

Effects of Colesevelam Hydrochloride on Low-Density Lipoprotein Cholesterol and High-Sensitivity C-Reactive Protein When Added to Statins in Patients With Hypercholesterolemia

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Elevated high-sensitivity C-reactive protein (hs-CRP) levels are associated with an increased risk of atherosclerotic coronary heart disease (CHD). The addition of the bile acid sequestrants, such as colesevelam hydrochloride (HCl), to statins further reduces low-density lipoprotein (LDL) cholesterol levels. However, the effects of approved cholesterol-lowering bile acid sequestrants on hs-CRP have not previously been reported. Three randomized, double-blind, placebo-controlled, parallel, 6-week clinical trials of similar design investigated the efficacy of adding colesevelam HCl to stable simvastatin, atorvastatin, or pravastatin treatment in 204 patients with primary hypercholesterolemia. The primary end point was the mean percent change in the LDL cholesterol levels. Secondary end points included the effects on other lipid parameters and hs-CRP levels. A pooled analysis showed that adding colesevelam HCl to statin therapy significantly lowered LDL cholesterol levels (21 mg/dl or 16% mean reduction from baseline, $p = 0.0013$, and 11 mg/dl or 9% mean reduction compared with placebo, $p = 0.0003$). Four times as many patients receiving colesevelam HCl plus a statin achieved a LDL cholesterol target of <100 mg/dl compared with patients receiving a statin plus placebo (39% vs 10%, respectively, $p < 0.0001$). The incidence of mild gastrointestinal adverse effects was slightly higher in the colesevelam HCl plus statin group than in the placebo plus statin group. Finally, the differences in the change in hs-CRP levels with colesevelam HCl plus statin therapy were significant compared with the changes with placebo plus statin (median change -23% , $p = 0.0069$). In conclusion, this is the first report suggesting that an approved cholesterol-lowering bile acid sequestrant, specifically colesevelam HCl, decreases hs-CRP levels when added to statin therapy. © 2006 Elsevier Inc. All rights reserved. (Am J Cardiol 2006;97:1198–1205)

Three recent clinical trials of similar design and methods investigated the efficacy of adding colesevelam hydrochloride (HCl), a specifically engineered bile acid sequestrant (BAS) polymer, compared with placebo in hypercholesterolemic patients on stable simvastatin, atorvastatin, or pravastatin therapy. The primary end point in all 3 studies was the mean percent change in low-density lipoprotein (LDL) cholesterol levels. The secondary end points were the effects of these drug combinations on other lipid parameters and high-sensitivity C-reactive protein (hs-CRP) levels. We present the results of these patient trials and a pooled analysis of all 3 trials.

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This study was supported by Sankyo Pharma Incorporated, Parsippany, New Jersey.

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Methods

Study design and patients: Data were obtained from 3 randomized, double-blind, placebo-controlled, parallel, multicenter trials conducted in the United States between November 2002 and July 2003. The methods and design of the 3 studies were similar (Figure 1).

After completing the informed consent process, patients who were ≥ 18 years of age and who had a LDL cholesterol level of ≥ 100 mg/dl but ≤ 250 mg/dl and a triglyceride level of ≤ 300 mg/dl while on stable doses of statin therapy (atorvastatin, pravastatin, or simvastatin) for ≥ 4 weeks were enrolled in the studies. The patients were randomized in a 2:1 ratio to receive either the BAS colesevelam HCl 3.75 g/day (6 \times 625-mg tablets daily) or matching tablets of placebo (6 tablets daily) for 6 weeks as an add-on therapy to their usual daily dose of statin therapy (Table 1). The patients and investigators were blinded to the colesevelam HCl treatment allocation, and identically appearing tablets were used to maintain blinding. The dosing regimen for colesevelam HCl during the 6-week treatment period was either 3 tablets twice daily with the

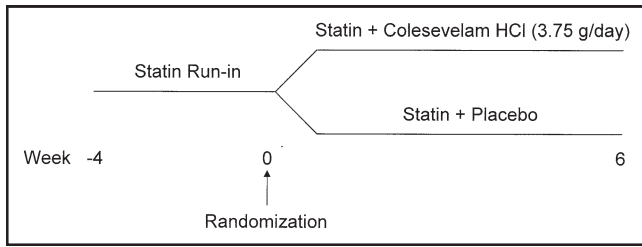


Figure 1. Study design. After completion of 4-week run-in period on their established statin dose, patients were randomized in a 2:1 ratio to receive colesevelam HCl 3.75 g/day or placebo in addition to established statin therapy for 6 weeks.

