doi: 10.1111/j.1368-5031.2005.00714.x

# Lipid-altering efficacy of switching from atorvastatin 10 mg/day to ezetimibe/simvastatin 10/20 mg/day compared to doubling the dose of atorvastatin in hypercholesterolaemic patients with atherosclerosis or coronary heart disease

V. BARRIOS,[1] N. AMABILE,[2] F. PAGANELLI,[2] J-W CHEN,[3] C. ALLEN,[4] A. O. JOHNSON-LEVONAS,[5] R. MASSAAD,[6] K. VANDORMAEL[6]

*Department of Cardiology,[1] Hospital Ramón y Cajal, Madrid, Spain, Clinical Investigation Center,[2] Hôpital Nord, Marseille, France, National Yang-Ming University School of Medicine and Department of Cardiology,[3] Taipei Veterans General Hospital, Taipei, Taiwan, Merck & Co., Inc., Whitehouse Station, NJ, USA,[4] Rahway, NJ, USA,[5] and Brussels, Belgium[6]*

## SUMMARY

This randomised, double-blind study evaluated the efficacy and safety of ezetimibe/simvastatin (EZE/SIMVA) 10/20 mg tablet compared to doubling the atorvastatin (ATV) dose in hypercholesterolaemic patients with atherosclerotic or coronary heart disease (CHD).

The study group included 435 male and female CHD patients (aged $\geq$18 years) who had not achieved their low-density lipoprotein cholesterol (LDL-C) goal of $<$2.50 mmol/l while on a stable dose of ATV 10 mg for $\geq$6 weeks. After a 1-week diet/stabilisation period, patients with LDL-C $\geq$2.50 mmol/l and $\leq$4.20 mmol/l were randomised (1:1) to EZE/SIMVA 10/20 mg/day (n = 221) or ATV 20 mg/day (n = 214) for 6 weeks. The primary efficacy objective was to determine the per cent reduction from baseline in LDL-C at week 6.

EZE/SIMVA 10/20 mg produced significantly greater mean per cent changes from baseline in LDL-C compared with ATV 20 mg (−32.8 vs. −20.3%; $p \leq 0.001$). A significantly greater proportion of patients achieved an LDL-C goal $<$2.50 mmol/l with EZE/SIMVA than ATV (77.9 vs. 51.9%; $p \leq 0.001$). Significant improvements in total cholesterol (−20.3 vs. −13.0%), non-high-density lipoprotein cholesterol (non-HDL-C) (−27.9 vs. −17.0%), apolipoprotein B (−23.4 vs. −14.7%) and HDL-C (1.8 vs. −0.4%) were observed after switching to EZE/SIMVA 10/20 mg for 6 weeks ($p < 0.05$ for all parameters). EZE/SIMVA 10/20 mg was generally well tolerated, with an overall safety profile similar to that of ATV 20 mg.

EZE/SIMVA 10/20 mg produced superior lipid-altering efficacy by dual inhibition of cholesterol synthesis and intestinal absorption compared with doubling the dose of ATV from 10 to 20 mg.

**Keywords:** Atorvastatin, ezetimibe/simvastatin, hypercholesterolaemia, tablet, efficacy, coronary heart disease



## INTRODUCTION

The relationship between elevated levels of low-density lipoprotein cholesterol (LDL-C) and coronary heart disease (CHD) is firmly established. Several large placebo-controlled outcome trials showed that lowering plasma LDL-C decreases coronary event rates in patients with and without CHD (1–3). On the basis of this evidence, expert organisations recommend tailoring the intensity of lipid-lowering therapy to match the patient's risk of CHD (4,5). Patients with clinically established CHD or CHD-risk-equivalent disease (i.e. other atherosclerotic disease, diabetes mellitus or 10-year CHD risk >20% based on Framingham scoring) stand to recognise the greatest benefit from lipid-lowering therapy and are recommended for the most aggressive LDL-C goals ($<$2.5 mmol/l or $<$100 mg/dl). More recently, clinical data comparing intensive vs. moderate lipid lowering suggest that reducing plasma LDL-C to approximately 1.8 mmol/l (70 mg/dl) may provide additional outcome benefits in patients with stable and acute CHD (6,7). Consequently, optimal clinical benefits may be achieved using a more intensive treatment regimen designed to achieve LDL-C goals well below current guidelines (8).

Statins, the current treatment standard which inhibit cholesterol biosynthesis, have proven highly effective in reducing LDL-C and coronary risk in primary and secondary

*Correspondence to:*
Dr Vivencio Barrios, Department of Cardiology. Hospital Ramón y Cajal., Crta. Colmenar Viejo, Km 9,1. 28034 Madrid, Spain
Tel.: + 34 91 336 82 59
Fax: + 34 91 336 86 65
Email: vbarrios.hrc@salud.madrid.org and vbarriosa@meditex.es

prevention patients (1–3,6,7,9). However, despite the existence of evidence-based treatment guidelines and the availability of safe and efficacious therapies, recommended LDL-C goals are rarely achieved in CHD patients who have the most aggressive LDL-C goals and are at greatest risk for future coronary events (10–12). Combination therapy with statins and other lipid-lowering agents can improve the achievement of LDL-C goals, because agents with complementary mechanisms of action appear to exert additive effects on plasma lipids. Ezetimibe (EZE), a novel chemical entity that inhibits intestinal absorption of dietary and biliary cholesterol and structurally related phytosterols by interacting with a transporter in the epithelial wall (13,14), has been shown to reduce LDL-C by 18–25% beyond that achieved with statin monotherapy (15–17). As a result, patients who fail to attain optimal LDL-C levels with statin monotherapy have an opportunity to realise additional LDL-C reductions through simultaneous inhibition of cholesterol synthesis and intestinal absorption.

In the light of the marked lipid-altering efficacy of co-administered EZE and simvastatin (SIMVA) (16,18) and the beneficial effects of SIMVA on cardiovascular outcomes (1,9), a single tablet containing EZE 10 mg in combination with the full range of marketed doses of SIMVA (10, 20, 40 and 80 mg) has been approved for the treatment of primary hypercholesterolaemia (19). At the recommended starting dose, EZE/SIMVA 10/20 mg has been shown to provide superior LDL-C reductions compared with the initial and alternative starting doses of atorvastatin (ATV) (10 and 20 mg/day, respectively) (20). The purpose of the present study was to examine the lipid-altering efficacy and safety profile of switching from ATV 10 mg/day to EZE/SIMVA 10/20 mg/day vs. doubling the dose of ATV (20 mg/day) in CHD patients who were above their LDL-C goal of $<$2.50 mmol/l at baseline.

