Effects of Simvastatin on Blood Pressure in Hypercholesterolemic Patients: An Open-Label Study in Patients with Hypertension or Normotension

Adriana Branchi, MD,¹ Anna Maria Fiorenza, MD,² Adriana Torri, MD,² Cristina Berra, MD,² Emanuela Colombo, MD,² Angelo Rovellini, MD,¹ and Domenico Sommariva, MD²

¹Department of Internal Medicine, University of Milan, Maggiore Hospital IRCCS, Milan, Italy, and ²Department of Internal Medicine 1, G. Salvini Hospital, Garbagnate Milanese, Milan, Italy

ABSTRACT

Background: Simvastatin has been reported to improve endothelium-dependent vascular relaxation in patients with hypercholesterolemia. The consequent decrease in arterial stiffness might be associated with a decrease in blood pressure (BP).

Objective: The aim of this study was to determine whether simvastatin 20 and 40 mg/d have an effect on systolic and diastolic blood pressure (SBP and DBP, respectively) in patients with hypercholesterolemia, and, if so, whether the effect is dose dependent and/or is related to the changes in the serum lipid profile.

Methods: This 6-month, open-label study was conducted at the Lipid Clinics of the Department of Internal Medicine, University of Milan, Maggiore Hospital IRCCS, and of the Department of Internal Medicine 1, G. Salvini Hospital, Garbagnate Milanese (Milan, Italy). Patients aged 18 to 80 years with primary hypercholesterolemia who were following a low-fat, low-cholesterol diet for >2 months before the study were enrolled. Patients at high risk for cardiovascular disease (CVD), according to the National Cholesterol Education Program Adult Treatment Panel II guidelines, were given simvastatin 20 mg (tablet) QD for 3 months, and those at low risk for CVD continued with diet only for 3 months (controls). Efficacy variables included body weight, SBP, DBP, and serum lipid levels (total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglycerides [TG]). At 3 months, patients in the simvastatin + diet group who reached their therapeutic goal continued to receive simvastatin 20 mg/d for 3 additional months. In simvastatin-treated patients who were normotensive at baseline or who became normotensive at 3 months but who did not reach the therapeutic goal, the simvastatin

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dosage was increased to 40 mg/d. Patients in both groups who remained hypertensive at 3 months were switched to hypotensive therapy. In the diet-only group, patients who were formerly normotensive or who became normotensive at 3 months but who did not reach their therapeutic goal continued with diet only or started lipid-lowering therapy. All other patients in the diet-only group continued to be treated with diet only, for 3 additional months. Efficacy variables were measured again at 6 months. Tolerability of simvastatin was assessed at each visit using patient interview and measurement of serum aminotransferase and creatine phosphokinase levels.

Results: The study population comprised 222 patients (132 women, 90 men; mean [SEM] age, 53.9 [0.95] years [range, 23–76 years]); 115 high-risk patients (57 with untreated stage 1 hypertension) were assigned to the simvastatin + diet group, and 107 low-risk patients (29 with untreated stage 1 hypertension) were assigned to the diet-only group. In the simvastatin group, after 3 months of therapy, mean SBP was decreased by 3.9 (1.49) mm Hg (change, –2.9%), mean DBP decreased by 3.0 (0.87) mm Hg (change, –3.7%), mean TC decreased by 90.6 (3.98) mg/dL (change, –27.0%), mean LDL-C decreased by 88.9 (3.88) mg/dL (change, –35.6%), and mean TG decreased by 26.3 (7.34) mg/dL (change, –15.8%) (all, $P < 0.001$). Mean HDL-C increased by 3.6 (1.16) mg/dL (change, 6.9%; $P < 0.001$). The BP-lowering effect was found only in patients with hypertension at baseline ($n = 57$); in these patients, mean SBP decreased by 7.2 (2.44) mm Hg (change, –4.8%; $P < 0.005$ vs baseline) and DBP decreased by 4.8 (1.29) mm Hg (change, –5.6%; $P < 0.001$ vs baseline). Also in the simvastatin group, 26 patients (22.6%) achieved their target SBP/DBP. In patients with normotension at baseline ($n = 58$), neither SBP nor DBP was changed significantly (changes, –0.8 [1.65] and –1.4 [1.15] mm Hg, respectively [–0.6% and –1.8%, respectively]). The changes in serum lipid levels were similar between hypertensive and normotensive patients in the simvastatin group. Forty-one patients (18 hypertensive and 23 normotensive at baseline) were treated with simvastatin 40 mg/d plus diet between months 3 and 6. At 6 months, no further significant decrease was observed in mean BP. In contrast, the expected dose-dependent response was observed for TC and LDL-C levels. In the diet-only group, no significant changes occurred in BP or serum lipid levels. Changes in BP, TC, LDL-C, TG, and HDL-C were significantly greater in the simvastatin + diet group than in the diet-only group (all, $P < 0.001$). Body weight did not change significantly in either group.