Table 1

Mean baseline statin dosages in colesevelam hydrochloride (HCl) and placebo groups

Statin (mg/d)	Placebo	Colesevelam HCl
Simvastatin	25.6	29.6
Atorvastatin	16.3	15.5
Pravastatin	23.5	25.5

noon and evening meals or 6 tablets once daily with the evening meal. The statin doses remained unchanged throughout the studies.

Patients were excluded if they had a history of dysphagia, swallowing disorders, or intestinal motility disorder; a serum creatinine concentration >2.0 mg/dl; an alanine or aspartate transaminase concentration >2.5 times the upper limit of normal; a fasting plasma glucose concentration ≥ 300 mg/dl; a creatine kinase concentration >3 times the upper limit of normal; or received treatment with lipid-lowering drugs (other than the entry criteria statin) within 10 weeks before visit 1. Patients were also excluded if they had serious or significant medical conditions that the investigators considered could potentially compromise study participant safety.

Efficacy and safety assessments: The primary efficacy parameter in all 3 studies was the mean percent change in LDL cholesterol levels from baseline to end point. Secondary efficacy parameters included the absolute change and the percent change in high-density lipoprotein (HDL) cholesterol, total cholesterol, apolipoprotein (apo) A-I, apo-B, and triglyceride levels, and the absolute change in hs-CRP level. Each study was powered to evaluate changes in LDL cholesterol. However, the studies were not powered to detect changes in additional secondary variables; thus, a pooled analysis was conducted to evaluate the changes in these variables. Additionally, a post hoc analysis was conducted to determine the median percent change in hs-CRP. Safety was assessed by evaluating the incidence of treatment-emergent adverse events, changes in laboratory safety parameters, vital signs, and physical examination findings. Efficacy and tolerability were assessed during weeks 4 and 6 of the treatment period.

Biochemical analyses: Lipid profiles and inflammatory markers were assayed at a central laboratory (Medical Research Laboratories International, Highland Heights, Kentucky). The total cholesterol and triglyceride levels were measured by enzyme assays. HDL cholesterol levels were measured by cholesterol oxidase assay of the supernatant from the precipitate of non-HDL lipoproteins with heparin and manganese chloride. LDL cholesterol levels were calculated by the Friedewald formula if the triglyceride level was <400 mg/dl. If the triglyceride concentration was ≥ 400 mg/dl, LDL cholesterol levels were determined directly by the betaquant method. Apo-B and apo-A-I levels were quantified by immunonephelometry. hs-CRP levels were quantified using a hs-CRP assay, also by immunonephelometry (Dade Behring, Deerfield, Illinois).

Statistical analysis: Sample sizes were determined using the following assumptions: a statistical significance level of 5%, a power of 80%, a dropout rate of 10%, a pooled SD of 12%, and a difference of 10% between the percent change in LDL cholesterol levels in the colesevelam HCl group and placebo group.

Safety analyses were performed on the population of all randomized subjects, which included all patients who took ≥ 1 dose of randomized study medication. Lipid parameters and hs-CRP data were reported for the intent-to-treat population, defined as all randomized subjects who took ≥ 1 dose of randomized study medication and had a baseline lipid measurement and ≥ 1 post-baseline lipid assessment taken within 72 hours of the last dose of randomized study medication.

Baseline measurements were taken at week 0 (after completion of the 4-week statin run-in phase), and the end point measurements were the last observed measurements taken within 72 hours of the last dose of randomized study medication. An analysis of covariance model was used for all efficacy end points, with treatment and center as factors and centralized baseline as a covariate. Least-square means, corresponding to 2-tailed 95% confidence intervals, and p values were calculated for treatment differences (colesevelam HCl vs placebo). The median values are reported for parameters not normally distributed. p Values were obtained from the Cochran-Mantel-Haenszel test in nonparametric analysis of covariance, and 95% confidence intervals were estimated using the Hodges-Lehmann estimator and Tukey method for mean values and the Hodges-Lehmann estimator and Moses method for median values.

