# Lipid-Lowering Effect of 2 Dosages of a Soy Protein Supplement in Hypercholesterolemia

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## ABSTRACT

The lipid-lowering effect of a soy-based protein supplement was evaluated in an 8-week randomized, placebo-controlled trial in patients with hypercholesterolemia. A total of 117 patients (63 men and 54 women) received soy protein, either 15 or 25 g/d or placebo. In the active treatment groups low-density lipoprotein cholesterol levels decreased significantly by 5.9% and 1.1% respectively, but increased by 3.6% with placebo. Total serum cholesterol and apolipoprotein B levels changed significantly in a similar manner. High-density lipoprotein cholesterol, triglycerides, homocysteine, folic acid, and vitamin $B_{12}$ levels did not change significantly compared with baseline in any of the study groups. All preparations were well tolerated. Soy protein 25 g/d was twice as effective as 15 g/d. In conclusion, soy protein supplementation may effectively reduce serum cholesterol levels and therefore is likely to diminish the risk for cardiovascular disease.

**Keywords:** blood lipids; cholesterol; cardiovascular disease; soy protein; nutritional supplements



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## INTRODUCTION

Cardiovascular disease (CVD) causes approximately 40% of all deaths in industrialized countries. Early recognition of related risk factors may lead to better control of this major public health problem. It is widely accepted that dyslipidemia, in particular hypercholesterolemia, is one of the leading risk factors for coronary heart disease.[1] Along with other risk factors, such as hypertension and tobacco consumption, increased cholesterol levels are responsible for approximately 50% of all cases of coronary heart disease.[2]

In view of the central role that elevated levels of blood lipids play in the genesis of atherosclerosis—especially low-density lipoprotein (LDL)-cholesterol—therapeutic and dietary approaches to treatment and prevention are highly relevant. Established lipid-lowering drugs, although effective, may be accompanied by serious adverse reactions.[3,4] Alternatives to such drugs may include early dietary interventions such as restriction of saturated fatty acids[3] and increased intake of dietary fiber[5,6] and protein-rich legumes, preferably soy beans.[7] The mechanism by which soy exerts a lipid-lowering effect is not yet fully understood. The possibilities under discussion include activation of the LDL receptor by small bioactive peptides in soy protein,[8-11] stimulation of fecal bile acid excretion by soy fiber,[12] and inhibition of endogenous cholesterol synthesis.[13] Numerous clinical studies have been completed demonstrating that soy protein can cause a significant decrease in serum levels of total cholesterol and LDL-cholesterol.[14-24] Published study results remain controversial, however. This may in part be attributed to variations in the composition of the soy products investigated in each study. Apart from differences in protein structure, soy preparations may vary in terms of the quantity of such soy components as isoflavones, phospholipids, and fiber. The study design has also varied considerably, with a treatment duration of 5 to 24 weeks[15,16,20,23] and soy protein intake of 17 to 124 g daily.[14]

A randomized, double-blind, placebo-controlled study was conducted comparing the cholesterol-lowering effect of a soy-based protein dietary supplement at 2 different dosages with that of placebo in patients with hypercholesterolemia, to determine the minimum amount of soy protein required to induce a significant reduction in serum lipid levels.

## METHODS

For this study 133 adults were enrolled, 121 of whom met the inclusion criteria: total serum cholesterol, 5.8 to 7.9 mmol/L; serum LDL-cholesterol, ≥4 mmol/L (≥3.4 mmol/L after amendment); serum triglycerides, <4.5 mol/L; aged 30 to 70 years; and willing to provide written informed consent. Subjects were excluded if they had severe cardiovascular, gastrointestinal, hepatic, renal, or endocrine disease; hypertension (>160/100 mm Hg); a history of myocardial infarction or stroke; familial hypercholesterolemia; diabetes mellitus (type 1 and type 2 and currently under medical treatment); obesity (body mass index, ≥30 kg/m$^2$); clinically significant lactose intolerance; drug or alcohol abuse; or HIV infection or clinically manifested AIDS. They were also excluded if they planned to lose weight during the study period, had used any lipid-lowering drugs during the 4 weeks prior to the study, were pregnant or breast-feeding at the time of enrollment or planned to become pregnant during the study period, had participated in a clinical trial within 4 weeks prior to the study, or had a potential for

compliance problems because of insufficient knowledge of the German language. Concomitant use of medications that could not be expected to notably influence results was permitted.

