Effects of Simvastatin, an HMG-CoA Reductase Inhibitor, in Patients with Hypertriglyceridemia

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Summary

Background: Patients with elevated levels of serum triglycerides (TG) often have other associated lipid abnormalities (e.g., low levels of high-density lipoprotein cholesterol [HDL-C]) and are at increased risk of developing coronary heart disease. Although the therapeutic benefits of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) in hypercholesterolemic patients have been well established, less is known about the effects of statins in patient populations with hypertriglyceridemia.

Hypothesis: The purpose of this study was to evaluate the lipoprotein-altering efficacy of simvastatin in hypertriglyceridemic patients.

Methods: This was a multicenter, randomized, double-blind, placebo-controlled study. In all, 195 patients with fasting serum triglyceride levels between 300 and 900 mg/dl received once daily doses of placebo or simvastatin 20, 40, or 80 mg for 6 weeks.

Results: Compared with placebo, simvastatin treatment across all doses resulted in significant reductions ($p < 0.05$ – < 0.001) in serum levels of triglycerides (–20 to –31% decrease) and TG-rich lipoprotein particles. Significant ($p < 0.001$) reductions were also seen in low-density lipoprotein cholesterol (–25 to –35%) and non-HDL-C (–26 to –40%). Levels of HDL-C were increased (7–11%) in the simvastatin groups compared with placebo ($p < 0.05$ – < 0.001).

Conclusion: The results of this study demonstrate the beneficial effects of simvastatin in patients with hypertriglyceridemia.

Key words: simvastatin, hypertriglyceridemia, triglycerides, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, lipoprotein

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Introduction

The lipid-altering efficacy of simvastatin and other 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase inhibitors (statins) in hypercholesterolemic patients has been extensively documented.^{1–3} However, few studies have investigated the efficacy of statins in patient populations with hypertriglyceridemia. This is, in part, due to the fact that low-

density lipoprotein cholesterol (LDL-C) is considered to be the principal treatment target of this class of drugs and because, until recently, the evidence implicating triglycerides (TG) as an independent risk factor for coronary heart disease (CHD) was equivocal.^{4,5} However, several recent epidemiologic studies have provided strong evidence that elevated TG levels correlate independently with increased CHD risk.⁶⁻⁹

Hypertriglyceridemia is associated with other CHD lipid risk factors such as low levels of high-density lipoprotein cholesterol (HDL-C), a preponderance of small, dense LDL particles, and elevated levels of intermediate-density lipoproteins (IDL).¹⁰ Furthermore, many of these patients have other medical conditions, such as central obesity, diabetes, and hypertension, that put them at increased risk for CHD. The presence of these risk factors with the above dyslipidemia has been described as the metabolic syndrome.¹¹ Thus, the coexistence of other major cardiovascular risk factors with hypertriglyceridemia signals a risk profile that may require management, including an effective and comprehensive lipid-altering treatment.¹²

The purpose of the present study was to evaluate the serum lipid-regulating efficacy and safety of simvastatin in patients with hypertriglyceridemia. The patient population selected for this study represents a cohort not previously studied with simvastatin and one that may be at increased risk of CHD.

Methods

Patients

Institutional review board approval was obtained at each study center, and all patients provided written informed consent. Eligible patients were men as well as women with a low risk of pregnancy, between 18 and 70 years of age, with average fasting TG levels of 300 to 900 mg/dl and an LDL-C level ≥ 75 mg/dl (1.9 mmol/l). The levels of alanine aminotransferase, aspartate aminotransferase, and creatine kinase had to be less than 1.5 $\times$ the upper limits of normal (ULN). None of the patients had a history of type I or V hyperlipidemia, homozygous familial hypercholesterolemia, or hyperlipidemic pancreatitis. Also excluded were individuals who had taken bile acid sequestrants, HMG-CoA reductase inhibitors, fish oil, or nicotinic acid within 6 weeks; fibrates within 8 weeks; or probucol within 1 year of study initiation, as well as patients whose TG levels were $> 1,000$ mg/dl prior to initiating lipid-altering therapy and those with CHD who were receiving lipid-lowering medication. Other exclusion criteria included use of immunosuppressive agents or anticoagulants, renal insufficiency, active liver disease, acute coronary insufficiency or vasospastic angina, uncontrolled hypertension, hypercholesterolemia due to hypothyroidism or nephrotic syndrome, and a diagnosis of Type 1 diabetes mellitus or Type 2 diabetes mellitus with hemoglobin A_{1c} $> 10\%$. Finally, none of the study participants had experienced a myocardial infarction or undergone percutaneous transluminal coronary angioplasty or coronary bypass surgery within 3 months of the study.