Results

Demographics: The flow of patients through the trials is depicted in Figure 2. A total of 204 patients were randomized in the 3 trials. In conducting the pooled analyses, it was discovered that 1 patient in the placebo group of the atorvastatin study had been dispensed medication from another

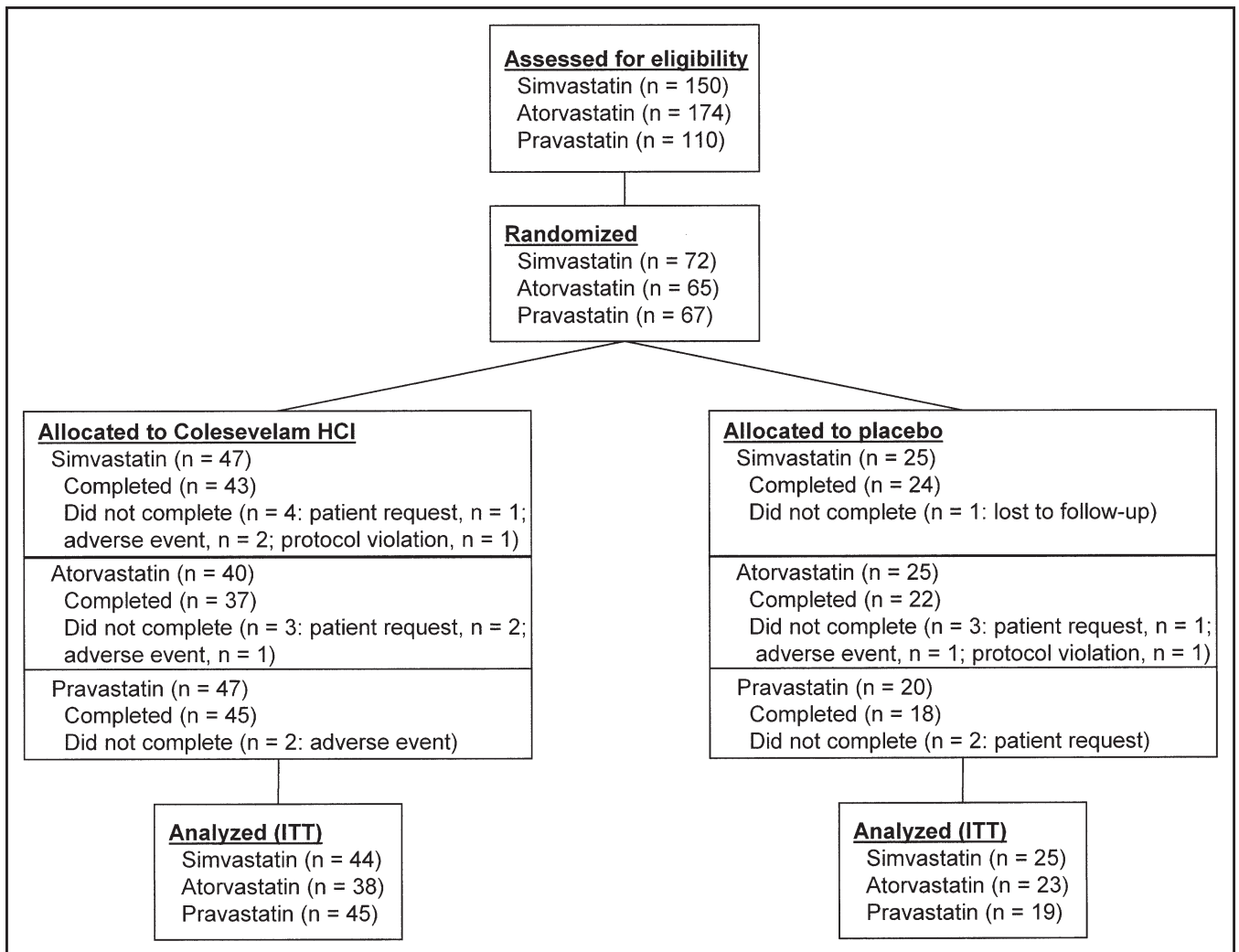


Figure 2. Flow of patients through trials. ITT = intent-to-treat population, defined as all randomized patients who took ≥ 1 dose of randomized study medication and had 1 baseline lipid measurement and ≥ 1 post-baseline lipid assessment taken within 72 hours of last dose of randomized study medication.