The study complied with the Good Clinical Practice guidelines of the European Union and was approved by the Ethics Committee of Humboldt University Medical School (Charité) in Berlin. Participants were assigned to one of the following 3 study groups: active treatment 1 (group AT1, which received a 77.5-g supplement containing 25 g soy protein), active treatment 2 (group AT2, which received 75.5-g supplement containing 15 g soy protein and 10 g milk protein), or placebo (group P, which received a 76.5-g supplement containing 25 g milk protein). Group assignments were made by means of a block randomization procedure. The soy protein products (containing SuproSoy from Solae, St. Louis, Mo, USA) and placebo preparation (produced by Contract Foods, Birmingham, UK) were distributed to participants daily in 2 separate sachets. For a list of ingredients, see Table 1. Participants were advised to dissolve each sachet in cold water and ingest it with their morning and evening meals. At each examination, compliance was assessed by counting returned sachets.

**Table 1. Composition of the Study Preparations***

| Ingredient | Active Treatment 1 | Active Treatment 2 | Placebo |
|---|---|---|---|
| Total protein, g | 36.4 | 37.1 | 36.6 |
| Soy protein, g | 32.2 | 19.9 | – |
| Caseinate, g | – | 13.3 | 25.1 |
| Fat, g | 10.3 | 7.7 | 2.6 |
| Carbohydrate, g | 30.7 | 35.3 | 46.8 |
| Sodium, g | 0.13 | 0.21 | 0.24 |
| Energy, kcal | 351 | 350 | 345 |
| Energy, kJ | 1468 | 1464 | 1443 |

*Per 100 g.

After a screening examination prior to the study, participants received their nutritional supplements for a run-in period of 2 weeks, after which baseline values were determined. Additional assessments were made 4, 6, and 8 weeks after baseline and involved an evaluation of the general clinical condition of each participant, and blood samples were analyzed to determine serum levels of total cholesterol, LDL- and high-density lipoprotein (HDL)-cholesterol, triglycerides, apolipoprotein B, and lipoprotein (a) (Lp[a]). At the screening and final assessments, patients were evaluated for serum levels of homocysteine, folic acid, and vitamin $B_{12}$. Tolerability was determined on the basis of basic clinical data and safety parameters, which were determined at the initial and final evaluations. A description of the general physical condition of each participant and the occurrence of undesirable events were recorded

during each assessment. Data were recorded using dBase IV software by means of a double data entry method and evaluated with SPSS for Windows using the full-analysis procedure. Statistical significance was established at $P<.05$.

The statistical analysis was carried out in a stepwise fashion. In the first step, after 8 weeks, univariate comparisons of the differences between corresponding values versus baseline for the 3 study groups were accomplished by means of analysis of variance. When group differences were significant, pairwise comparisons were made using the Student's *t* test. An active treatment was considered superior when its results were significant compared with placebo. When no significant difference between the treatment groups and placebo was observed, a multivariate analysis of variance for repeated measurements (4 visits) was performed to take the entire time course of the study into consideration. Because the rather stringent multivariate preconditions on the study data were not fulfilled in the study, a nonparametric procedure was established.[25] Subsequent contradictory univariate and multivariate findings have been recognized as (partly significant) differences in baseline values for the groups being compared. Following the recommendations of the European Agency for the Evaluation of Medicinal Products (known as EMEA) guidelines (European Medicines Agency, CPMP/EWP/2863/99: Points to Consider on Adjustment for Baseline Covariates), we applied a new multivariate nonparametric analysis of covariance (MANCOVA) for repeated measures, with the baseline value as the covariate[26] that provided significant differences compared with placebo in every case for both active treatments.