## PATIENTS AND METHODS

### Study Population

Eligible patients included men and women $\geq$18 years with documented hypercholesterolaemia and atherosclerotic or CHD. Patients had serum LDL-C between 2.5 and 4.2 mmol/l (100 to 160 mg/dl) and triglycerides (TG) $<$4.0 mmol/l (350 mg/dl) while on a stable dose of ATV 10 mg for $\geq$6 weeks prior to randomisation. Patients were considered to have CHD if they qualified as a CHD-risk equivalent by the National Cholesterol Education Program ATP III or ESC guidelines (e.g. diabetes) or if they presented with one or more of the following features: documented stable angina, history of myocardial infarction (MI) or percutaneous coronary intervention and/or documented history of unstable angina or non-Q wave MI. Atherosclerotic vascular disease included symptomatic peripheral vascular disease, documented history of atherosclerosis or atherothrombotic cerebrovascular disease. Patients of childbearing age were eligible to participate if they had negative pregnancy test results and were considered, by the study investigator, highly unlikely to conceive.

Key exclusion criteria included congestive heart failure; MI, coronary artery bypass surgery or angioplasty within the past 3 months; poorly controlled or newly diagnosed (within 3 months) Type I or II diabetes; uncontrolled hypertension (systolic $>$160 mmHg or diastolic $>$100 mmHg); uncontrolled endocrine or metabolic disease known to influence serum lipids; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels $>$1.5 times the upper limit of normal (ULN) and creatine kinase (CK) levels $>1.5\times$ ULN.

Patients could be withdrawn from the study for the following predefined reasons: positive pregnancy test, treatment with excluded concomitant medications (i.e. immunosuppressants, corticosteroids or potent inhibitors of cytochrome P450 3A4), two consecutive elevations in ALT and AST values $\geq 3\times$ ULN, two consecutive elevations in CK values of 5–10 or $\geq 10\times$ ULN with or without muscle symptoms or a significant clinical or laboratory adverse event (AE).

### Study Design

This study was conducted between March 2004 and November 2004. The protocol for this study was approved by the Institutional Review Board at each study centre, and all patients provided written informed consent. This approximately 9-week (1-week diet/stabilisation active run-in period followed by a 6-week active treatment period and a follow-up phone call/clinic visit 2 weeks thereafter), randomised, double-blind, active-controlled, parallel-group study was conducted according to Good Clinical Research Practice at 42 sites in seven countries (Estonia, France, Latvia, Netherlands, Slovenia, Spain and Taiwan) (Figure 1). Patients discontinued from all lipid-altering treatments other than ATV 10 mg for at least 6 weeks before the study start ($\geq$8 weeks for fibrates). Eligible patients entered a 1-week baseline period while continuing to receive open-label ATV 10 mg and counselling for a low-cholesterol diet. Qualifying patients were randomised (1:1) by a computer-generated allocation schedule to receive either blinded EZE/SIMVA 10/20 mg or blinded ATV 20 mg once daily for 6 weeks. Clinical visits were scheduled at week $-1$ (screening), day 1 (randomisation) and week 6 (lipid profile and efficacy assessment). A follow-up phone call or poststudy visit, if necessary, was scheduled 14 days after the final dose of study medication (week 8). Mean per cent compliance with study medication was defined as (number of compliant therapy days/number of

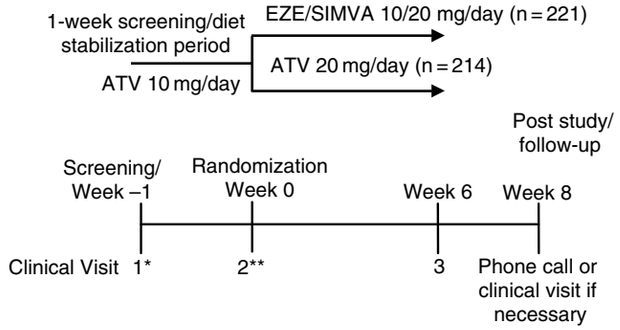


**Figure 1** Schematic study design. *During the screening period, blood was drawn for lipid measurements: low-density lipoprotein cholesterol, total cholesterol, triglycerides, high-density lipoprotein cholesterol and apolipoprotein B. Eligibility for randomisation was determined based on lipid measurements at visit 1. **Randomisation to double-blind treatment with ezetimibe/simvastatin (EZE/SIMVA) 10/20 mg or atorvastatin (ATV) 20 mg occurred at visit 2. Baseline measurements and samples for efficacy and safety parameters were taken at this visit

days between the randomisation date and the last day of treatment phase) × 100.

### Efficacy Assessments

The primary efficacy variable was mean per cent change from baseline in LDL-C at study endpoint. Endpoint was defined as the last postbaseline lipid measurement during the 6-week double-blind treatment period. Predefined secondary efficacy variables included mean per cent change from baseline to endpoint in total cholesterol (TC; key secondary endpoint), TG, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, LDL-C/HDL-C and TC/HDL-C ratios and apolipoprotein (apo) B. The per cent of patients in the treatment groups achieving an LDL-C goal <2.5 mmol/l after 6 weeks of randomised assignment was a predefined tertiary efficacy variable.

### Safety and Tolerability Assessments

Safety and tolerability were evaluated by reviewing patient-reported adverse signs and symptoms, investigators' observations and assessments and various laboratory tests including blood analyses. Investigators determined the severity of AEs (mild, moderate, severe or life threatening) and the potential relationship to study drug (definitely not, probably not, possibly, probably and definitely) while blinded to study medication. Key safety variables were the incidence of any clinical or laboratory AEs, treatment-related AEs, serious AEs and discontinuations because of AEs. Prespecified safety variables included the incidence of consecutive or presumed consecutive elevations in ALT and AST ≥3× ULN and single CK elevations of 5–10 or ≥10× ULN. Consecutive elevations in liver enzymes that were considered clinically important were defined as follows: (i) measurements ≥3× ULN observed on 2 or more consecutive visits; (ii) a single measurement ≥3× ULN which was the last available measurement (was referred to as 'presumed consecutive'); (iii) measurements >3× ULN during treatment or within 2 days after the end of treatment and followed by a measurement <3× ULN which was taken more than 2 days after the last dose of treatment (was referred to as 'presumed consecutive'). Myopathy was prospectively defined as CK elevations ≥10× ULN associated with muscle symptoms with no other plausible aetiology such as exercise or trauma.