Conclusions: In this group of patients with hypercholesterolemia, the starting dosage of simvastatin (20 mg/d) was associated with reductions in SBP and DBP within 3 months of treatment in patients with hypertension, and this effect was independent of the lipid-lowering properties of the drug. Although the decrease in BP was modest, it is likely clinically relevant. Further studies on this topic are advisable. (*Curr Ther Res Clin Exp.* 2004;65:239–254) Copyright © 2004 Excerpta Medica, Inc.

Key words: blood pressure, hypercholesterolemia, simvastatin.

INTRODUCTION

Simvastatin has been shown to reduce cardiovascular morbidity and mortality in patients with hypercholesterolemia (serum cholesterol >135 mg/dL).^{1,2} This effect is probably due to the drug's ability to decrease atherogenic lipid levels and to increase high-density lipoprotein cholesterol (HDL-C) levels. However, simvastatin has additional effects that may play a role in reducing the risk for cardiovascular disease (CVD), including improving endothelial function, which is typically altered in patients with hypercholesterolemia.³⁻⁵ Improvement in endothelium-dependent vascular relaxation may decrease vascular tone and arterial stiffness, and as a consequence, may increase arterial distensibility and compliance.³ The final effect might be a decrease in arterial pressure. A decrease in diastolic blood pressure (DBP) after treatment with simvastatin 20 mg/d was reported in a study of hypertensive patients with type 2 diabetes mellitus (DM),⁶ but not in other studies in patients with hypercholesterolemia and without hypertension treated with simvastatin 10 to 20 mg/d.^{4,7,8}

The aim of the present study was to determine whether simvastatin 20 and 40 mg/d have an effect on systolic blood pressure (SBP) and DBP in patients with hypercholesterolemia, and if so, whether the effect is dose dependent and is related to the changes in the serum lipid profile.

PATIENTS AND METHODS

Study Design

This 6-month, open-label study was conducted at the Lipid Clinics of the Department of Internal Medicine, University of Milan, Maggiore Hospital IRCCS, and of the Department of Internal Medicine 1, G. Salvini Hospital, Garbagnate Milanese (Milan, Italy). The study was conducted according to the guidelines of the Declaration of Helsinki, and the study protocol was approved by the local ethics committee.

Patients

The study population included male and female outpatients aged 18 to 80 years with primary hypercholesterolemia, some of whom had stage 1 hypertension (SBP $\geq$ 140 mm Hg and/or DBP $\geq$ 90 mm Hg).⁹ Exclusion criteria were hypertension requiring therapy,⁹ treatment with hypotensive drugs, hepatic and renal dysfunction, uncontrolled hypothyroidism, type 1 DM, and uncontrolled type 2 DM. Pregnant, possibly pregnant, or breastfeeding women were excluded from the study. Women of childbearing age were required to use an effective method of birth control throughout the study. All eligible patients provided verbal informed consent to participate.