Table 2

Pooled baseline demographics at screening of all patients randomized to treatment who received at least one dose of study medication

Demographic Characteristic	Statin	
	+ Placebo (n = 69)	+ Colesevelam HCl (n = 134)
Age (yrs) (mean \pm SD)	58.0 \pm 10.2	57.3 \pm 11.3
Men	32 (46%)	59 (44%)
Women	37 (54%)	75 (56%)
White	45 (65%)	87 (65%)
Black	7 (10%)	12 (9%)
Asian	0 (0%)	3 (2%)
Hispanic	17 (25%)	32 (24%)
Coronary heart disease or peripheral vascular disease	4 (6%)	14 (10%)
Type 2 diabetes mellitus*	10 (14%)	18 (13%)
Mean body mass index (kg/m ²)	28.8 \pm 4.3	28.5 \pm 4.6

No significant differences were reported between pooled treatment groups.

* Mean baseline fasting glucose level was 104.1 \pm 25.2 and 105.2 \pm 34.1 mg/dl in placebo and colesevelam HCl groups, respectively; mean end-of-study glucose level was 104.4 \pm 29.2 and 103.0 \pm 27.7 mg/dl in placebo and colesevelam HCl group, respectively.

study. Thus, that patient's data were excluded from the population of all randomized patients. This did not affect the numbers of patients included in the efficacy analyses (intent-to-treat population). Pooled subject demographics were similar among the 3 groups (Table 2).

Lipids: A pooled analysis of all 3 trials showed that the groups receiving colesevelam HCl plus statin therapy had significantly greater mean reductions in LDL cholesterol levels compared with baseline values and compared with the end-of-study placebo plus statin groups (Table 3). Four times as many patients administered colesevelam HCl achieved a LDL cholesterol target level of <100 mg/dl¹ compared with patients administered placebo (39% vs 10%, respectively, $p < 0.0001$). Colesevelam HCl plus statins also significantly lowered total cholesterol levels from baseline values and more than the placebo plus statin values, although the reduction in apo-B levels with colesevelam HCl plus statins compared with that with placebo plus statins was not significant. Triglyceride and apo-A-I levels in-

Table 3
Pooled analysis of absolute and percent change in lipid parameters from baseline to end point in patients receiving statins (atorvastatin, simvastatin, or pravastatin) alone or in combination with colesevelam hydrochloride (HCl)

	Baseline	End Point	LS Absolute Change from Baseline (95% CI)	Absolute Treatment Difference (95% CI)	LS % Change from Baseline (95% CI)	% Treatment Difference (95% CI)
Mean LDL-C (mg/dl)						
Statin + placebo (n = 67)	129.9	120.2	-10.2 (-15.5 to -4.9)		-6.5 (-10.5 to -2.5)	
Statin + colesevelam HCl (n = 127)	132.6	111.3	-21.0 (-24.9 to -17.2)	-10.8 (-17.4 to -4.3)*	-15.7 (-18.6 to -12.9)	-9.2 (-14.1 to -4.3)†
Mean HDL-C (mg/dl)						
Statin + placebo (n = 67)	51.8	51.5	-0.3 (-1.7 to 1.1)		-0.4 (-3.0 to 2.2)	
Statin + colesevelam HCl (n = 127)	51.6	51.5	-0.1 (-1.2 to 0.9)	+0.2 (-1.4 to 1.8)	0.0 (-1.9 to 2.0)	+0.5 (-2.6 to 3.5)
Mean total cholesterol (mg/dl)						
Statin + placebo (n = 67)	211.9	203.8	-8.6 (-14.4 to -2.7)		-3.4 (-6.1 to -0.7)	
Statin + colesevelam HCl (n = 127)	214.1	197.6	-16.3 (-20.5 to -12.0)	-7.7 (-14.9 to -0.5)‡	-7.2 (-9.2 to -5.3)	-3.9 (-7.2 to -0.5)‡
Median triglycerides (mg/dl)						
Statin + placebo (n = 67)	154.0	139.0	+4.3 (-5.5 to 12.5)		+4.1 (-1.8 to 9.9)	
Statin + colesevelam HCl (n = 127)	137.0	159.0	+20.9 (12.8 to 29.8)	+15.5 (3.0 to 30.0)‡	+16.3 (10.5 to 23.4)	+11.0 (2.2 to 19.8)‡
Mean apo-A-I (mg/dl)						
Statin + placebo (n = 67)	160.5	159.4	-1.0 (-4.8 to 2.8)		-0.2 (-2.6 to 2.2)	
Statin + colesevelam HCl (n = 127)	158.9	166.1	+7.2 (4.5 to 10.0)	+8.2 (3.6 to 12.9)†	+4.8 (3.1 to 6.6)	+5.1 (2.1 to 8.0)†
Mean apo-B (mg/dl)						
Statin + placebo (n = 67)	127.5	119.7	-8.5 (-13.0 to -4.0)		-5.8 (-9.2 to -2.3)	
Statin + colesevelam HCl (n = 127)	131.1	119.3	-11.4 (-14.8 to -8.1)	-2.9 (-8.4 to 2.5)	-8.3 (-10.9 to -5.8)	-2.5 (-6.7 to 1.6)

Treatment difference = colesevelam HCl - placebo.