### Laboratory Methods

All analyses were conducted on fasting blood samples at a certified central laboratory (MRLI Brussels, Belgium) according to standards specified by the National Heart Lung and Blood Institute and Centres for Disease Control and Prevention (12). All lipid measurements were blinded after randomisation. TC, HDL-C, TG and apo B were measured at all visits, and LDL-C levels were calculated with the Friedewald equation (LDL-C = TC − (TG/5) − HDL-C) (21). Ultracentrifugation was utilised to measure LDL-C values in patients with TG ≥4.52 mmol/l. Non-HDL-C levels were calculated by subtracting HDL-C from TC values. Apo B was quantified using radioimmunoassay methods.

### Statistical Analysis

A sample size of 290 patients (145 patients per group) was needed to detect a difference of 6% between the treatment groups for mean per cent change in LDL-C with 95% power and a significance level of 0.05 (two-tailed) assuming a standard deviation of 14%. The primary efficacy analysis was based on an all patient-treated approach, including those patients who received at least one dose of randomised treatment, had a lipid measurement at baseline and at least one lipid measurement following the start of treatment.

The per cent change from baseline to endpoint in LDL-C and other lipid parameters was assessed by an analysis of variance (ANOVA) model with terms for treatment and study centre. Data were expressed as within-group means and between-group differences in least square mean ± standard error of the mean. Median per cent change was calculated for TG, because this parameter is asymmetrically distributed and the between-treatment group difference was computed utilising Hodges–Lehmann estimate. Predefined subgroup analyses were performed for per cent LDL-C reduction on the following subgroups: age (<65 vs. ≥65 years), sex, race (Caucasian, Black and others; an analysis of subgroups Caucasian and non-Caucasian was performed due to small numbers of Blacks enrolled in this study), baseline LDL-C (<3.40 vs. ≥3.40 mmol/l), body mass index (<30 kg/m$^2$ vs. ≥30 kg/m$^2$), as well as patient

history of hypertension (no and yes) or diabetes mellitus (no and yes). An ANOVA model with terms for treatment, centre, subgroup and treatment-by-subgroup effect was tested at the $\alpha = 0.100$ level. The Gail-Simon test was used to determine the nature (qualitative vs. quantitative) of significant interaction terms.

A logistic regression model with terms for treatment and baseline LDL-C was used to analyse the per cent of patients reaching LDL-C target of <2.50 mmol/l. Odds ratio estimates derived from the logistic regression model and 95% confidence intervals (CI) were used to quantify the treatment effect. An analysis of LDL-C goal <1.8 mmol/l was performed in a post hoc manner.

Data from all randomised patients were included in safety and tolerability assessments. Fisher's Exact test was used to compare between-treatment incidences of predefined AEs (patients with any AE, treatment-related AEs, serious AEs and discontinuations because of AEs) and the proportion of patients with clinically important elevations in ALT and AST (individual and consecutive elevations ≥3× ULN) as well as CK (5–10 and ≥10× ULN).

## RESULTS

### Disposition, Demographics and Baseline Characteristics

A total of 752 patients were screened for randomisation. Of those screened, 317 (317/752 = 42%) were excluded from participation and 435 (435/752 = 58%) were enrolled in the study. The following reasons were given for exclusion: lack of eligibility per protocol (n = 305; 305/317 = 96%), consent withdrawn (n = 9; 9/317 = 3%) and AEs reported during the 1-week baseline/screening period (n = 3; 3/317 = 1%). Of those excluded due to lack of eligibility, 251 (251/305 = 82%) did not meet the established lipid entry criteria. The remaining 435 (58%) patients were randomised to treatment with EZE/SIMVA 10/20 mg (n = 221) or ATV 20 mg (n = 214). Of those randomised, 419 (96%) patients successfully completed the 6-week double-blind treatment period. Sixteen patients (4%; seven in the EZE/SIMVA group and nine in the ATV group) were discontinued from the study for the following reasons: clinical AE [n = 13 (3%)], patient withdrew consent [n = 1 (<1%)], protocol deviation [n = 1 (<1%), this patient receiving ATV 10 mg was already at LDL-C goal <2.5 mmol/l at baseline] and noncompliance with the protocol [n = 1 (<1%)].

The treatment groups were generally well balanced with respect to patient demographics, concomitant therapies and baseline lipid variables (Table 1). After an active run-in period with open-label ATV 10 mg, mean baseline LDL-C values were 3.19 and 3.24 mmol/l in the EZE/SIMVA and ATV groups, respectively. A total of eight patients (2%; four patients in each of the treatment groups) were excluded from the primary efficacy analysis because of clinical AE [n = 5 (1%)], consent withdrawn [n = 1 (<1%)], protocol deviation [n = 1 (<1%)] and noncompliance with protocol [n = 1 (<1%)]. Mean per cent compliance with study medication was similar between the treatment groups (98.0% EZE/SIMVA vs. 98.4% ATV).

### Efficacy

Switching from ATV 10 mg to EZE/SIMVA 10/20 mg produced a mean per cent reduction in LDL-C from baseline of 32.8% compared with 20.3% for ATV 20 mg (treatment difference in LS means = −12.6%, 95% CI, −15.8, −9.4; $p \leq 0.001$) (Figure 2, Table 2). In general, greater reductions in LDL-C were observed for EZE/SIMVA across subgroups defined by age, sex, body mass index, patient history of disease (hypertension and diabetes) and baseline LDL-C (Figure 3). A significant interaction between treatment and baseline LDL-C category was observed ($p = 0.090$) suggesting a slightly greater treatment difference in patients with lower baseline LDL-C levels (<3.4 mmol/l). Patients with baseline LDL-C <3.4 mmol/l demonstrated a mean per cent change from baseline in LDL-C of −31.1% with EZE/SIMVA vs. −16.5% with ATV 20 mg, while patients with baseline LDL-C ≥3.4 mmol/l had reductions of −37.0% with EZE/SIMVA vs. −26.9% with ATV.