Methods

Treatment

All patients had been following a low-fat (fat 25% of daily energy intake: saturated fatty acids, 8%; monounsaturated fat, 15%; and polyunsaturated fat, 2%),

low-cholesterol (<300 mg/d) diet for >2 months before entering the study. They were instructed to keep their diet and physical activity constant throughout the study. For each patient, the absolute CVD risk profile was assessed according to the guidelines of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) II.¹⁰ Patients at high risk for CVD were assigned to therapy with simvastatin 20 mg (tablet) QD after the evening meal, and patients at low risk for CVD continued with diet only (controls). Randomization was not used because it was considered unethical to delay drug therapy for hypercholesterolemia in patients at high risk for CVD. Delaying hypotensive drug therapy in patients with stage 1 hypertension was considered safe and in line with the suggestions of the World Health Organization (WHO).⁹

A subanalysis of each study group was performed, with patients subclassified into 2 groups: patients with stage 1 hypertension and normotensive patients (SBP <140 mm Hg and DBP <90 mm Hg). At 3 months, patients in the simvastatin + diet group who reached their therapeutic goal according to the ATP II guidelines¹⁰ continued to receive simvastatin 20 mg/d for 3 additional months. In patients who were formerly normotensive or who became normotensive but who did not reach their therapeutic goal, the dosage was increased to 40 mg QD after the evening meal, given for 3 months. Patients in both groups who remained hypertensive at 3 months were switched to hypotensive therapy according to the WHO guidelines.⁹ In the diet-only group, patients who were formerly normotensive or who became normotensive at 3 months but who did not reach their therapeutic goal continued with diet only or started lipid-lowering therapy, as recommended in the new guidelines in the NCEP ATP III,¹¹ which were published while our study was in progress. All other patients in the diet-only group continued to be treated with diet only, for 3 additional months.

Efficacy Analysis

At each visit (months 0 [baseline], 3, and 6), blood pressure (BP) was measured in the sitting position after a 15-minute rest, using a mercury sphygmomanometer, by the same observer and in the same patient arm. The observer was blinded to the serum lipid levels and the treatment group of the patient. SBP/DBP was obtained at Korotkoff's phases I and V. Blood samples were collected 2 days before each visit by a nurse, on the morning after an overnight fast, and immediately centrifuged at 3000 rpm for 10 minutes at 4°C. Analytical determinations were performed after 3 hours by laboratory technicians. Serum HDL-C level was determined using the HDL-C Olympus System (Olympus Diagnostica GmbH, Clare, Ireland). Serum total cholesterol (TC) level was measured using the cholesterol oxidase-peroxidase-4-aminophenazone (CHOD-PAP) method,¹² and serum triglyceride (TG) level, using the glycerophosphate oxidase-peroxidase-4-aminophenazone (GPO-PAP) method¹³ (Olympus Diagnostica GmbH). Measurements of serum lipid levels were performed using the Olympus AU 560 autoanalyzer (Olympus Optical Co., Sizuoka, Japan). The accuracy of lipid determination was assessed according to the Intra- and Inter-laboratory

Quality Control Program UNITY (Bio-Rad Laboratories Srl, Segrate, Italy). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula.¹⁴

Tolerability Analysis

Tolerability of simvastatin was assessed at each visit using patient interview and measurement of serum aminotransferases and creatine phosphokinase (CPK) levels.

Statistical Analysis

Data are presented as mean (SEM). Potential treatment effects on BP and on serum lipid levels were analyzed using the Student *t* test for paired data and repeated-measures analysis of variance (ANOVA). The Tukey test was used to compare any 2 means between which the ANOVA test detected a statistically significant difference. Comparisons of data between groups were analyzed using the Student *t* test for unpaired data and the chi-square test in the case of discrete variables. To avoid the effect of regression toward the mean, analysis of covariance (ANCOVA) was used when appropriate. Single regression analysis was used to assess the relationship between serum lipid levels and BP and their changes. Multiple regression analysis was used to determine the independent variables able to predict BP changes during the study. The 2-tailed significance threshold was set at $P < 0.05$. All statistical analyses were performed using SPSS software version 10.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Study Population

The study comprised 222 patients (132 women, 90 men; mean [SEM] age, 53.9 [0.95] years [range, 23–76 years]). The 115 patients (73 women, 42 men) who were at high risk for CVD (57 [49.6%] with untreated stage 1 hypertension) were assigned to the simvastatin + diet group, and the 107 patients (59 women, 48 men) who were at low risk for CVD (29 [27.1%] with untreated stage 1 hypertension) were assigned to the diet-only group (**Figure 1**). The baseline demographic and clinical characteristics of the study patients are shown in **Table 1**.