Study Design

This was a randomized, double-blind, parallel-group, four-arm, placebo-controlled, multicenter study. Visits were scheduled at Week -4 (first screening), Week -1 (second screening), Week 1 (randomization), and Week 6. Following a 4-week placebo plus diet run-in period, 195 patients were randomized to four treatment groups: placebo or simvastatin 20, 40, or 80 mg/day (Zocor, Merck & Co., Inc., Whitehouse Station, N.J., USA) for 6 weeks. During the run-in period and throughout the 6-week treatment period, patients were asked to limit alcohol consumption to no more than seven drinks per week and were placed on an American Heart Association Step 1 or similar cholesterol-reduction diet. The patients were stratified according to their Week -1 TG levels (300–450 mg/dl = “low TG” or 451–900 mg/dl = “high TG”), so as to allow patients with low and high TG to be equally distributed among the four treatment groups. For TG, total cholesterol (total-C), LDL-C, very low-density lipoprotein cholesterol (VLDL-C), non-HDL-C, and HDL-C, baseline values were determined by averaging the Week -1 and Week 1 (predrug) values. For all other lipid parameters, the Week 1 (predrug) measurement was used as baseline. Placebo and simvastatin 20, 40, and 80 mg were administered orally once daily in the evening, and efficacy measurements were performed at the end of the 6-week treatment period. Patients were monitored throughout the study for clinical and laboratory adverse experiences.

Laboratory Analyses

Blood samples were collected in the fasting state (10–12 h) in ethylenediaminetetraacetate and centrifuged within 30 min to obtain the plasma which was shipped overnight at 4°C to Medical Research Laboratories, Highland Heights, Kentucky, where all determinations were performed. Throughout the study, the laboratory participated in and remained certified by the National Heart, Lung, and Blood Institute, Centers for Disease Control Part III program.¹³ Plasma cholesterol, TG, and HDL-C were determined using enzymatic methods.¹⁴ High-density lipoprotein cholesterol was measured after precipitation of the apo B-containing lipoproteins (LDL and VLDL) by heparin-manganese chloride.¹⁵ Low-density lipoprotein cholesterol and VLDL-C were determined by ultracentrifugation.¹⁶ The apolipoproteins (apo) B and A-I were measured by radioimmunoassay,¹⁷ and lipoprotein (Lp) A-I and Lp A-I:A-II were measured using immunochromatography.¹⁸ Other lipoprotein parameters including LDL and VLDL subfractions, IDL, and the apolipoproteins E and CIII were also measured and will be the subject of another publication.

Statistical Analyses

All efficacy endpoints were analyzed for % change from baseline at Week 6. The primary (TG) and secondary efficacy endpoints were analyzed using an analysis of variance (ANOVA) model with factors for treatment, study center, stratum (TG ≤ 450 or > 450 mg/dl), treatment-by-center interaction,

and treatment-by-stratum interaction. Interaction terms were removed from the model if nonsignificant ($p > 0.05$) or quantitative in nature. The adjusted trend test for a multicenter study (and step-down trend test, when necessary) was used to assess the progressiveness of response, in terms of increasing or decreasing trends, of the active doses of simvastatin relative to placebo. Significance in the trend test also indicated a significant pairwise difference between placebo and the highest dose of the test. However, this study was not powered to assess the dose–response relationship across the active doses of simvastatin.