## RESULTS

Of the 133 subjects initially enrolled, 4 left during the run-in period and 12 were excluded after the evaluation of baseline values because their lipid levels did not meet study requirements. Another 5 participants were terminated from the study prematurely but underwent a final evaluation. The 117 participants (54 women and 63 men) who could be included in the analysis were well matched (Table 2): based on their characteristics, as well as clinical data and lifestyle assessments, the 3 study groups appeared to be homogeneous in terms of baseline values.

Serum LDL-cholesterol was the primary efficacy parameter (Table 3, Fig 1). By week 8, LDL-cholesterol levels had fallen by 0.26±0.47 mmol/L in the AT1 group, corresponding to a decline of 5.9% compared with baseline and 9.5% compared with placebo. In the AT2 group, LDL-cholesterol decreased by 0.05±0.66 mmol/L—a decline of 1.1% compared with baseline and 4.7% compared with placebo. In the placebo group, an increase in LDL-cholesterol of 0.15±0.59 mmol/L was observed. MANCOVA revealed that the differences in LDL-cholesterol changes in each active treatment group versus the placebo group were statistically significant (AT1 vs placebo, $P=.002$; AT2 vs placebo, $P=.011$).

Changes in total serum cholesterol were similar to those for LDL-cholesterol (Fig 2, Table 4). By week 8, values in the AT1 group had decreased by 0.30±0.58 mmol/L, indicating a 4.6% decline compared with baseline and a 7.4% decline compared with placebo. In the AT2 group, total cholesterol levels remained virtually unchanged, with a very small decline of 0.01±0.75 mmol/L. In the placebo group, an increase in total cholesterol of 0.18±0.51 mmol/L was observed (2.8% compared with baseline).

The differences between the AT1 and AT2 groups compared with placebo were multivariate and significant ($P$=.0002 for AT1 vs placebo; $P$=.0001 for AT2 vs placebo).

**Table 2. Characteristics of Participants**

| Group | Sex (F/M) | Age mean±SD (range) | Height, cm mean±SD (range) | Weight, kg mean±SD (range) |
|---|---|---|---|---|
| AT1 | 15/24 | 53.3±8.6 (34–70) | 172.4±8.4 (158–190) | 76.4±13.1 (54–118) |
| AT2 | 20/19 | 56.3±9.3 (31–70) | 168.7±8.1 (154–186) | 76.9±15.5 (41–120) |
| Placebo | 19/20 | 51.1±10.8 (31–70) | 172.5±8.3 (160–188) | 76.1±11.9 (43–102) |
| *P* value* | .49 | .06 | .08 | .97 |

*Placebo vs mean for active treatment groups.

**Table 3. Primary Efficacy Parameter: Serum LDL-Cholesterol Levels**

| Time Point | AT1, mmol/L | AT2, mmol/L | Placebo, mmol/L | *P* Value* |
|---|---|---|---|---|
| Screening | 4.34±0.37 | 4.20±0.41 | 4.32±0.34 | .22 |
| Baseline | 4.31±0.45 | 4.10±0.39 | 4.18±0.43 | .10 |
| 4 weeks | 4.50±0.59 | 4.31±0.51 | 4.47±0.54 | .25 |
| Change from baseline | 0.20±0.44 | 0.18±0.50 | 0.30±0.48 | .49 |
| 6 weeks | 4.27±0.53 | 4.24±0.44 | 4.46±0.55 | .14 |
| Change from baseline | –0.04±0.42 | 0.11±0.50 | 0.29±0.45 | .01 |
| 8 weeks | 4.06±0.48 | 4.06±0.65 | 4.33±0.58 | .06 |
| Change from baseline† | –0.26±0.47‡ | –0.05±0.66§ | 0.15±0.59 | .01 |

*Analysis of variance.
†Pairwise group comparison based on *t* test results: AT1/AT2, $P$=.11; AT1/placebo, $P$=.001; AT2/placebo, $P$=.18.
‡$P$=.002 vs placebo (by multivariate analysis).
§$P$=.011 vs placebo (by multivariate analysis).