* p < 0.01; † p ≤ 0.001; ‡ p < 0.05.

CI = confidence interval; HDL-C = HDL cholesterol; LDL-C = LDL cholesterol; LS = least square.

Table 4

Percent change in lipid parameters from baseline to end point in patients receiving statins (atorvastatin, simvastatin, or pravastatin) alone or in combination with colessevelam hydrochloride (HCl)

	Mean Baseline (mg/dl)	Mean End Point (mg/dl)	LS Mean Percent Change from Baseline (95% CI)	Percent Treatment Difference (95% CI)
LDL-C				
Simvastatin + placebo (n = 25)	126.1	123.3	-1.1 (-8.4 to 6.2)	
Simvastatin + colessevelam HCl (n = 44)	132.1	107.6	-18.6 (-24.1 to -13.1)*	-17.5 (-26.7 to -8.3) [‡]
Atorvastatin + placebo (n = 23)	131.7	112.9	-13.5 (-20.0 to -7.0)*	
Atorvastatin + colessevelam HCl (n = 38)	133.2	109.9	-17.2 (-22.3 to -12.1)*	-3.7 (-12.0 to 4.5)
Pravastatin + placebo (n = 19)	132.6	125.0	-4.7 (-12.4 to 2.9)	
Pravastatin + colessevelam HCl (n = 45)	132.7	116.0	-11.9 (-17.4 to -6.3)*	-7.1 (-14.9 to 0.6)
HDL-C				
Simvastatin + placebo (n = 25)	57.0	57.0	1.0 (-3.6 to 5.6)	
Simvastatin + colessevelam HCl (n = 44)	52.2	53.2	2.0 (-1.4 to 5.5)	1.0 (-4.8 to 6.8)
Atorvastatin + placebo (n = 23)	49.1	48.7	-1.0 (-5.4 to 3.4)	
Atorvastatin + colessevelam HCl (n = 38)	51.3	51.6	1.0 (-2.4 to 4.3)	2.0 (-3.6 to 7.5)
Pravastatin + placebo (n = 19)	48.3	47.5	-1.1 (-5.8 to 3.6)	
Pravastatin + colessevelam HCl (n = 45)	51.4	49.9	-2.5 (-5.9 to 1.0)	-1.3 (-6.1 to 3.4)
Total cholesterol				
Simvastatin + placebo (n = 25)	211.4	208.9	-0.7 (-5.7 to 4.3)	
Simvastatin + colessevelam HCl (n = 44)	214.7	196.7	-8.2 (-12.0 to -4.4)*	-7.5 (-13.8 to -1.2) [‡]
Atorvastatin + placebo (n = 23)	214.0	198.3	-6.6 (-11.3 to -1.9)*	
Atorvastatin + colessevelam HCl (n = 38)	213.4	194.7	-8.4 (-12.1 to -4.8)*	-1.8 (-7.7 to 4.2)
Pravastatin + placebo (n = 19)	210.1	203.8	-3.0 (-7.5 to 1.5)	
Pravastatin + colessevelam HCl (n = 45)	214.1	201.0	-5.3 (-8.3 to -2.4)*	-2.3 (-7.6 to 3.0)
Triglycerides (median)				
Simvastatin + placebo (n = 25)	146.0	128.0	2.1 (-7.3 to 11.3)	
Simvastatin + colessevelam HCl (n = 44)	140.8	174.0	17.8 (8.1 to 28.5)*	15.0 (1.3 to 28.7) [‡]
Atorvastatin + placebo (n = 23)	163.5	161.0	9.4 (-6.2 to 25.3)	
Atorvastatin + colessevelam HCl (n = 38)	125.5	151.5	15.5 (5.5 to 28.3)*	8.8 (-6.7 to 23.1)
Pravastatin + placebo (n = 19)	155.5	139.0	4.7 (-6.6 to 13.5)	
Pravastatin + colessevelam HCl (n = 45)	145.5	152.0	16.4 (3.8 to 29.4)*	9.4 (-6.4 to 30.9)
Apo A-I				
Simvastatin + placebo (n = 25)	169.9	167.0	-1.3 (-5.8 to 3.2)	
Simvastatin + colessevelam HCl (n = 44)	162.2	171.3	5.7 (2.3 to 9.0)*	6.9 (1.3 to 12.6) [‡]
Atorvastatin + placebo (n = 23)	158.6	160.0	1.7 (-2.3 to 5.6)	
Atorvastatin + colessevelam HCl (n = 38)	156.2	163.7	4.9 (1.9 to 8.0)*	3.3 (-1.7 to 8.2)
Pravastatin + placebo (n = 19)	150.5	148.8	-1.3 (-5.8 to 3.1)	
Pravastatin + colessevelam HCl (n = 45)	157.9	163.1	4.1 (1.2 to 6.9)*	5.4 (0.1 to 10.7) [‡]
Apo B				
Simvastatin + placebo (n = 25)	124.4	118.3	-4.4 (-10.7 to 1.8)	
Simvastatin + colessevelam HCl (n = 44)	131.1	116.4	-10.7 (-15.3 to -6.0)*	-6.2 (-14.0 to 1.6)
Atorvastatin + placebo (n = 23)	129.5	117.2	-8.9 (-15.0 to -2.7)*	
Atorvastatin + colessevelam HCl (n = 38)	130.3	116.9	-9.6 (-14.4 to -4.9)*	-0.8 (-8.5 to 7.0)
Pravastatin + placebo (n = 19)	129.1	124.7	-3.4 (-8.7 to 1.8)	
Pravastatin + colessevelam HCl (n = 45)	131.8	124.3	-4.8 (-8.2 to -1.4)*	-1.4 (-7.6 to 4.9)