Results

Patients

Patient characteristics are listed in Table I. In all, 195 patients (ages 25–70) were enrolled in the study. Of these, 188 (96.4%) completed the study. One (2.0%), 2 (4.1%), 3 (6.3%), and 1 (2.1%) patients in the placebo, simvastatin 20, 40, and 80 mg treatment groups, respectively, withdrew from the study. Although all patients had elevated TG levels, approximately 60% of patients had LDL-C levels < 130 mg/dl and were classified as having Type IV hyperlipidemia. The other 40% of patients had elevated TG and LDL-C and were classified as having combined hyperlipidemia. In addition to high TG levels, this study population had a below average level of HDL-C as defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines.¹²

TABLE I Patient demographics and baseline characteristics

Demographics and secondary diagnoses (n = 195)	
Mean age (years)	51
Gender (% males)	73
Race (% white)	93
Cardiovascular disease (%) ^a	3
Hypertension (%)	24
Diabetes mellitus (%) ^b	16
Baseline lipids (n=189)	mg/dl; mean (SD)
Triglycerides ^c	405 (201)
Total cholesterol	251 (49)
LDL-cholesterol	123 (37)
Non-HDL-cholesterol	213 (48)
Apolipoprotein B	154 (35)
HDL-cholesterol	37 (9)
Apolipoprotein A-I	141 (28)

^a Includes coronary artery disease and myocardial infarction.

^b Defined as history of type II diabetes mellitus or fasting serum glucose ≥ 126 mg/dl on two consecutive visits.

^c Values are medians.

Abbreviations: LDL = low-density lipoprotein, HDL = high-density lipoprotein, SD = standard deviation.

Effects of Simvastatin on Triglycerides and Triglyceride-Rich Lipoproteins

Compared with placebo, TG levels were reduced significantly by simvastatin 20 ($p < 0.05$), 40 ($p < 0.001$), and 80 mg ($p < 0.001$; Table II, Fig. 1). A subgroup analysis of TG by TG

TABLE II Baseline, Week 6, and median % change from baseline values for triglyceride-related lipoproteins and apolipoproteins

Lipid parameter	Treatment group	n	Median (mg/dl)		Median % change (SD)	p Value ^a
			Baseline (SD)	Week 6 (SD)		
TG	Placebo	49	401 (188)	373 (193)	−10.1 (38.9)	
	S 20 mg	47	424 (212)	299 (180)	−19.6 (21.0)	0.021
	S 40 mg	46	387 (206)	297 (143)	−23.7 (23.9)	< 0.001
	S 80 mg	47	423 (201)	291 (181)	−30.8 (25.4)	< 0.001
VLDL-C	Placebo	49	77 (38)	71 (32)	−5.2 (48.1)	
	S 20 mg	47	77 (48)	59 (30)	−29.1 (27.1)	< 0.001
	S 40 mg	46	75 (41)	54 (27)	−34.9 (24.9)	< 0.001
	S 80 mg	47	88 (45)	45 (34)	−41.9 (21.0)	< 0.001
VLDL-TG	Placebo	46	287 (140)	279 (173)	0.5 (41.6)	
	S 20 mg	42	312 (161)	227 (157)	−19.6 (34.5)	0.045
	S 40 mg	44	307 (195)	218 (124)	−25.7 (42.1)	0.004
	S 80 mg	45	310 (221)	213 (158)	−31.0 (34.9)	< 0.001
VLDL-apo B	Placebo	47	22 (15)	23 (10)	13.0 (85.6)	
	S 20 mg	39	23 (14)	20 (8)	−12.5 (52.8)	0.013
	S 40 mg	39	24 (11)	19 (11)	−28.2 (49.0)	0.003
	S 80 mg	40	27 (15)	18 (9)	−24.4 (39.9)	0.001

^a Active treatment versus placebo.

Abbreviations: TG = triglyceride, VLDL-C = very low-density lipoprotein cholesterol, apo = apolipoprotein, S = simvastatin, SD = standard deviation.

FIG. 1 Median $\pm$ standard error (SE) % change from baseline in triglycerides (TG) and TG-related lipoproteins and apolipoproteins (Apo). Patients received the indicated treatment once daily for 6 weeks. Asterisks indicate a significant difference between active treatment and placebo (* $p < 0.05$; ** $p < 0.001$). VLDL = very low-density lipoprotein. $\square$ = Placebo, $\boxtimes$ = simvastatin 20 mg, $\blacksquare$ = simvastatin 40 mg, $\boxdot$ = simvastatin 80 mg.

stratum (≤ 450 or > 450 mg/dl) demonstrated that the median percent changes in patients with baseline TG values ≤ 450 mg/dl were -8.3 , -18.0 , -19.6 , and -28.8% for the placebo and simvastatin 20, 40, and 80 mg treatment groups, respectively. For patients with baseline TG > 450 mg/dl, the corresponding changes were -12.7 , -32.5 , -35.9 , and -33.0% , respectively. The treatment-by-TG stratum interaction was significant ($p = 0.031$).