**Fig 1. Serum LDL-cholesterol levels.**

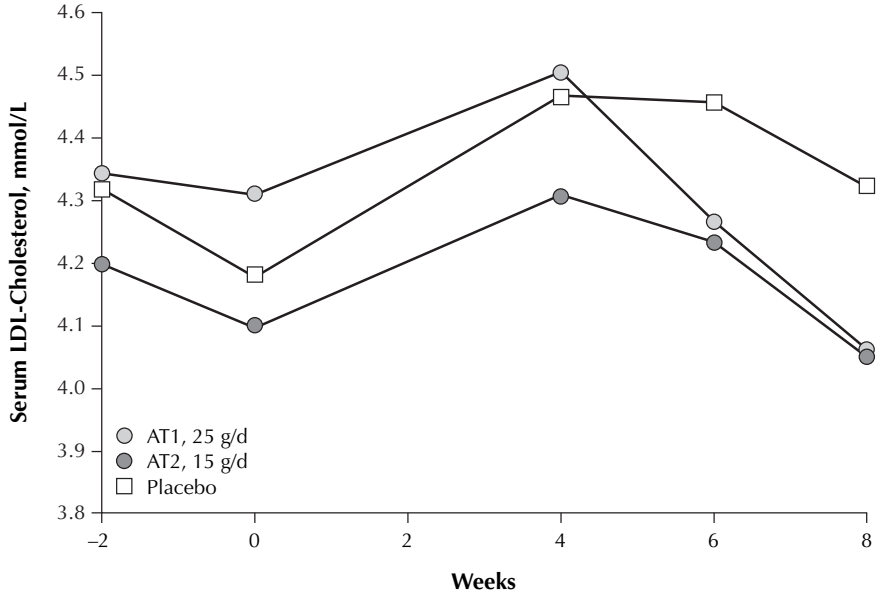



**Fig 2. Total serum cholesterol levels.**

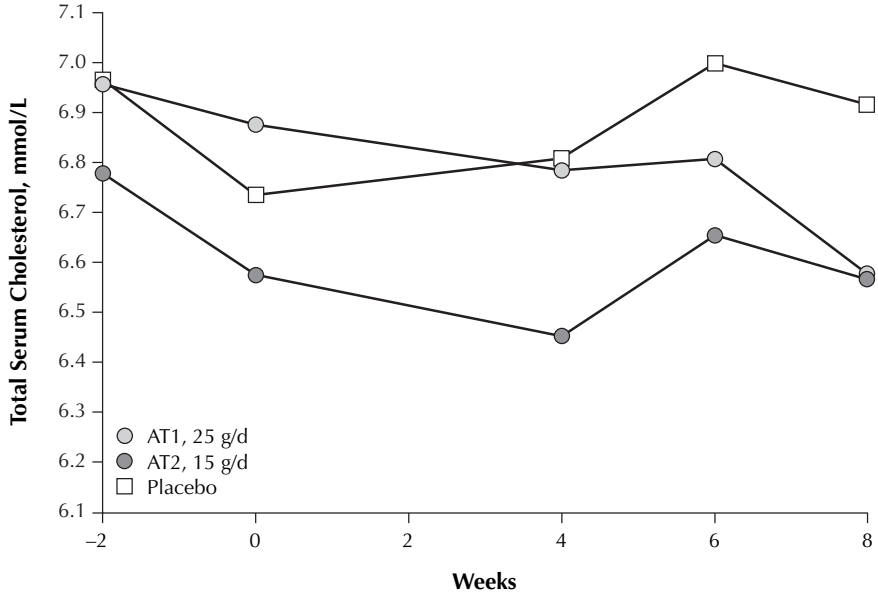


**Table 4. Secondary Efficacy Parameters: Total Cholesterol, HDL-Cholesterol, and Triglycerides**

| Parameter | AT1 | AT2 | Placebo | *P* Value* |
|---|---|---|---|---|
| Total cholesterol, mmol/L | | | | |
| Screening | 6.96±0.52 | 6.79±0.51 | 6.97±0.46 | .18 |
| Baseline | 6.88±0.46 | 6.58±0.46 | 6.74±0.60 | .04 |
| 4 weeks | 6.79±0.66 | 6.46±0.56 | 6.81±0.70 | .03 |
| Change from baseline | –0.09±0.50 | –0.14±0.48 | 0.07±0.62 | .20 |
| 6 weeks | 6.81±0.74 | 6.66±0.45 | 7.00±0.72 | .09 |
| Change from baseline | –0.07±0.57 | 0.07±0.49 | 0.26±0.49 | .02 |
| 8 weeks | 6.58±0.67 | 6.57±0.75 | 6.92±0.61 | .04 |
| Change from baseline† | –0.30±0.58‡ | – 0.01±0.75§ | 0.18±0.51 | .002 |
| HDL-cholesterol, mmol/L | | | | |
| Screening | 1.51±0.34 | 1.50±0.28 | 1.50±0.28 | .99 |
| Baseline | 1.46±0.35 | 1.44±0.27 | 1.43±0.29 | .92 |
| 4 weeks | 1.52±0.38 | 1.47±0.30 | 1.46±0.26 | .67 |