The distribution of plasma LDL-C values at endpoint in the group of patients treated with EZE/SIMVA 10/20 mg and ATV 20 mg is illustrated in Figure 4. A significantly greater proportion of patients in the EZE/SIMVA group vs. the ATV group achieved an LDL-C goal of <2.50 mmol/l after 6 weeks of treatment [77.9% (n/N = 169/217) vs. 51.9% (n/N = 109/210); $p \leq 0.001$; Figures 4 and 5]. The estimated treatment effect [odds ratio (95% CI)] between the two groups was 3.3 in favour of EZE/SIMVA with a 95% CI of (2.1, 5.1). A post hoc analysis demonstrated that 26.7% (n/N = 58/217) of patients on EZE/SIMVA vs. 7.1% (n/N = 15/211) of patients on ATV 20 mg achieved the more aggressive LDL-C goal of <1.8 mmol/l ($p \leq 0.001$; Figure 5). The estimated treatment effect [odds ratio (95% CI)] between the two groups was 4.7 in favour of EZE/SIMVA with a 95% CI of (2.5, 8.6). Overall, three (1.4%) and seven (3.3%) patients demonstrated an increase in LDL-C >10% while receiving EZE/SIMVA 10/20 mg and ATV 20 mg, respectively.

In addition to producing significantly greater reductions in LDL-C, EZE/SIMVA also improved TC (−20.3 vs. −13.0%; $p \leq 0.001$), non-HDL-C (−27.9 vs. −17.0%; $p \leq 0.001$), Apo B (−23.4 vs. −14.7%; $p \leq 0.001$) and HDL-C (1.8 vs. – 0.4%; $p \leq 0.05$) relative to doubling the dose of ATV (Figure 2, Table 2). There was no statistically significant difference between the two treatment groups with

**Table 1** Patient characteristics and baseline lipid concentrations

| | *EZE/SIMVA 10/20 mg (n = 221)* | *ATV 20 mg (n = 214)* |
|---|---|---|
| **Age (years)** | | |
| Mean (SD) | 63.5 (9.6) | 63.4 (10.2) |
| Range | 43–90 | 32–86 |
| Number of patients ≥65 years (%) | 108 (48.9) | 98 (45.8) |
| **Number of females n (%)** | 80 (36.2) | 86 (40.2) |
| **Race n (%)** | | |
| White | 205 (92.8) | 197 (92.1) |
| Black | 1 (0.5) | 3 (1.4) |
| Other | 15 (6.8) | 14 (6.5) |
| **Weight; mean ± SD (kg)** | 80.9 (14.4) | 77.8 (13.3) |
| **Body mass index; mean ± SD (kg/m$^2$)** | 29.0 (4.4) | 28.0 (4.1) |
| **Duration of hypercholesterolaemia; mean ± SD (year)** | 7.5 (6.7) | 7.9 (7.1) |
| **Patient history of disease n (%)** | | |
| Hypertension | 141 (63.8) | 116 (54.2) |
| DM | 59 (26.7) | 53 (24.8) |
| **Concomitant therapies n (%)** | | |
| Drugs used in diabetes | 50 (22.6) | 41 (19.2) |
| Antithrombotic agents | 42 (19.0) | 53 (24.8) |
| Antihypertensive agents* | 193 (87.3) | 177 (82.7) |
| Cardiac therapy§ | 66 (29.9) | 79 (36.9) |
| Peripheral vasodilators | 8 (3.6) | 8 (3.7) |
| Vasoprotectives | 9 (4.1) | 6 (2.8) |
| **Baseline lipids; mean ± SD (mmol/l)** | | |
| LDL-C | 3.19 (0.45) | 3.24 (0.49) |
| TC | 5.31 (0.60) | 5.39 (0.64) |
| TG† | 1.48 (0.68) | 1.37 (0.73) |
| HDL-C | 1.38 (0.31) | 1.44 (0.35) |
| non-HDL-C | 3.93 (0.55) | 3.95 (0.59) |
| LDL-C/HDL-C ratio | 2.41 (0.60) | 2.38 (0.65) |
| TC/HDL-C ratio | 3.99 (0.83) | 3.92 (0.86) |
| Apo B‡ | 1.28 (0.18) | 1.27 (0.18) |

Apo, apolipoprotein; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides. *Includes agents acting on the renin-angiotensin system, beta blocking agents, calcium channel blockers, and diuretics. †Median values [standard deviation for medians calculated by (Q3 − Q1)/1.075]. §Includes cardiac glycosides, antiarrhythmics class I and III, vasodilators used in cardiac diseases and other cardiac preparations. ‡Expressed as g/l.

regard to median per cent change from baseline in plasma TG ($p = 0.268$).

## Safety and Tolerability

Treatment with EZE/SIMVA 10/20 mg was generally well tolerated, with an overall safety profile similar to that of ATV 20 mg (Table 3). There were no significant differences between the two treatment groups with regard to the type or frequency of clinical [44 (20%) vs. 51 (24%), respectively] and laboratory [4 (2%) vs. 4 (2%), respectively] AEs, discontinuations because of clinical [5 (2%) vs. 8 (4%), respectively] and laboratory (zero patients in each treatment group) AEs or serious clinical [5 (2%) vs. 2 (1%), respectively] and laboratory (zero patients in each treatment group) AEs. The most frequently reported clinical AE (≥2% frequency in either treatment group) in the two groups included myalgia [6 (2.7%) EZE/SIMVA vs. 5 (2.3%) ATV] and headache [3 (1.4%) EZE/SIMVA vs. 8 (3.7%) ATV]. Overall, serious AEs occurred in five patients receiving EZE/SIMVA 10/20 mg (four patients had an overdose and one patient had chest pain) and two patients receiving ATV 20 mg (one patient had acute coronary syndrome and one patient had pelvic fracture). None of these events were fatal, and none were considered by study investigators to be related to study medication.