Efficacy

After 3 months, 31 patients (27.0%) in the simvastatin + diet group and 23 patients (21.5%) in the diet-only group were still hypertensive and were therefore started on therapy with hypotensive drugs. Forty-one patients (35.7%) in the simvastatin + diet group (18 hypertensive at baseline and 23 normotensive at baseline) were normotensive at 3 months but did not reach their therapeutic goal¹² and thus had their simvastatin dosage increased to 40 mg/d. Six patients

Figure 1. Study design. *Stage 1 hypertension = SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg. $^{\dagger}P < 0.001$ versus diet-only group. AEs = adverse events.

(5.6%) in the diet-only group did not continue the protocol after the 3-month study visit because they were started on lipid-lowering therapy.

Six patients (5.2%) in the simvastatin + diet group and 29 patients (27.1%) in the diet-only group were lost to follow-up after the first 3-month treatment period (χ^2 , 21.683; $P < 0.001$). This difference may have been due to poor motivation to continue the study with diet only in low-risk patients. All patients who started the study completed the first 3-month period and were included in the 3-month statistical analysis. The patients who withdrew after the first 3-month period were not included in the final, 6-month analysis. Using the last-observation-carried-forward method to analyze the withdrawals was ruled out because that method is based on the debatable assumption that values under observation are relatively stable throughout the study.

At baseline, hypertension was significantly more prevalent in simvastatin-treated patients than in patients treated with diet only (57 patients [49.6%] vs

Table I. Baseline demographic and clinical characteristics of study patients (N = 222). (Values are expressed as mean [SEM] unless otherwise noted.)

Characteristic	Value
Demographic	
Age, y	
Mean (SEM)	53.9 (0.95)
Range	23–76
Sex, no. (%)	
Women	132 (59.5)
Men	90 (40.5)
Race, no. (%)	
White	222 (100.0)
Clinical	
BMI, kg/m ²	26.3 (0.32)
SBP, mm Hg	131.6 (1.12)
DBP, mm Hg	81.8 (0.55)
Serum lipid levels, mg/dL	
TC	292.6 (4.28)
LDL-C	209.3 (4.28)
HDL-C	51.3 (1.00)
TG	160.7 (5.38)
Clinical diagnoses, no. (%)	
Stage 1 hypertension*	86 (38.7)
Obesity (BMI ≥30 kg/m ²)	29 (13.1)
Osteoarthritis	8 (3.6)
Peripheral arterial disease	4 (1.8)
Asthma	3 (1.4)
Atrial fibrillation	3 (1.4)
Internal carotid artery disease	3 (1.4)
Type 2 diabetes mellitus	3 (1.4)
Chronic venous insufficiency	2 (0.9)
Gallstones	2 (0.9)
Transient ischemic attacks	2 (0.9)
Aortic stenosis	1 (0.5)
Migraine	1 (0.5)
Mitral regurgitation	1 (0.5)
Concomitant medications	
Aspirin	10 (4.5)
NSAIDs	5 (2.3)
Inhaled beta ₂ -agonists	3 (1.4)
Glyburide	2 (0.9)
Propafenone	1 (0.5)
Digoxin	1 (0.5)
Warfarin	1 (0.5)

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; NSAIDs = nonsteroidal anti-inflammatory drugs.

*Stage 1 hypertension = SBP ≥140 mm Hg and/or DBP ≥90 mm Hg.⁹

29 patients [27.1%]; χ^2 , 11.386; $P < 0.001$), resulting in a significantly higher initial mean SBP in the simvastatin + diet group than in the diet-only group ($P < 0.001$). Patients in the diet-only group had significantly lower mean serum TC and LDL-C levels (both, $P < 0.001$) and a significantly higher mean body weight ($P < 0.05$) than patients in the simvastatin + diet group (**Table II**). After 3 months of treatment with simvastatin 20 mg/d, mean SBP and DBP decreased significantly (by 3.9 [1.49] mm Hg [change, -2.9%] and 3.0 [0.87] mm Hg [change, -3.7%], respectively; both, $P < 0.001$). The changes in mean SBP and DBP were significantly greater in the simvastatin + diet group than in the diet-only group ($P < 0.005$ and $P < 0.02$, respectively); mean BP did not change significantly in the diet-only group (SBP, 1.6 [1.22] mm Hg; DBP, -0.3 [0.19] mm Hg). To rule out the possibility that the changes in BP were an artifact due to regression to the mean, data were analyzed taking into account baseline values. ANCOVA confirmed that the changes in SBP ($F = 40.08$; $P < 0.01$) and DBP ($F = 34.83$; $P < 0.01$) were greater in the simvastatin + diet group than in the diet-only group.