The effects of treatment on VLDL-C, VLDL-TG, and VLDL-apo B are shown in Table II and Figure 1. The levels of all VLDL components were significantly reduced by simvastatin treatment compared with placebo ($p < 0.05$ – < 0.001).

Effects of Simvastatin on Cholesterol-Rich Lipoproteins

Baseline, Week 6, and mean percent change from baseline values for LDL-C, LDL-TG, LDL-apo B, total apo B, and non-HDL-C are given in Table III. Total cholesterol values are shown for comparison. For all parameters except LDL-apo B, treatment with any dose of simvastatin produced significant ($p < 0.001$) reductions compared with placebo. Levels of

TABLE III Baseline, Week 6, and mean % change from baseline values for cholesterol-rich apo B-containing lipoproteins and apolipoproteins

Lipid parameter	Treatment group	n	Mean mg/dl		Mean % change (SD)	p Value ^a
			Baseline (SD)	Week 6 (SD)		
Total-C	Placebo	49	252 (40)	250 (72)	-1.2 (13.9)	
	S 20 mg	47	254 (57)	198 (47)	-21.5 (12.4)	< 0.001
	S 40 mg	46	244 (52)	180 (41)	-25.8 (10.1)	< 0.001
	S 80 mg	47	252 (47)	170 (35)	-32.5 (8.5)	< 0.001
LDL-C	Placebo	49	130 (35)	127 (37)	-0.8 (16.5)	
	S 20 mg	47	127 (35)	93 (28)	-25.0 (14.8)	< 0.001
	S 40 mg	46	116 (40)	82 (30)	-27.0 (17.1)	< 0.001
	S 80 mg	47	119 (36)	75 (25)	-35.4 (13.3)	< 0.001
LDL-TG ^b	Placebo	48	38 (27)	35 (27)	3.6 (73.9)	
	S 20 mg	45	38 (18)	27 (16)	-36.4 (46.3)	0.001
	S 40 mg	45	46 (26)	23 (20)	-35.3 (54.9)	< 0.001
	S 80 mg	43	40 (23)	17 (16)	-59.7 (46.9)	< 0.001
LDL-apo B	Placebo	48	130 (28)	128 (32)	-1.0 (15.2)	
	S 20 mg	45	124 (37)	99 (28)	-12.9 (45.1)	— ^c
	S 40 mg	45	115 (41)	86 (32)	-13.5 (66.7)	0.159
	S 80 mg	47	123 (36)	79 (27)	-32.9 (23.0)	0.001
Apo B	Placebo	48	160 (27)	157 (29)	-1.7 (9.3)	
	S 20 mg	46	160 (44)	122 (28)	-22.5 (13.8)	< 0.001
	S 40 mg	46	145 (33)	108 (28)	-24.9 (10.4)	< 0.001
	S 80 mg	46	153 (33)	102 (25)	-32.4 (11.2)	< 0.001
Non-HDL-C	Placebo	49	213 (39)	212 (73)	-1.9 (15.4)	
	S 20 mg	47	216 (54)	158 (44)	-26.4 (14.0)	< 0.001
	S 40 mg	46	207 (50)	140 (41)	-32.3 (12.2)	< 0.001
	S 80 mg	47	217 (48)	130 (36)	-40.0 (10.2)	< 0.001

^a Active treatment versus placebo.

^b LDL-TG values are medians.

^c Test not performed because of nonsignificant result at previous higher dose.

Abbreviations as in Tables I and II.