None of the patients in the ATV group and one patient in the EZE/SIMVA group had presumed consecutive elevations in ALT and AST values ≥3× ULN. The patient's elevated ALT and AST values resolved while continuing on EZE/SIMVA therapy. There were no cases of hepatitis, jaundice or other clinical signs of hepatic dysfunction reported in this

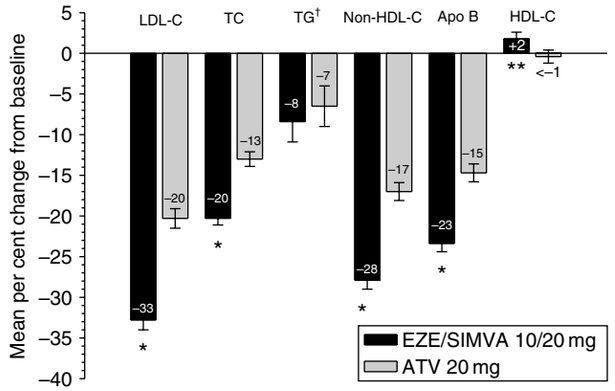


**Figure 2** Mean per cent change (±SE) from baseline in lipid parameters following 6 weeks of treatment with ezetimibe/simvastatin (EZE/SIMVA) 10/20 mg or atorvastatin (ATV) 20 mg (*$p \leq 0.001$ EZE/SIMVA vs. ATV; **$p < 0.050$ EZE/SIMVA vs. ATV). †Expressed as median per cent change (±SE of median). Apo B, apolipoprotein B; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides

study, including the one patient with high ALT and/or AST values. No patients in either treatment group had elevations in CK levels (≥3 to <5× ULN, ≥5 to <10× ULN or ≥10× ULN), and there were no reported cases of myopathy or rhabdomyolysis. Results of other laboratory tests, including routine serum chemistries, and haematologic parameters as well as vital signs and findings on physical examinations revealed no evidence of additional safety concerns with EZE/SIMVA therapy.

## DISCUSSION

Cholesterol treatment guidelines emphasise LDL-C lowering as an essential strategy for reducing cardiovascular risk. The Third European Joint Task Force (European) and National Cholesterol Education Program Adult Treatment Panel III (United States) guidelines recommend an optional LDL-C treatment target of <2.5 mmol/l for patients with established CHD or CHD-risk-equivalent disease (2,5). Recent evidence suggests that patients with stable and acute CHD may realise additional clinical benefits with the achievement of LDL-C levels substantially below 2.5 mmol/l (6,7,9). In the past, physicians increased the intensity of lipid lowering by upwardly titrating the statin dose or switching to a more potent statin. However, many statin-treated patients remain under treated because of insufficient pharmacologic effects of marketed statins, a lack of willingness on the part of physicians and patients to perform multiple dose escalations, as well as concerns over safety risks at the highest statin doses (22,23).

A new treatment paradigm, a single cogranulated tablet containing EZE 10 mg in combination with the full range of marketed doses of SIMVA (10–80 mg), is available for the management of LDL-C levels in patients who are not at their treatment goals (19). Previous studies showed that EZE/SIMVA is more effective than statin monotherapy in improving plasma lipid profiles in patients with hypercholesterolaemia (15,20). The enhanced efficacy of the EZE/SIMVA tablet may improve LDL-C goal attainment in high-risk patients by simultaneously inhibiting cholesterol synthesis and intestinal absorption while avoiding the safety risks (hepatotoxicity and myotoxicity) associated with high-dose statin monotherapy.

The present study demonstrated that EZE/SIMVA is more effective than ATV titration in reducing LDL-C among hypercholesterolaemic patients with atherosclerotic or CHD. In this study of atherosclerotic and CHD patients on a stable dose of ATV 10 mg/day, the recommended starting dose of EZE/SIMVA 10/20 mg reduced LDL-C levels by 33% compared with only 20% with the alternative minimum starting

**Table 2** Mean per cent change in efficacy parameters from baseline to endpoint

| | *Mean per cent change (±SE)* | | *Between-group treatment difference* | |
|---|---|---|---|---|
| *Efficacy parameter* | *EZE/SIMVA 10/20 mg (n = 215–217)* | *ATV 20 mg (n = 207–210)* | *Difference in least squares per cent change (SE)* | *p value* |
| LDL-C | −32.8 (1.2) | −20.3 (1.2) | −12.6 (1.6) | ≤0.001 |
| TC | −20.3 (0.8) | −13.0 (0.9) | −7.2 (1.2) | ≤0.001 |
| TG* | −8.4 (2.5) | −6.5 (2.5) | −3.2 (3.7)† | ns‡ |
| HDL-C | +1.8 (0.8) | −0.4 (0.8) | +2.5 (1.2) | <0.050 |
| Non-HDL-C | −27.9 (1.1) | −17.0 (1.1) | −10.8 (1.5) | ≤0.001 |
| LDL-C/HDL-C ratio | −33.2 (1.3) | −19.1 (1.3) | −14.4 (1.8) | ≤0.001 |
| TC/HDL-C ratio | −20.9 (1.0) | −11.7 (1.0) | −9.3 (1.4) | ≤0.001 |
| Apo B | −23.4 (1.0) | −14.7 (1.1) | −8.5 (1.4) | ≤0.001 |

Apo, apolipoprotein; ATV, atorvastatin; EZE, ezetimibe; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ns, not significant at $p > 0.050$; TC, total cholesterol; TG, triglycerides; SE, standard error; SIMVA, simvastatin. *Median values (standard error for medians). †Difference in medians was obtained by Hodges–Lehmann estimation. ‡Test based on nonparametric analysis using ANOVA on the normalised (Tukey's) rank transformation.