* p < 0.05 compared with baseline; † p < 0.001 compared with statin + placebo; ‡ p < 0.05 compared with statin + placebo.

Abbreviations as in Table 3.

creased significantly in the colessevelam HCl plus statin group compared with baseline and compared with the placebo plus statin group. However, the increase in HDL cholesterol levels with colessevelam HCl was not significant in the pooled data.

The lipid results of the patient trials are given in Table 4.

hs-CRP levels: The pooled analysis of all 3 trials showed that the change in hs-CRP levels with colessevelam HCl added to statins was significant compared with the change in hs-CRP when placebo was added to statin therapy (Table 5). Although not powered to detect changes in ad-

ditional secondary variables, the results from these patient trials showed that combining colessevelam HCl with either simvastatin (p = 0.0154) or pravastatin (p = 0.0279) was associated with significantly greater median percent reductions in hs-CRP levels (data not shown). The absolute median hs-CRP levels at baseline and end point for the patient trials are shown in Figure 3.

Safety: No serious drug-related adverse events were reported by any study patient. One patient in the colessevelam HCl group and 1 in the placebo group of the pravastatin study experienced a serious adverse event (cholecystitis and

Table 5

Pooled analysis of median percent change in high-sensitivity C-reactive protein (hs-CRP) levels from baseline to end point in patients receiving statins (atorvastatin, simvastatin, or pravastatin) alone or in combination with colesevelam hydrochloride (HCl)

Treatment	Baseline (mg/L)	End Point (mg/L)	LS Median Percent Change from Baseline at End Point (95% CI)
Statin + placebo (n = 64)	1.6	2.0	+17.2 (2.8 to 35.0)
Statin + colesevelam HCl (n = 123)	1.6	1.3	-6.2 (-15.8 to 5.9)
Treatment difference (%)			-23.3 (-40.0 to -6.3)*

Treatment difference = colesevelam HCl - placebo.

* $p < 0.01$.

Abbreviations as in Table 3.

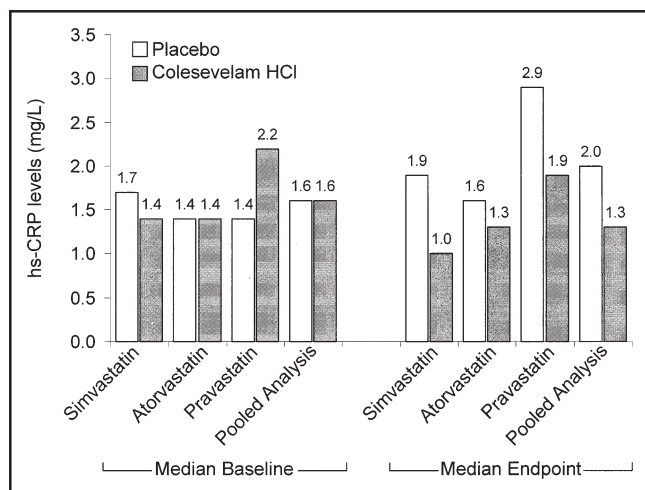


Figure 3. Median hs-CRP levels at baseline and end point for each patient trial. Baseline measurements were taken at week 0 (after completion of 4-week statin run-in phase). End point defined as last observed measurement taken within 72 hours of last dose of randomized study medication.