In simvastatin-treated patients, mean serum TC level decreased by 90.6 [3.98] mg/dL (change, -27.0%), LDL-C by 88.9 [3.88] mg/dL (change, -35.6%), and TG by 26.3 [7.34] mg/dL (change, -15.8%) (all, $P < 0.001$). Mean serum HDL-C level increased by 3.6 [1.16] mg/dL (change, 6.9%; $P < 0.001$). As expected, because the patients were already following the prescribed diet at the beginning of the study, no significant changes in serum lipid levels occurred in patients in the diet-only group (Table II).

The decrease in SBP and DBP after simvastatin therapy correlated significantly with baseline values ($r = 0.47$ and 0.56 , respectively; both, $P < 0.001$), suggesting that the BP-lowering effect of the drug was greater in patients with higher BP than in patients with lower BP. In the simvastatin + diet group, 57 patients (49.6%) were hypertensive (mean [SEM] SBP, 150.1 [1.85] mm Hg; mean [SEM] DBP, 86.2 [1.14] mm Hg) and 58 (50.4%) patients were normotensive (mean [SEM] SBP, 123.2 [1.06] mm Hg; mean [SEM] DBP, 77.3 [0.73] mm Hg). In the diet-only group, 29 patients (27.1%) were hypertensive (mean [SEM] SBP, 144.5 [1.67] mm Hg; mean [SEM] DBP, 89.9 [1.56] mm Hg), and 78 (72.9%) patients were normotensive (mean [SEM] SBP, 119.6 [0.89] mm Hg; mean [SEM] DBP, 78.9 [0.58] mm Hg). Baseline mean SBP was significantly higher in both hypertensive and normotensive patients of the simvastatin + diet group than in hypertensive and normotensive patients of the diet-only group ($P < 0.05$ and $P < 0.01$, respectively). Baseline mean DBPs in hypertensive and normotensive patients in the 2 groups were not significantly different. Mean baseline serum lipid levels and body weight in hypertensive and normotensive patients in the 2 groups were similar. Significant decreases in mean SBP (7.2 [2.44] mm Hg [change, -4.8%]; $P < 0.005$ vs baseline) and DBP (4.8 [1.29] mm Hg [change, -5.6%]; $P < 0.001$ vs baseline) occurred in hypertensive patients treated with simvastatin + diet but not in hypertensive patients treated with diet alone (changes, -0.5 [2.42] and -1.5 [1.51] mm Hg, respectively [-0.3% and -1.7%, respectively]) or in normotensive patients in both groups (**Figure 2**).

Table II. Clinical characteristics of patients before (baseline) and after 3 months of treatment with simvastatin 20 mg/d + diet or diet only (N = 222). (Values are expressed as mean [SEM].)

Characteristic	Simvastatin + Diet Group (n = 115)			Diet-Only Group (n = 107)		
	Baseline	3 Months	Change	Baseline	3 Months	Change
Body weight, kg	65.7 (1.06)	66.2 (1.05)	0.5 (0.21)	70.1 (1.15)*	69.8 (1.14)	-0.3 (0.19)
SBP, mm Hg	136.5 (1.65)	132.6 (1.62) [†]	-3.9 (1.49) [‡]	126.3 (1.34) [§]	127.9 (1.58)	1.6 (1.22)
DBP, mm Hg	81.7 (0.79)	78.7 (0.78)	-3.0 (0.87)	81.9 (0.76)	81.6 (0.81)	-0.3 (0.78)
Serum lipid levels, mg/dL						
TC	335.0 (4.88)	244.4 (3.92)	-90.6 (3.98) [#]	247.1 (3.69) [§]	247.2 (3.60)	0.1 (2.85)
LDL-C	249.6 (5.34)	160.7 (4.06)	-88.9 (3.88) [#]	165.8 (3.45) [§]	166.5 (3.31)	0.7 (2.75)
HDL-C	52.1 (1.42)	55.7 (1.33)	3.6 (1.16)	48.8 (2.53)	48.0 (1.93)	-0.8 (0.94)
TG	166.3 (7.34)	140.0 (6.98)	-26.3 (7.34) [‡]	154.6 (7.90)	152.7 (7.80)	-1.9 (6.97)

SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides.