| Change from baseline | 0.06±0.13 | 0.04±0.14 | 0.02±0.13 | .32 |
| 6 weeks | 1.48±0.40 | 1.48±0.27 | 1.46±0.29 | .94 |
| Change from baseline | 0.02±0.17 | 0.05±0.16 | 0.01±0.14 | .54 |
| 8 weeks | 1.48±0.35 | 1.50±0.31 | 1.46±0.25 | .89 |
| Change from baseline | 0.02±0.18 | 0.06±0.17 | 0.03±0.13 | .54 |
| Triglycerides, mg/dL | | | | |
| Screening | 159.1±90.5 | 147.9±63.0 | 170.2±72.4 | .44 |
| Baseline | 162.6±77.7 | 151.6±71.9 | 176.9±72.7 | .32 |
| 4 weeks | 151.5±79.2 | 146.2±68.5 | 175.7±76.0 | .19 |
| Change from baseline | –11.1±47.5 | –4.8±54.1 | 1.3±61.1 | .61 |
| 6 weeks | 167.5±116.9 | 149.9±59.7 | 175.7±64.7 | .42 |
| Change from baseline | 4.9±71.7 | –3.0±58.9 | 1.3±62.5 | .87 |
| 8 weeks | 142.8±68.2 | 152.2±83.2 | 173.0±71.7 | .20 |
| Change from baseline | –19.7±46.8 | 0.6±65.1 | –3.9±67.8 | .26 |

*Analysis of variance.
†Pairwise group comparison based on *t* test results: AT1/AT2, *P*=.11; AT1/placebo, *P*=.001; AT2/placebo, *P*=.18.
‡*P*=.002 vs placebo (by multivariate analysis).
§*P*=.0001 vs placebo (by multivariate analysis).