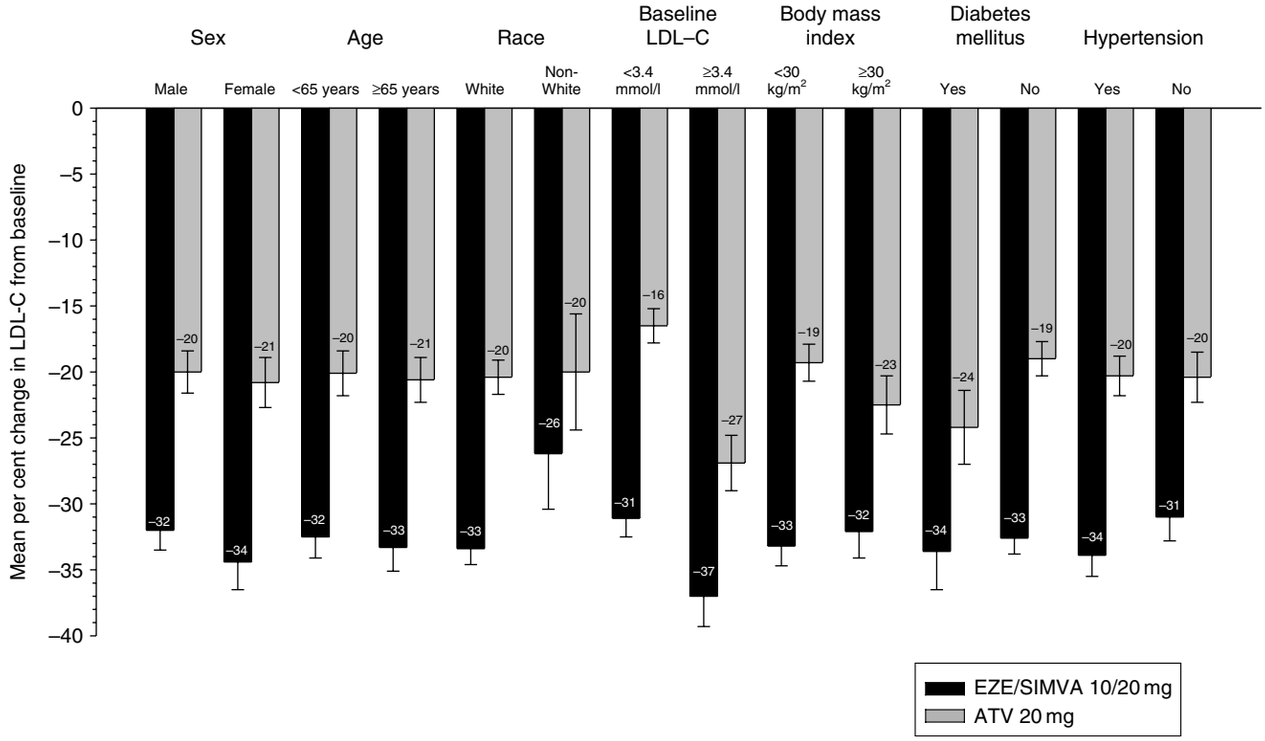


**Figure 3** Mean per cent change from baseline in low-density lipoprotein cholesterol (LDL-C) across subgroups defined by sex, age, race, baseline LDL-C, body mass index, and patient history of disease (diabetes, hypertension). ATV, atorvastatin; EZE/SIMVA, ezetimibe/simvastatin

dose of ATV 20 mg, leading to a between-treatment group difference of −13% ($p \leq 0.001$). In general, the enhanced LDL-C-lowering efficacy of EZE/SIMVA was consistent across the patient subgroups examined [age, sex, body mass index and patient history of disease (diabetes and hypertension)] and baseline LDL-C. There was a significant treatment-by-subgroup interaction ($p = 0.090$) when data were stratified according to baseline LDL-C; however, patients achieved greater LDL-C reductions with EZE/SIMVA than ATV alone, irrespective of their baseline LDL-C values. Relative to ATV, treatment with EZE/SIMVA allowed significantly more CHD patients to achieve an LDL-C goal of

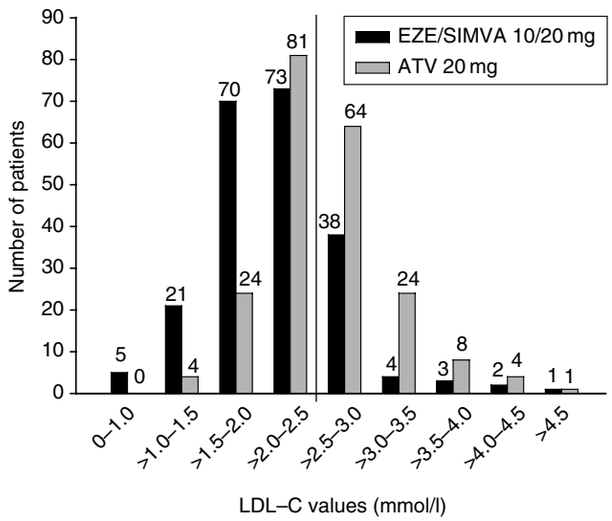


**Figure 4** Frequency histogram showing the distribution in plasma low-density lipoprotein cholesterol (LDL-C) levels (mmol/l) following 6 weeks of treatment with ezetimibe/simvastatin (EZE/SIMVA) 10/20 mg or atorvastatin (ATV) 20 mg

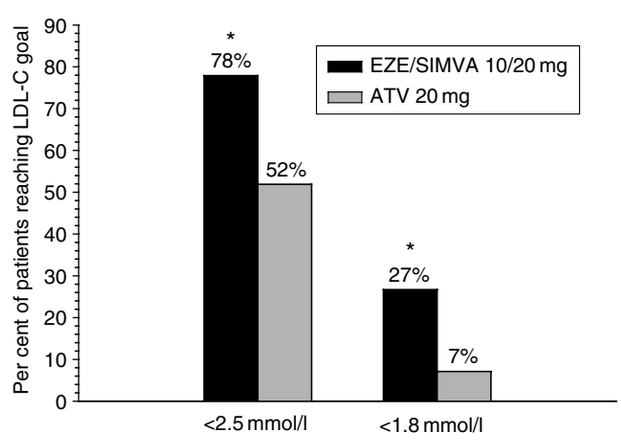


**Figure 5** Per cent of patients [expressed as number of patients achieving low-density lipoprotein cholesterol (LDL-C) goal/number of patients above LDL-C goal at baseline] reaching an LDL-C goal of <2.5 mmol/l or <1.8 mmol/l following 6 weeks of treatment with ezetimibe/simvastatin (EZE/SIMVA) 10/20 mg or atorvastatin (ATV) 20 mg (*$p \leq 0.001$ EZE/SIMVA vs. ATV)

**Table 3** Overall summary of safety results [n/N (%)]

| *Adverse event* | *EZE/SIMVA 10/20 mg* | *ATV 20 mg* | *p value** |
|---|---|---|---|
| Number of patients randomised | 221 | 214 | |
| Number of patients completing study | 214 | 205 | |
| **Number of patients** (%) | | | |
| With one or more clinical AEs | 44 (19.9) | 51 (23.8) | 0.354 |
| With treatment-related† clinical AEs | 17 (7.7) | 23 (10.7) | 0.320 |
| With serious clinical AEs | 5 (2.3) | 2 (0.9) | 0.450 |
| With serious treatment-related† clinical AEs | 0 | 0 | – |
| Discontinued due to clinical AEs | 5 (2.3) | 8 (3.7) | 0.410 |
| Discontinued due to treatment-related† clinical AEs | 5 (2.3) | 8 (3.7) | – |
| With one or more laboratory AEs‡ | 4/217 (1.8) | 4/210 (1.9) | 1.000 |
| With treatment-related† laboratory AEs‡ | 3/217 (1.4) | 2/210 (1.0) | 1.000 |
| With serious laboratory AEs | 0 | 0 | 1.000 |
| Discontinued due to laboratory AEs‡ | 0 | 0 | 1.000 |
| Consecutive $\geq$3× ULN elevations in ALT and/or AST‡§ | 1/217 (0.5) | 0 | 1.000 |
| CK $\geq$10× ULN | 0 | 0 | 1.000 |

AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATV, atorvastatin; CK, creatine kinase; EZE, ezetimibe; N, number of patients randomised to treatment groups; SIMVA, simvastatin; ULN, upper limit of normal. *Calculated based on Fisher's Exact test. †Rated as possibly, probably or definitely treatment related by study investigator. ‡Expressed as number of patients with a laboratory AE/number of patients with one or more laboratory tests postbaseline. §This category includes those subjects with (i) two consecutive measurements for ALT and/or AST $\geq$3× ULN and (ii) a single, last measurement $\geq$3× ULN or (iii) a measurement $\geq$3× ULN followed by a measurement <3× ULN that was taken more than 2 days after the last dose of study medication.

<2.5 mmol/l (52 vs. 78%, respectively; $p \leq 0.001$) and <1.8 mmol/l (7 vs. 27%, respectively; $p \leq 0.001$). The post hoc analysis of the more aggressive, but optional, LDL-C target of <1.8 mmol/l confirmed that very few CHD patients can achieve this goal with the alternative minimum starting dose of ATV 20 mg. This finding highlights the need for alternative lipid-lowering therapies that are well tolerated in high-risk patients.

Both ATV 10 mg and SIMVA 20 mg are known to lower LDL-C to a similar degree (−33 to −37%) (24,25); thus, the incremental reduction in LDL-C observed with EZE/SIMVA 10/20 mg was primarily attributable to EZE component of the tablet. Of note, patients in the EZE/SIMVA 10/20 mg group demonstrated a larger than anticipated reduction in LDL-C (−33%) compared with the −25% decrease previously observed in similarly designed studies (17,26). Additionally, the LDL-C response observed upon doubling the dose of ATV (−20%) was much greater than the 10–11% incremental reduction that is normally seen in patients receiving statin therapy at baseline (27). In statin naïve patients, each doubling of the statin dose produces an average incremental reduction in LDL-C of 5–6% based on untreated baseline LDL-C value (the so-called 'rule of 6' for statins).

A limitation of our study is that our findings may have been observed due to chance or influenced by two statistical phenomena, namely regression to the mean and bias of the mean per cent change statistics (28,29). The selection of a sample of patients with LDL-C $\geq$2.5 mmol/l while receiving ATV 10 mg may induce regression to the mean because of the weak correlation between baseline and on-treatment LDL-C values in both the EZE/SIMVA and the ATV groups ($\rho = 0.3$ for both the groups). Furthermore, the incremental mean per cent change in LDL-C is a function of baseline LDL-C values (calculated as change in LDL-C/baseline LDL-C). Patients in this study had lower baseline LDL-C levels because of prior treatment with ATV 10 mg thereby inflating mean per cent change in both the treatment groups. This phenomenon also explains why the 'rule of 6' for doubling the statin dose should only be applied to statin-naïve patients. Despite these issues, however, the present study demonstrates that EZE/SIMVA 10/20 mg provides superior reductions in LDL-C compared with doubling the ATV dose to 20 mg.

In addition to producing beneficial effects on LDL-C, administration of EZE/SIMVA 10/20 mg led to significantly greater improvements in TC, HDL-C, non-HDL-C, LDL-C/HDL-C, TC/HDL-C and apo B ($p < 0.050$ for all endpoints). The TG decreases observed with EZE/SIMVA 10/20 mg, although significant compared with baseline, did not differ from that achieved with ATV 20 mg. A previous study of low- and high-risk hypercholesterolaemic patients also demonstrated comparable TG reductions with EZE/SIMVA vs. ATV monotherapy at milligram-equivalent statin dose comparisons (e.g. EZE/SIMVA 10/20 mg vs. ATV 20 mg) (20).

EZE/SIMVA 10/20 mg was well tolerated in this population of high-risk patients with an overall safety profile similar to ATV 20 mg. There were no clinically meaningful differences between the treatment groups with regard to the incidence of clinical or laboratory AEs, including those related to muscle and liver toxicity. None of the 221 patients receiving

EZE/SIMVA had CK elevations ≥10× ULN, and only one patient (<1%) had presumed consecutive elevations in ALT and AST values ≥3× ULN. Overall, the safety profile of EZE/SIMVA 10/20 mg tablet was consistent with that observed in previous studies (15,20).

In summary, this study of hypercholesterolaemic patients with atherosclerotic or CHD who had elevated LDL-C levels despite treatment with ATV 10 mg/day clearly demonstrated that the strategy of switching to EZE/SIMVA 10/20 mg is more effective in improving the atherogenic lipid profile (LDL-C, TC, HDL-C, non-HDL-C, LDL-C/HDL-C, TC/HDL-C and apo B) than doubling the dose of ATV to 20 mg. Thus, through dual inhibition of two sources of plasma cholesterol, hepatic synthesis and intestinal absorption, EZE/SIMVA offers a well-tolerated and highly efficacious treatment option for managing LDL-C levels in high-risk patients who are not at their treatment goals.