* $P < 0.05$ versus simvastatin + diet group.

[†] $P < 0.005$ versus baseline.

[‡] $P < 0.005$ versus diet-only group ($P < 0.01$ by analysis of covariance [ANCOVA]).

[§] $P < 0.001$ versus simvastatin + diet group.

^{||} $P < 0.001$ versus baseline.

[#] $P < 0.02$ versus diet-only group ($P < 0.01$ by ANCOVA).

^{||} $P < 0.001$ versus diet-only group ($P < 0.001$ by ANCOVA).

Figure 2. Mean (SEM) (A) baseline values and (B) changes at 3 months in systolic and diastolic blood pressure (BP) (SBP and DBP, respectively) in patients treated with simvastatin + diet or diet only (control). Mean (SEM) (C) baseline and (D) changes at 3 months in body weight (BW) and serum levels of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) in study patients. * $P < 0.001$ versus normotensive patients in the same group; $^{\dagger}P < 0.05$ versus hypertensive patients in the diet-only group; $^{\ddagger}P < 0.01$ versus normotensive patients in the diet-only group; $^{\S}P < 0.01$ versus normotensive patients in the simvastatin + diet group (ANCOVA). $^{\parallel}P < 0.05$ versus normotensive patients in the simvastatin + diet group (ANCOVA).

ANCOVA with baseline BP value as a covariate showed that the decreases in mean SBP ($F = 9.83$; $P < 0.01$) and DBP ($F = 3.90$; $P < 0.05$) were significantly greater in hypertensive than in normotensive patients in the simvastatin + diet group. Twenty-six of 57 hypertensive patients (45.6%) in the simvastatin + diet group achieved SBP/DBP $<140/<90$ mm Hg at the end of 3 months of therapy. No relationship was found between the decrease in BP and the changes in body weight and serum lipid levels. Multiple regression analysis with the change in SBP or DBP as the dependent variable showed that only baseline SBP and DBP contributed independently to changes in SBP and DBP (partial F , 32.837 and 51.826; both, $P < 0.001$). In the diet-only group, 6 of the 29 initially hypertensive patients (20.7%) achieved an SBP/DBP $<140/<90$ mm Hg at the end of 3 months. The number of patients who became normotensive in the simvastatin + diet group was significantly greater than that in the diet-only group (χ^2 , 4.10; $P < 0.05$).

Forty one normotensive patients had their daily dosage of simvastatin increased to 40 mg/d. The group included 18 patients (43.9%) who were hypertensive at the beginning of the study and were normotensive after 3 months of treatment with simvastatin 20 mg/d. After 3 months of treatment with simvastatin 40 mg/d, mean SBP (-7.7 [2.31] mm Hg [change, -5.8% ; $P < 0.01$) and DBP (-3.3 [1.32] mm Hg [change, -4.1% ; $P < 0.05$) were significantly lower than at baseline but not significantly different from values recorded after treatment with simvastatin 20 mg/d (**Table III**). In contrast, the decreases in serum TC and LDL-C levels were significantly greater after 3 months of treatment with simvastatin 40 mg/d than after 3 months of treatment with simvastatin 20 mg/d (both, $P < 0.01$). At both dosages of simvastatin, serum TG level was significantly lower than at baseline ($P < 0.01$), and HDL-C was significantly higher ($P < 0.01$). No significant change in BP or in serum lipid levels was observed in the 49 normotensive patients in the diet-only group followed up for 6 months.