transient ischemic attack, respectively) during treatment, but these events were not considered by the investigators to be related to the study drugs. No deaths occurred during any of the studies. The incidence of drug-related treatment-emergent adverse event rates was higher in patients receiving colesevelam HCl in combination with simvastatin, atorvastatin, or pravastatin (26%, 20%, and 13%, respectively) than in those receiving statins plus placebo (0% to 13%), but most adverse events were mild. The adverse events reported in $\geq 5\%$ of patients in any 1 treatment group are listed in Table 6. The incidence of mild gastrointestinal adverse effects was numerically higher in the colesevelam HCl plus statin group than in the placebo plus statin group. Fewer than 5% of patients in any of the statin-plus-placebo or statin-plus-colesevelam HCl treatment groups withdrew from the studies as a result of adverse events.

Discussion

The BASs, cholestyramine and colestipol, have been shown to reduce the risk of CHD events when administered either as monotherapy²⁻⁶ or as a part of combination therapy.⁷⁻¹⁰

These BASs also effectively reduce LDL cholesterol levels,²⁻⁵ but are often poorly tolerated and have significant drug interactions.¹¹ Colesevelam HCl is a specifically engineered BAS that has also shown efficacy in reducing LDL cholesterol levels and is generally well tolerated, with fewer drug interactions than seen with conventional BASs.¹¹ These studies were conducted to determine the effects of colesevelam HCl plus stable statin therapy with regard to the mean percent change in the levels of LDL cholesterol, other lipid parameters, and hs-CRP.

All 3 presented studies were similar in design and end points assessed. A limitation to these studies was that an unexpected, unusually large, favorable statin-plus-placebo effect on lipid variables was observed in 2 of the studies, which helped account for the lack of statistical significance observed for some of the lipid parameters in the colesevelam HCl plus statins group when compared with the placebo plus statin group. These findings were at odds with previous trials of colesevelam HCl and statin combination therapy in which the combination significantly reduced LDL cholesterol levels more than statins alone,¹¹⁻¹⁴ and the unanticipated reduced effect on lowering LDL cholesterol levels compared with placebo likely contributed to the lack of statistical significance found in the effects of colesevelam HCl on apo-B levels in the pooled analysis. A potential confounder was that although patients were required to be on a stable statin dose to meet the entry criteria of the study, the statin dose and stabilization before study entry were not confirmed beyond the patient reports. It is thus possible that the unexpected, large reduction in LDL cholesterol levels in the statin-plus-placebo group could have been due to improved statin compliance once the patients entered the trial, even if such improved compliance involved only a few study participants, given the relatively small number of subjects in the statin-plus-placebo groups. Additionally, statin compliance was not formally assessed throughout the trials, and LDL cholesterol levels are known to vary for reasons other than the type and dose of statins prescribed, including issues regarding patient compliance and adherence to therapy.¹⁵

In contrast to some of the lipid findings in the individual trials of colesevelam HCl plus a statin, data from the pooled analysis revealed that the addition of colesevelam HCl to

Table 6

Summary of treatment-emergent adverse events by system organ class and preferred term for individual trials ($\geq 5\%$ in one or two treatment groups) for all randomized patients