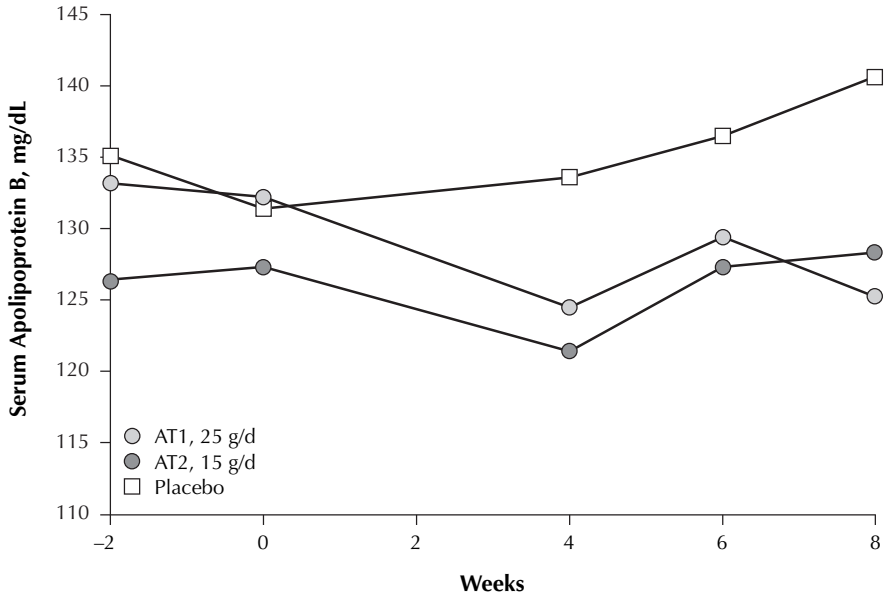
Among the secondary efficacy parameters, serum HDL-cholesterol and triglyceride levels were not significantly different between treatment groups (Table 4). HDL-cholesterol concentrations increased slightly and triglyceride levels decreased in all study groups. Apolipoprotein B levels fell significantly in the AT1 group by 7.0±24.0 mg/dL (5.9%). In the AT2 group, they increased slightly by 0.9±17.1 mg/dL (0.7%), and in the placebo group they rose significantly by 6.9±12.4 mg/dL (5.2%) (Table 5; Fig 3). MANCOVA revealed that the differences between each active treatment group and placebo were significant ($P<.001$ for AT1 vs placebo; $P=.0002$ for AT2 vs placebo). A large variance in baseline Lp(a) values was observed between groups (Table 5). They returned to baseline by the final evaluation in both active treatment groups while a 13.4% decline was observed in the placebo group.

**Table 5. Secondary Efficacy Parameters: Lipoproteins**

| Parameter | AT1 | AT2 | Placebo | *P* Value* |
|---|---|---|---|---|
| Apolipoprotein B, mg/dL | | | | |
| Screening | 133.2±20.0 | 126.5±29.7 | 135.2±16.3 | .21 |
| Baseline | 132.4±18.3 | 127.4±14.6 | 131.6±18.2 | .39 |
| 4 weeks | 124.6±15.3 | 121.7±19.0 | 133.6±20.6 | .02 |
| Change from baseline | –7.8±11.2 | –6.2±13.2 | 1.8±13.2 | .002 |
| 6 weeks | 129.1±25.8 | 127.3±22.0 | 136.4±18.8 | .18 |
| Change from baseline | –3.4±16.0 | –0.8±18.5 | 4.7±15.1 | .10 |
| 8 weeks | 125.4±30.3 | 128.3±16.2 | 140.5±19.3 | .01 |
| Change from baseline† | –7.0±24.0‡ | 0.9±17.1§ | 6.9±12.4 | <.001 |
| Lp(a), mg/dL | | | | |
| Screening | 47.9±45.7 | 27.7±29.6 | 42.9±49.2 | .10 |
| Baseline | 47.9±46.5 | 30.3±31.3 | 43.4±47.0 | .17 |
| 4 weeks | 51.1±51.4 | 33.7±35.3 | 39.9±46.0 | .24 |
| Change from baseline | 5.8±21.9 | 2.4±7.7 | –0.4±10.8 | .20 |
| 6 weeks | 48.2±46.8 | 28.6±29.6 | 35.9±41.8 | .11 |
| Change from baseline | 0.3±12.6 | –3.2±9.5 | –4.8±11.8 | .15 |
| 8 weeks | 47.5±47.2 | 29.8±31.9 | 36.5±40.8 | .16 |
| Change from baseline | 0.4±29.1 | –0.5±8.0 | –6.9±12.1 | .35 |