## ACKNOWLEDGEMENTS

This study was funded by Merck/Schering-Plough Pharmaceuticals, North Wales, Pennsylvania. The authors gratefully acknowledge Margaret Lund, RN, as central study coordinator, and Janice E. Grant for assistance with preparing this manuscript for publication. We thank the following investigators for participating in the study: **Estonia**: T. Laks, MD, Tallinn (n = 9), A. Mesikepp, MD, Tallinn (n = 11), M. Viigimaa, MD, Tartu (n = 16); **France**: R. Arnou, MD, Angers (n = 12), C. Belliard, MD, Mayenne (n = 2), P.-Y. Benhamou, Prof, Grenoble cedex (n = 1), J.-C. Bodart, MD, Valenciennes cedex (n = 1), H. Bosquet, MD, Cherbourg (n = 3), F. Brault, MD, Château Gontier (n = 12), E. Decoulx, MD, Tourcoing cedex (n = 3), A. Dutour-Meyer, Prof, Marseille cedex (n = 3), M. Goralski, MD, Orleans (n = 6), G. Haddad, MD, Pontoise (n = 3), J-M. Kuhn, Prof, Bois Guillaume (n = 2), A. Marquand, MD, Fréjus (n = 1), J.-P. Normand, MD, Le Chesnay cedex (n = 1), F. Paganelli, Prof, Marseille cedex (n = 7), D. Richter, MD, Jarny (n = 15), C. Ridel, MD, Nantes (n = 5), M. Rodier, MD, Nimes (n = 2); **Latvia**: U. Kalnins, MD, Riga (n = 10), J. Raibarts, MD, Riga (n = 10), I.A. Rubine, MD, Riga (n = 10); **Netherlands**: B.J. van den Berg, MD, Capelle a/d Ijssel (n = 5), C. von Birgelen, MD, Enschede (n = 18), A. Derks, MD, Hengelo (n = 2), W. Jaarsma, Nieuwegein (n = 4), L.H.J. van Kempen, MD, Velp (n = 7), A.J.M. Oude Ophuis, MD, Nijmegen (n = 11), A.J.A.M. Withagen, MD, Delft (n = 6); **Slovenia**: V. Kanic, Sp Int. MD, Maribor (n = 4), F. Skrabi-Mocr, MD, Celje (n = 12); **Spain**: V. Barrios Alonso, MD, and A. Amador Borrego, MD, Madrid (n = 23), V. Bertomeu Martinez, MD, Alicante (n = 11), I. Gonzalez-Maqueda, MD, Madrid (n = 5), M. Jimenez Navarro, MD, Malaga (n = 6), A. Palencia Perez, MD, Valencia (n = 8), C. Pallares Monleon, MD, Barcelona (n = 5), J. Ruiz Ros, MD, Murcia (n = 4), L. Silva Melchor, MD, Madrid (n = 4); **Taiwan**: J.-W. Chen, MD, Taipei (n = 11), C.-C. Wu, MD, Taipei (n = 15).

## REFERENCES

1 Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; **344**: 1383–9.

2 Shepherd J, Cobbe SM, Ford I et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West Scotland Coronary Prevention Study Group. *N Engl J Med* 1995; **333**: 1301–7.

3 Downs JR, Clearfield M, Weis S et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998; **279**: 1615–22.

4 De Backer G, Ambrosioni E, Borch-Johnsen K et al. European guidelines on cardiovascular disease prevention in clinical practice. Third joint task force of European and other societies on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2003; **24**: 1601–10.

5 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of The National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* 2001; **285**: 2486–97.

6 LaRosa JC, Grundy SM, Waters DD et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005; **352**: 1425–35.

7 Cannon CP, Braunwald E, McCabe CH et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004; **350**: 1495–504.

8 Grundy SM, Cleeman JI, Merz CN et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Arterioscler Thromb Vasc Biol* 2004; **24**: e149–61.

9 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360**: 7–22.

10 EUROASPIRE II Study Group. Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries; principal results from EUROASPIRE II Euro Heart Survey Programme. *Eur Heart J* 2001; **22**: 554–72.

11 EUROASPIRE I and II Group. Clinical reality of coronary prevention guidelines: a comparison of EUROASPIRE I and II in nine countries. EUROASPIRE I and II Group. European Action on Secondary Prevention by Intervention to Reduce Events. *Lancet* 2001; **357**: 995–1001.

12 Pearson TA, Laurora I, Chu H, Kafonek S. The lipid treatment assessment project (L-TAP): a multicenter survey to evaluate the

percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Arch Intern Med* 2000; **160**: 459–67.

13 Altmann SW, Davis HR Jr, Zhu LJ et al. Niemann-Pick C1 Like 1 protein is critical for intestinal cholesterol absorption. *Science* 2004; **303**: 1201–4.

14 Garcia-Calvo M, Lisnock J, Bull HG et al. The target of ezetimibe is Niemann-Pick C1-Like 1 (NPC1L1). *Proc Natl Acad Sci USA* 2005; **102**: 8132–7.

15 Bays HE, Ose L, Fraser N et al. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared with ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. *Clin Ther* 2004; **26**: 1758–73.

16 Davidson MH, McGarry T, Bettis R et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. *J Am Coll Cardiol* 2002; **40**: 2125–34.

17 Gagne C, Bays HE, Weiss SR et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. *Am J Cardiol* 2002; **90**: 1084–91.

18 Goldberg AC, Sapre A, Liu J, Capece R, Mitchel YB. Efficacy and safety of ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc* 2004; **79**: 620–9.

19 Vytorin [package insert], North Wales (PA); Merck/Schering-Plough Pharmaceuticals, 2004. 2005.

20 Ballantyne CM, Abate N, Yuan Z, King TR, Palmisano J. Dose-comparison study of the combination of ezetimibe and simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia: the Vytorin Versus Atorvastatin (VYVA) study. *Am Heart J* 2005; **149**: 464–73.

21 Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972; **18**: 499–502.

22 Anonymous. Cholesterol rethink for high-risk patients. *Med Lett Drugs Ther* 2004; **46**: 37–9.

23 Hoerger TJ, Bala MV, Bray JW, Wilcosky TC, LaRosa J. Treatment patterns and distribution of low-density lipoprotein cholesterol levels in treatment-eligible United States adults. *Am J Cardiol* 1998; **82**: 61–5.

24 Heinonen TM, Stein E, Weiss SR et al. The lipid-lowering effects of atorvastatin, a new HMG-CoA reductase inhibitor: results of a randomized, double-masked study. *Clin Ther* 1996; **18**: 853–63.

25 Farnier M, Portal JJ, Maigret P. Efficacy of atorvastatin compared with simvastatin in patients with hypercholesterolemia. *J Cardiovasc Pharmacol Ther* 2000; **5**: 27–32.

26 Pearson TA, Denke MA, McBride PE, Battisti WP, Brady WE, Palmisano J. A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: the ezetimibe add-on to statin for effectiveness (EASE) trial. *Mayo Clin Proc* 2005; **80**: 587–95.

27 Stein E, Stender S, Mata P et al. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: efficacy and safety of ezetimibe co-administered with atorvastatin. *Am Heart J* 2004; **148**: 447–55.

28 Morton V, Torgerson DJ. Regression to the mean: treatment effect without the intervention. *J Eval Clin Pract* 2005; **11**: 59–65.

29 Bonate P. *Analysis of Pretest-Posttest Designs*, Boca Raton, Florida: Chapman & Hall/CRC 2000.

*Paper received June 2005, accepted September 2005*