TABLE IV Baseline, Week 6, and mean % change from baseline values for high-density lipoprotein-related lipoproteins and apolipoproteins

Lipid parameter	Treatment group	n	Mean mg/dl		Mean % change (SD)	p Value ^a
			Baseline (SD)	Week 6 (SD)		
HDL-C	Placebo	49	38 (8)	39 (9)	1.1 (8.5)	
	S 20 mg	47	38 (10)	41 (10)	7.3 (15.0)	0.005
	S 40 mg	46	37 (10)	40 (11)	9.3 (10.1)	<0.001
	S 80 mg	47	35 (7)	39 (8)	11.4 (9.8)	<0.001
Apo A-I	Placebo	48	142 (28)	143 (27)	0.6 (8.8)	
	S 20 mg	46	143 (31)	147 (31)	3.2 (10.2)	— ^b
	S 40 mg	46	139 (32)	144 (29)	4.2 (10.0)	0.064
	S 80 mg	46	137 (22)	143 (21)	4.4 (9.2)	0.041
HDL-TG	Placebo	49	51 (16)	54 (18)	11.6 (44.3)	
	S 20 mg	47	48 (15)	52 (20)	12.2 (36.1)	— ^b
	S 40 mg	46	49 (16)	48 (16)	4.3 (39.0)	— ^b
	S 80 mg	47	51 (13)	47 (14)	−2.5 (34.0)	0.053
Lp A-I	Placebo	48	46 (11)	46 (12)	3.8 (18.6)	
	S 20 mg	44	45 (9)	45 (11)	−0.8 (18.0)	— ^b
	S 40 mg	46	46 (15)	47 (16)	2.4 (17.5)	— ^b
	S 80 mg	46	45 (8)	45 (10)	0.3 (15.7)	0.544
Lp A-I:A-II	Placebo	48	97 (20)	96 (20)	−0.3 (11.2)	
	S 20 mg	44	98 (24)	103 (27)	5.1 (15.7)	0.083
	S 40 mg	46	93 (20)	97 (18)	6.1 (17.5)	0.030
	S 80 mg	46	92 (19)	98 (18)	7.2 (14.3)	0.013

^a Active treatment versus placebo.

^b Test not performed because of nonsignificant result at previous higher dose.

Abbreviation: Lp = lipoprotein. Other abbreviations as in Tables I and II.

LDL-apo B were also reduced significantly ($p = 0.001$) by simvastatin 80 mg, but not by 40 or 20 mg.

Effects of Simvastatin on High-Density Lipoprotein and Apolipoprotein A-I-Containing Lipoproteins

The effects of simvastatin on HDL-related particles are summarized in Table IV. The HDL-C levels were significantly increased by all doses of simvastatin compared with placebo, and significant increases by one or more doses of simvastatin were observed for apo A-I and Lp A-I:A-II. Simvastatin had no effect on Lp A-I particles.

Effects of Simvastatin in Type IV Hyperlipidemic Patients

The Type IV subgroup was similar to the study cohort in terms of age (mean age 51 years), gender (79% male), and race (91% white). Relative to the study cohort, the Type IV patients had slightly higher baseline levels of TG (459 ± 204 mg/dl) and similar or slightly lower baseline levels of total-C (233 ± 42 mg/dl), LDL-C (100 ± 23 mg/dl), HDL-C (35 ± 7 mg/dl), and non-HDL-C (198 ± 42). The effects of simvastatin on TG, LDL-C, and HDL-C levels in the Type IV hyperlipidemic subgroup were similar to those observed for the whole study cohort (Fig. 2). Comparable treatment effects between

FIG. 2 Effect of simvastatin on selected lipids/lipoproteins in a subgroup ($n = 116$) of patients with Type IV hyperlipidemia (TG 300–900 mg/dl; LDL-C < 130 mg/dl) compared with the whole study cohort. Patients received the indicated treatment once daily for 6 weeks. Asterisks indicate a significant difference between active treatment and placebo (* $p < 0.05$; ** $p < 0.001$). TG = triglycerides, LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, SE = standard error. Column shading as in Figure 1. ^a Triglyceride levels are medians.

the two study populations also were observed for total-C, VLDL-C, apo B, and apo A-I (data not shown).

Safety

No significant differences were observed between the treatment groups in the incidence of clinical adverse experiences considered by the investigator to be possibly, probably, or definitely drug related (2/50, 1/49, 3/48, and 3/48 patients in the placebo and simvastatin 20, 40, and 80 mg treatment groups, respectively). There were no serious drug-related adverse experiences or discontinuations because of a drug-related adverse experience. No patient experienced elevation of alanine aminotransferase and/or aspartate aminotransferase $> 3 \times \text{ULN}$, and there were no cases of myopathy or elevation of creatine kinase $> 10 \times \text{ULN}$.