*Analysis of variance.
†Pairwise group comparison based on *t* test results: AT1/AT2, $P=.08$; AT1/placebo, $P=.01$; AT2/placebo, $P=.018$.
‡$P=.001$ vs placebo (by multivariate analysis).
§$P=.0002$ vs placebo (by multivariate analysis).

**Fig 3. Serum apolipoprotein B levels.**




Plasma levels of homocysteine, folic acid, and vitamin $B_{12}$ did not change significantly during the trial period, nor did they differ significantly between study groups. The same holds true for clinical data such as body weight, heart rate, blood pressure, or body temperature.

During the study, 41 subjects experienced nonserious adverse events. For 11 of these patients (9 of whom were in the active treatment groups), the study preparations could not be ruled out as a possible cause of the adverse effect. The adverse effects were eczema, sensation of fullness, heartburn, nausea, constipation, flatulence, diarrhea, and impaired sexual function. Three participants were withdrawn from the study by a clinical investigator because of these effects; 2 other participants left by their own choice.

## DISCUSSION

A meta-analysis of 38 studies of the effect of soy protein on serum lipids[14] showed an average reduction in total cholesterol and LDL-cholesterol of 9.3% and 12.9%, respectively. A cholesterol reduction of this magnitude can significantly diminish the risk for CVD and is therefore highly relevant in affluent societies. The meta-analysis also showed that LDL-cholesterol was not reduced in every study and the observed effects varied considerably. This variability may be related to the way in which the soy protein was processed, the protein structure, the nonprotein content of the soy product, or the dosage. Previously reported trials failed to identify a clear

dosage-efficacy relationship, however.[20,23] The administration of soy protein dosages of 20, 30, 40, and 50 g daily, over a period of 6 weeks did not lead to consistently graded effects on cholesterol and apolipoprotein B concentrations.

The present study demonstrated that during 8 weeks of treatment, the lipid-lowering effect of 25 g of soy protein daily was approximately twice that of 15 g soy protein daily compared with placebo. Treatment with soy protein at both dosages resulted in significant reductions in LDL-cholesterol, total cholesterol, and apolipoprotein B compared with placebo. These results correspond well with those obtained in other trials[14] and encourage the use of soy protein supplements as an uncomplicated method to reduce the risk for CVD. In this study, the maximum effect was not reached before the final assessment (ie, after 8 weeks of treatment). As in previous studies, no significant influence of soy protein on serum levels of HDL-cholesterol, triglycerides, or Lp(a) was observed. The rise in total cholesterol and apolipoprotein B levels in the placebo group may correlate with changes in behavior (eg, an increase in fat intake) usually associated with festivities occurring during October–January, the time of the study. Otherwise, the effect of active treatment would have seemed even more pronounced.

No significant differences in any other efficacy or safety parameters were observed at week 8 compared with baseline. Tolerability of the study preparations was generally good. Most of the adverse effects reported were not likely to be related to treatment. Nine participants in the active treatment groups and 2 in the placebo group experienced nonserious adverse events that may have been related to the test preparation.

## CONCLUSION

Based on the observations that soy protein is associated with significant decreases in serum concentrations of total cholesterol, LDL-cholesterol, and apolipoprotein B, the efficacy of the soy protein supplements (15 g vs 25 g) was approximately equivalent. Only nonserious, predominantly nontreatment-related adverse effects were reported. Soy protein supplementation may be a safe and effective approach to reducing the risk for CVD.

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