronary heart disease of baseline high-density and low-density lipoprotein cholesterol among Frederickson type IIa subjects in the Helsinki Heart Study. *Am J Cardiol* 1990;66:24A–27A
16. Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, Jacobs DR, Bangdiwala S, Tyroler HA: High-density lipoprotein cholesterol and cardiovascular disease: Four prospective American studies. *Circulation* 1989;79:8–15
17. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J, for the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group: Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med* 1999;341:410–418
18. Mikhailidis DP, Wierzbicki AS: HDL Cholesterol and the treatment of coronary heart disease: Contrasting effects of atorvastatin and simvastatin. *Curr Med Res Opin* 2000;16:139–146
19. Wierzbicki AS, Lumb PL, Chik G, Crook MA: High-density lipoprotein cholesterol and triglyceride response with simvastatin versus atorvastatin in familial hypercholesterolemia. *Am J Cardiol* 2000;86:547–549
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. Dart A, Jerums G, Nicholson G, d'Emden M, Hamilton-Craig I, Tallis G, Best J, West M, Sullivan D, Bracs P, Black D: A multicenter, double-blind, one-year study comparing safety and efficacy of atorvastatin versus simvastatin in patients with hypercholesterolemia. *Am J Cardiol* 1997;80:39–44
22. Farnier M, Portal J-J, Maigret P: Efficacy of atorvastatin compared with simvastatin in patients with hypercholesterolemia. *J Cardiovasc Pharmacol Ther* 2000;5:27–32
23. 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;285:2486–2497
24. Timar O, Sestier F, Levy E: Metabolic syndrome X: A review. *Can J Cardiol* 2000;16:779–789
25. Ford ES, Giles WH, Dietz WH: Prevalence of the metabolic syndrome among US adults. *J Am Med Assoc* 2002;287:356–359
26. Ballantyne CM, Olsson AG, Cook TJ, Mercuri MF, Pedersen TR, Kjekshus J: Influence of low high-density lipoprotein cholesterol and elevated triglyceride on coronary heart disease events and response to simvastatin therapy in 4S. *Circulation* 2001;104:3046–3051
27. Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB: Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837–1847