ORIGINAL ARTICLE

The efficacy of statin monotherapy uptitration versus switching to ezetimibe/simvastatin: results of the EASEGO study*


*Oosterscheldeziekenhuizen, Goes, The Netherlands
*Amphia Ziekenhuis, Breda; Department of Pharmacology, University of Groningen, The Netherlands
*Academic Medical Center, Amsterdam, The Netherlands
*Leiden University Medical Center, Leiden, The Netherlands

Address for correspondence: J. Wouter Jukema, MD Professor of Cardiology, Department of Cardiology, C5/P, Leiden University Medical Center, PO Box 9600, 2300RC Leiden, The Netherlands. j.w.jukema@lumc.nl

Key words: Atorvastatin – Cardiovascular disease – Ezetimibe – LDL-C lowering – LDL-subfractions – Simvastatin

ABSTRACT

Objective: To assess the incremental low-density lipoprotein-cholesterol (LDL-C) lowering efficacy of doubling the statin dose or switching to the ezetimibe/simvastatin 10/20 mg combination tablet (EZE/SIMVA) in patients on simvastatin 20 mg or atorvastatin 10 mg not at LDL-C target < 2.5 mmol/L.

Study design and methods: Patients with documented coronary heart disease (CHD) and/or type 2 diabetes (DM2) with LDL-C ≥ 2.5 and < 5.0 mmol/L despite treatment with atorvastatin 10 mg or simvastatin 20 mg were randomized to (1) double statin dose or (2) switch to ezetimibe/simvastatin 10/20, according to a PROBE study design. LDL-C, lipoprotein subfractions and safety data were assessed during the study.

Results: 119 of 178 (67%) patients in the EZE/SIMVA group and 49 of 189 (26%) in the doubling statin group reached target LDL-C < 2.5 mmol/L. The odds ratio of success for EZE/SIMVA versus doubling statin treatment in reaching the LDL-C target of < 2.5 mmol/L was 5.7 (95% CI: 3.7–9.0, p < 0.0001). A reduction in total cholesterol (TC), total/high density lipoprotein (HDL) cholesterol ratio and apolipoprotein B was observed in both groups, but this reduction was significantly more pronounced in the EZE/SIMVA group as compared with the doubling statin dose group. Treatment was well tolerated and no difference was observed between the two groups with regard to adverse effects.

Conclusions: In CHD/DM2 patients treated with simvastatin or atorvastatin with LDL-C persistently ≥ 2.5 mmol/L, switching to the EZE/SIMVA was more effective in attaining the LDL-C target of < 2.5 mmol/L than doubling the statin dose.

Introduction

The importance of achieving low-density lipoprotein-cholesterol (LDL-C) treatment levels of < 2.5 mmol/L, with < 2.0 mmol/L recommended in very high-risk patients, is well established. These treatment goals in patients with coronary heart disease (CHD) or diabetes type 2 (DM2) are well defined in international guidelines. Atorvastatin and simvastatin are widely used in these patients, with

* Study results were presented at the WCN research congress, November 22, 2007; Amsterdam
recommended starting doses of 10 and 20 mg daily, respectively. A large proportion of these patients do not attain target LDL-C levels during treatment with these recommended starting doses\(^{4}\). In general there are three treatment options for patients on statin therapy and LDL-C levels above target: (1) increase the statin dose, (2) switch to a more potent statin, or (3) add a drug with an effect complementary to that of a statin, for example, a cholesterol absorption inhibitor like ezetimibe\(^{7}\).

Doubling the statin dose in patients with insufficient LDL-C lowering on recommended starting doses may not lead to the desired effect for lack of efficacy\(^{4}\). A higher statin dose has proven less effective in further decreasing hepatic cholesterol synthesis and may even lead to increased intestinal cholesterol absorption\(^{7}\). While a switch to a more potent statin may improve cholesterol biosynthesis inhibition, it may not solve the problem of cholesterol absorption abnormalities. Theoretically, therefore, the addition of a cholesterol absorption inhibitor would seem an attractive alternative to doubling the statin dose or switching to a more potent statin.