Discussion

Hypertriglyceridemia is associated with increased risk of atherosclerosis. In addition to elevated TG, hypertriglyceridemic patients may have normal LDL-C (familial hypertriglyceridemia; Type IV) or elevated LDL-C plasma levels (familial combined hyperlipidemia; Type IIb) and often have other known CHD risk factors such as low HDL-C, type II diabetes, or obesity.¹⁹

In a previously reported study, simvastatin was shown to modify beneficially the lipid/lipoprotein profile of patients with elevated cholesterol and triglyceride levels: mixed (Type IIb) hyperlipidemia.²⁰ The current study demonstrates similar benefits in a cohort with predominant hypertriglyceridemia.

All patients in the present study had elevated TG levels (300–900 mg/dl) and were classified as having either Type IV (60%) or combined (40%) hyperlipidemia. This study is one of the largest, most rigorously controlled evaluations of the efficacy of an HMG-CoA reductase inhibitor in patients with hypertriglyceridemia ever reported. In one other published study evaluating a statin in this patient population, treatment with atorvastatin resulted in reductions in TG, LDL-C, and apo B.²¹ The study was limited by a small sample size (approximately 15 patients/group), but suggested that HMG-CoA reductase inhibitors could provide an effective treatment for this type of patient.

Simvastatin was effective in lowering TG levels across the dosage range, and although this study was not powered to assess dose–response relationships, greater reductions in TG levels were observed with increasing doses of simvastatin. Previous data suggested that patients with higher baseline TG levels achieve larger TG reductions with statins.²² This effect was observed in the present study; however, the differences between the TG strata, although significant, were primarily present at the 20 and 40 mg doses. The small numbers of patients in each treatment group per stratum and the variability of these data make them difficult to interpret with certainty. Consistent with the effects on triglycerides, VLDL, the main triglyceride carrying lipoprotein in the fasting state, and all of

its components were reduced by simvastatin. The decreases in VLDL-apo B suggest a reduction in the number of circulating VLDL particles.

Simvastatin produced large, significant reductions in LDL-C and other LDL components across the dosage range; however, the LDL-C and apo B reductions seen were somewhat smaller than those seen in patients with normal triglyceride levels.²³ This has been seen previously in hypertriglyceridemic patients treated with statins^{20,21} and may reflect competition for LDL receptors by TG-rich lipoproteins.

Simvastatin also produced significant reductions in non-HDL-C. Non-HDL-C represents a measure of the cholesterol in apo-B-containing lipoproteins including LDL, VLDL, and IDL. It is considered by some to be a better estimate of CHD risk than LDL-C, particularly in patients with hypertriglyceridemia,²⁴ and was identified as a secondary target of therapy for patients with TG levels ≥ 200 mg/dl in the recently released NCEP ATP III guidelines.¹² In addition, since LDL-C levels cannot be accurately assessed using the Friedewald equation in patients with TG levels > 400 mg/dl, non-HDL-C provides physicians with a measurable marker in these patients which can be targeted for lipid-altering therapy.

The relatively low baseline HDL-C levels of patients in this study (mean = 37.2 mg/dl) are typical of patients with hypertriglyceridemia and represent another target of therapy in these patients. Simvastatin produced significant increases in HDL-C across all doses. Apo A-I was also increased, but to a lesser extent and with no evidence of a dose–response relationship. The levels of LpA-I:A-II but not LpA-I were increased in the simvastatin groups, indicating that the simvastatin effect on apo A-I was due to an increased number of particles containing both apo A-I and apo A-II. Similar effects of simvastatin 40 and 80 mg on HDL-C and apo A-I have been observed in patients with hypercholesterolemia^{25,26} and mixed hyperlipidemia.²⁰ In the latter study, however, increases in apo A-I by simvastatin were associated with comparable increases in both Lp A-I and LpA-I:A-II.²⁰

Conclusion

The consensus statement from a recent symposium on the role of statins in patients with hypertriglyceridemia included the recommendation that statins be used as a first-line treatment for moderate hypertriglyceridemia (200–500 mg/dl).²⁷ The present study is the first large, placebo-controlled, clinical trial in hypertriglyceridemic patients showing that simvastatin 20, 40, and 80 mg daily is well tolerated and produces significant beneficial modifications of a wide variety of lipids, lipoproteins, and apolipoproteins.

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