Adverse Event	Simvastatin		Atorvastatin		Pravastatin	
	+ Placebo (n = 25)	+ Colesevelam HCl (n = 47)	+ Placebo (n = 24)	+ Colesevelam HCl (n = 40)	+ Placebo (n = 20)	+ Colesevelam HCl (n = 47)
Gastrointestinal disorders	3 (12.0)	12 (25.5)	1 (4.2)	8 (20.0)	2 (10.0)	7 (14.9)
Constipation	0 (0.0)	4 (8.5)	0 (0.0)	5 (12.5)	—	—
Dyspepsia	1 (4.0)	4 (8.5)	0 (0.0)	2 (5.0)	—	—
Abdominal pain lower	—	—	—	—	1 (5.0)	0 (0.0)
Abdominal tenderness	—	—	—	—	1 (5.0)	1 (2.1)
Diarrhea NOS	—	—	—	—	1 (5.0)	1 (2.1)
Nausea	—	—	—	—	1 (5.0)	2 (4.3)
Musculoskeletal and connective tissue disorders	4 (16.0)	3 (6.4)	7 (29.2)	1 (2.5)	1 (5.0)	5 (10.6)
Myalgia	2 (8.0)	1 (2.1)	2 (8.3)	0 (0.0)	—	—
Arthralgia	—	—	4 (16.7)	0 (0.0)	1 (5.0)	2 (4.3)
Joint crepitation	—	—	2 (8.3)	0 (0.0)	—	—
Infections and infestations	—	—	2 (8.3)	6 (15.0)	1 (5.0)	6 (12.8)
Urinary tract infection NOS	—	—	0 (0.0)	2 (5.0)	—	—
Tooth abscess	—	—	—	—	1 (5.0)	0 (0.0)
Hepatobiliary disorders	—	—	—	—	1 (5.0)	0 (0.0)
Cholecystitis NOS	—	—	—	—	1 (5.0)	0 (0.0)

Data are presented as numbers (percentages).

Dash indicates that, in that trial, adverse event occurred in $<5\%$ of patients in both the colesevelam HCl and placebo groups.

NOS = not otherwise specified.

patients already on stable statin therapy resulted in the expected, superior mean reductions in levels of total cholesterol (treatment difference -8 mg/dl, $p < 0.05$) and LDL cholesterol (treatment difference -11 mg/dl, $p < 0.01$), with a greater median reduction in hs-CRP levels (treatment difference -0.3 mg/L, $p < 0.05$). Also, significant additional mean increases in apo-A-I levels (treatment difference $+8$ mg/dl, $p \leq 0.001$) were noted that may be clinically significant because low levels of apo-A-I may increase the risk of cardiovascular events.

A search and review of published data suggested that this is the first report of the effects of an approved cholesterol-lowering BAS on hs-CRP levels, probably because most of the studies on BAS were conducted before hs-CRP was routinely measured. This finding is consistent with previous data that cholesterol lowering, presumably through reducing the risk of CHD, reduces inflammatory markers of atherosclerosis. It is also consistent with data that nonabsorbable noncalcium-based hydrogels, approved as phosphate-binding agents in patients with renal failure, and which also bind bile acids, have been reported to reduce hs-CRP levels, possibly related to associated cholesterol lowering.¹⁶

For example, in the Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial (ADVENT), extended-release niacin was found to reduce hs-CRP levels, but not significantly (47% of patients were on concomitant statin therapy).¹⁷ Although niacin and statin combination therapy lowers LDL cholesterol and hs-CRP better than niacin alone, niacin monotherapy has been shown to have only moderate effects on lowering LDL cholesterol levels, which may help explain why little evidence is available to

support that niacin monotherapy lowers hs-CRP levels.¹⁸ Similarly, ezetimibe alone has not been shown to reduce hs-CRP levels¹⁹; however, the combination of ezetimibe and statins has been shown to reduce hs-CRP levels more than have statins alone.^{19,20} Consequently, although BASs are effective LDL cholesterol lowering drugs, the magnitude of LDL cholesterol reduction is less than that achieved with statin monotherapy. Therefore, it may be more difficult to achieve a statistically significant reduction in hs-CRP levels with these agents when used as monotherapy. However, our study has demonstrated that, when added to statin therapy, colesevelam HCl further reduces hs-CRP levels, likely as a result of improving CHD risk factors, such as reducing LDL cholesterol levels beyond that with statins alone, and other potential complementary and beneficial effects on other CHD risk factors.

In addition to statins,²¹ and colesevelam HCl plus statins, a reduction in hs-CRP levels has also been shown in response to other interventions that are generally associated with a reduction in CHD risk, such as lifestyle habits, including dietary intervention,²² LDL cholesterol apheresis,²³ and treatment with fenofibrate^{24–27} (but perhaps not all fibrates),²⁸ extended-release niacin plus lovastatin,¹⁸ ezetimibe plus simvastatin,^{19,20} some antidiabetes and hypertensive treatments, aspirin, and clopidogrel.^{29,30} These data collectively suggest that a correlation exists between the reduction in CHD risk and the reduction in hs-CRP levels by multiple interventions. Given the favorable effects on LDL cholesterol and hs-CRP levels found in this study, the addition of colesevelam HCl to a statin provides additional CHD risk reduction over the same dose of statin alone.

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