Ezetimibe is a cholesterol absorption inhibitor with demonstrated efficacy and tolerability, introducing a LDL-C-lowering mechanism independent of cholesterol biosynthesis inhibition\(^{10}\).

To test this hypothesis, the Ezetimibe And Simvastatin versus doubleE statin reach new lipid treatment GOals study (EASEGO), was designed.

The EASEGO study assesses the incremental LDL-C lowering efficacy of either (1) doubling the statin dose or (2) switching to the ezetimibe/simvastatin 10/20 mg tablet (EZE/SIMVA) in CHD/DM2 patients on the recommended starting doses of simvastatin 20 mg or atorvastatin 10 mg who failed to achieve the recommended European Society of Cardiology target of LDL-C < 2.5 mmol/L.

The primary endpoint was to assess the percentages of patients reaching the ESC goal\(^{1}\) of LDL-C < 2.5 mmol/L when switched to EZE/SIMVA versus doubling the statin dose.

Patients and methods

Study design

The study was conducted between December 2005 and March 2007 at 21 cardiology outpatient clinics in the Netherlands. At the end of the predetermined inclusion period (May 2006) less than 100 patients were included in the study. The inclusion period was, therefore, prolonged by 6 months. The inclusion of patients on simvastatin was then completed; the inclusion of patients on atorvastatin was not fully completed by this time due to difficulties in enrolling CHD/DM2 patients treated with atorvastatin 10 mg. Nevertheless, approximately 180 patients were included in each group, which was sufficient to provide > 95% power for the primary effect parameter. The protocol was approved by the Medical Ethical Committee (Independent Review Board, Amsterdam) and was conducted according to Good Clinical Research Practice and the World Medical Association Declaration of Helsinki. All patients provided written informed consent.

This prospectively randomized, open label, blinded endpoint (PROBE design) comparative study was designed to assess the incremental LDL-C-lowering efficacy of (1) doubling the statin dose or (2) switching to EZE/SIMVA in CHD/DM2 patients on the recommended starting doses of simvastatin 20 mg or atorvastatin 10 mg who failed to achieve the recommended European Society of Cardiology target of LDL-C < 2.5 mmol/L.

The primary endpoint was to assess the percentages of patients reaching the ESC goal\(^{1}\) of LDL-C < 2.5 mmol/L when switched to EZE/SIMVA versus doubling the statin dose.

Furthermore, mean total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), apolipoprotein (apo-B) and TC/HDL-C ratio values were compared between the two groups (secondary endpoint). Additionally, treatment effect was evaluated in a patient subset with respect to the change in cholesterol concentration in LDL subfractions, isolated by means of gradient ultracentrifugation.

Safety and tolerability of EZE/SIMVA was also assessed throughout the study.

Study duration was 15 weeks: 1 week run-in period, 12 weeks treatment period, followed by a post-study follow-up phone call or visit after 2 weeks.

Eligible patients started with a 1 week run in period. Medical history was reviewed and a physical examination performed. Patients received counseling for a cholesterol-lowering diet and fasting blood samples were drawn for analyses of plasma lipids and liver enzymes in a central laboratory. After 1 week the investigator was informed by the central laboratory if the patient met the biochemical inclusion criteria and could be randomized. Eligible patients were randomized after this week by a computer-generated schedule to continuation of statin monotherapy at a double dose (atorvastatin 20 mg or simvastatin 40 mg) or to EZE/SIMVA. The study design is summarized in a flow diagram (Figure 1).