Tolerability

All of the patients were included in the tolerability analysis. In the simvastatin + diet group, based on laboratory analysis, 3 patients (2.6%) had a transient elevation of serum CPK activity <3 times the upper limit of normal (ULN), and 1 (0.9%) had an elevation of serum alanine aminotransferase activity $<2 \times$ ULN. Also in this group, based on patient interview, 1 patient (0.9%) reported mild, transient nausea; 1 (0.9%) mild, transient diarrhea; and 1 (0.9%) mild insomnia. All of the adverse effects occurred during the first 3 months of therapy with simvastatin 20 mg/d and resolved within a few days, without requiring discontinuation of therapy. One patient (0.9%) reported mild myalgia but did not have elevated serum CPK activity after 4 months of therapy (during treatment with simvastatin 40 mg/d), and discontinued treatment. All of the adverse effects were considered drug related. One patient (0.9%) in the diet-only group had a transitory elevation of serum CPK activity $<3 \times$ ULN.

Table III. Clinical characteristics of patients before (baseline) and during therapy with simvastatin 20 or 40 mg/d in patients who were normotensive after 3 months of treatment with simvastatin 20 mg/d + diet or after 6 months of treatment with diet only (n = 90). (Values are expressed as mean [SEM].)

Study Group/ Characteristic	Baseline	3 Months*	6 Months†
Simvastatin + diet group (n = 41)			
Body weight, kg	63.4 (2.22)	65.0 (1.67)	65.3 (1.71)
SBP, mm Hg	133.8 (2.86)	124.3 (1.84) [‡]	126.1 (2.23) [‡]
DBP, mm Hg	80.9 (1.37)	77.0 (1.12) [§]	77.6 (1.39) [§]
Serum lipid levels, mg/dL			
TC	351.6 (9.57)	271.0 (6.37) [‡]	246.8 (6.53) [‡]
LDL-C	270.6 (10.40)	191.5 (6.47) [‡]	168.4 (7.00) [‡]
HDL-C	44.5 (1.85)	50.1 (1.88) [‡]	49.7 (2.00) [‡]
TG	182.5 (13.59)	146.7 (12.51) [‡]	143.8 (12.31) [‡]
Diet-only group (n = 49)			
BW, kg	69.2 (1.39)	69.1 (1.36)	69.6 (1.42)
SBP, mm Hg	120.0 (1.01)	121.4 (1.33)	122.1 (1.46)
DBP, mm Hg	78.7 (0.71)	78.9 (0.90)	78.8 (0.84)
Serum lipid levels, mg/dL			
TC	243.5 (4.58)	241.4 (4.44)	247.3 (3.82)
LDL-C	159.4 (4.23)	160.2 (4.56)	164.5 (3.82)
HDL-C	52.1 (1.81)	51.3 (1.43)	51.2 (1.58)
TG	160.2 (10.62)	149.6 (10.51)	157.9 (11.23)

TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides.

*Treatment: simvastatin + diet group, simvastatin 20 mg/d + diet; diet-only group, diet only.

†Treatment: simvastatin + diet group, simvastatin 40 mg/d + diet; diet-only group, diet only.

[‡]P < 0.01 versus baseline (by analysis of variance [ANOVA] for repeated measurements; significant differences based on the Tukey test).

[§]P < 0.05 versus baseline (by ANOVA for repeated measurements; significant differences based on the Tukey test).

^{||}P < 0.01 versus 3 months (ie, simvastatin 20 mg) (by ANOVA for repeated measurements; significant differences based on the Tukey test).

DISCUSSION

In this series of hypercholesterolemic patients, simvastatin was associated with the expected effects on serum lipid levels. After 3 months of treatment with the initial 20-mg/d dosage of simvastatin, serum TC, LDL-C, and TG levels were decreased significantly and HDL-C level was increased significantly. A dose-dependent effect was seen for serum TC and LDL-C levels, but not for serum TG and HDL-C levels.

In addition to its well-known effect on serum lipid levels, simvastatin therapy has been associated with a BP-lowering effect. In patients treated with diet only, BP did not change. Baseline SBP, and serum TC and LDL-C levels differed between the 2 groups. This difference may be a limitation of the study. However,

no relationship was found between baseline serum TC and LDL-C levels and the changes in BP. Furthermore, the reduction in BP was independent of the changes in the serum lipid profile and, in particular, in the decrease in serum TC and LDL-C levels. Regarding the difference in baseline SBP between the simvastatin + diet and diet-only groups, ANCOVA confirmed the statistical significance of the decrease in SBP and DBP in simvastatin-treated patients. In the diet-only group, 6 patients who were hypertensive at the beginning of the study were found to be normotensive after the first 3 months. Spontaneous reduction in BP in hypertensive patients may suggest regression to the mean. The possibility that the reduction in BP in the simvastatin + diet group merely represented a statistical artifact due to regression to the mean can be ruled out on the basis of the earlier-mentioned statistical analysis. On the other hand, the number of hypertensive patients who became normotensive after 3 months was significantly greater in the simvastatin + diet group than in the diet-only group.

The effect of simvastatin, as well as other statins, on BP has not been systematically studied. Large primary and secondary intervention trials carried out with statins, including the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA) study¹⁵ of hypertensive patients, did not provide information on this topic. In a randomized, crossover study, Tonolo et al⁶ compared the effects of simvastatin 20 mg QD and cholestyramine 6 g TID on BP in 26 hypertensive patients with type 2 DM. They found that simvastatin, but not cholestyramine, was associated with a significant decrease in DBP. In contrast to our results, SBP was similar after 10 months of therapy. Serum LDL-C level similarly decreased during the 2 treatment periods, and no evidence of a relationship between the decrease in LDL-C and the decrease in DBP was found.

A decrease in BP has been reported in hypertensive patients treated with other statins. Fluvastatin has been shown to significantly decrease SBP and DBP in 49¹⁶ and 23¹⁷ hypertensive patients with hypercholesterolemia. In 25 patients with hypertension and primary hypercholesterolemia, Glorioso et al¹⁸ found that pravastatin 20 to 40 mg/d was associated with decreased SBP and DBP of 5%. The investigators did not find significant differences in decreases in BP between patients treated with 20 mg/d and patients treated with 40 mg/d of pravastatin. No relationship was found between the changes in BP and the changes in the serum lipid profile. In 22 patients with stage 1 isolated systolic hypertension, Ferrier et al¹⁹ found a significant decrease in SBP and DBP and a reduction of systemic arterial stiffness after atorvastatin therapy.

Statins, such as pravastatin 20 to 40 mg/d or simvastatin 10 to 40 mg/d²⁰ and lovastatin 20 mg/d or pravastatin 10 mg/d,²¹ have also been reported to improve BP control in patients with hypertension and hypercholesterolemia treated with different antihypertensive drugs. In contrast, D'Agostino et al²² and O'Callaghan et al²³ did not find that lovastatin or pravastatin, in combination with various antihypertensive medications, was associated with a greater reduction in BP.

The mechanism by which simvastatin and other statins may decrease elevated BP in patients with hypercholesterolemia is not clear.²⁴ The effect of the different statins on BP is not related to their hypolipidemic activity or to the dose of the drug.^{6,18,20,21} This finding might suggest that the effect of statins on BP is due to a direct action on the regulation of vascular tone through an increase in nitric oxide^{5,25} and a decrease in endothelin-1 production.^{20,26} In addition, a reduction in vascular angiotensin II type 1 receptors,²⁷ a decrease in plasma aldosterone level,²⁸ and an increase of arachidonic acid synthesis²⁹ have been reported after treatment with different statins (eg, pravastatin, simvastatin, atorvastatin). All of these activities may play a role in BP reduction.

We did not observe any significant difference in the effect of the drug on BP between the 2 doses of simvastatin in normotensive patients. Similarly, simvastatin^{4,7,8} and pravastatin³⁰⁻³² have not been found by other investigators to decrease BP in normotensive patients. The differential effects of statins on BP in hypertensive and normotensive patients support the possibility that the drugs exert their antihypertensive effects by counteracting some of the mechanisms responsible for hypertension.

CONCLUSIONS

In this group of patients with hypercholesterolemia, the starting dosage of simvastatin (20 mg/d) was associated with reductions in SBP and DBP within 3 months of treatment in patients with hypertension, and this effect was independent of the lipid-lowering properties of the drug. Although the decrease in BP was modest, it is likely clinically relevant. Further studies on this topic are advisable.

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Address correspondence to: Adriana Branchi, MD, Dipartimento di Medicina Interna, Padiglione Granelli, Università degli Studi di Milano, Ospedale Maggiore IRCCS, Via Francesco Sforza, 35, 20121 Milano, Italy. E-mail: adriana.branchi@unimi.it