The protocol provided for an exploratory objective in a patient subgroup, by collecting an extra blood sample from the patients who were first enrolled.
Efficacy of switching to ezetemibe/simvastatin: EASEGO study

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Extensive analyses of cholesterol concentrations in the isolated lipoprotein fractions were performed in this subgroup by two different lipoprotein isolation procedures using the ultracentrifuge. The changes in total cholesterol concentration, in very-low-density lipoprotein (VLDL)-C, intermediate-density lipoprotein (IDL)-C and LDL-C were analyzed after isolation of these lipoproteins by means of standard Redgrave gradient. The change in cholesterol concentration in LDL subfractions was measured by isolation of LDL subfractions using a specific ultracentrifugation step as described by Griffin.

Safety and tolerability assessment was performed for all patients throughout the study.

Study population

Inclusion criteria for the EASEGO study included men and women > 18 years of age with controlled stable DM2 (> 3 months) and/or established CHD. CHD was defined as at least one of the following: stable angina; history of myocardial infarction; history of percutaneous coronary intervention; coronary stenosis on angiography; history of unstable angina or non-Q wave myocardial infarction; history of coronary artery bypass graft surgery (CABG) or positive isotope myocardial perfusion scan. Patients had to be in a stable medical condition.

Patients were required to be on a stable daily statin dose of either atorvastatin 10 mg or simvastatin 20 mg for at least 4 weeks. In principle this is the minimum acceptable duration for relatively stable lipid values and, therefore, acceptable. (Note: in our study virtually all patients appeared to be on stable statin therapy for > 3 months.)

Entry lipid values while on statin monotherapy were: LDL-C ≥ 2.5 mmol/L and < 5.0 mmol/L, TG ≤ 4.0 mmol/L and TC ≤ 7.0 mmol/L. Female patients were postmenopausal, surgically sterilized or otherwise judged by the investigator as ‘highly unlikely to conceive’ during the study due to use of an acceptable method of birth control. Any female patient on hormone therapy (including hormone replacement therapy, or any estrogen antagonist/agonist) had to be on a stable dose of hormone therapy for at least 8 weeks without need to change the regimen throughout the study.

Exclusion criteria: cholesterol-lowering medication regime changed in the previous 4 weeks; patients treated with any other investigational drug within 3 months; patients who were pregnant or lactating and any condition or situation which, in the investigator’s opinion, might pose a risk to the patient or interfere with participation in the study. Furthermore patients were not included if they suffered from: congestive heart failure NYHA class III or IV, uncontrolled hypertension (treated or untreated) with systolic blood pressure > 160 mmHg or diastolic > 100 mmHg; poorly controlled diabetes mellitus (HbA1c > 10.0%) or newly diagnosed diabetes mellitus (within 3 months) or a change in antidiabetic pharmacotherapy within 3 months; uncontrolled endocrine or metabolic disease (treated or untreated) known to influence serum lipids or lipoproteins; impaired renal function (creatinine ≥ 177 µmol/L) or nephrotic syndrome; disorders of the hematologic, digestive or central nervous system, including cerebrovascular disease and degenerative disease that would limit study evaluation or participation; history of mental instability and/or drug/alcohol abuse within the past 5 years.

Patients using medications that are potent inhibitors of CYP3A4 as well as lipid lowering agents such as bile acid sequestrants, niacin and fibrates were also excluded. Oral corticosteroids were only allowed as replacement therapy for pituitary/adrenal disease on a stable regimen for at least 6 weeks.

Safety and tolerability measurements

Safety assessments included recording of any adverse event at each visit and any adverse sign or symptom...
reported by the patient. An adverse event was classified as serious if it met one or more of the following criteria: fatal, life-threatening, hospitalization, resulting in disability, cancer, overdose, congenital anomaly/birth defect or another important medical event. Laboratory safety measurements included aspartate aminotransferase, alanine aminotransferase, creatinine, creatine kinase (CK), total bilirubin, and thyroid-stimulating hormone. Key safety variables were the incidence of any clinical or laboratory adverse events (AEs), treatment-related AEs, serious AEs (SAEs) and discontinuations because of AEs.

In patients with > 5-fold CK elevations and associated muscle symptoms, the drug had to be interrupted immediately and a follow-up blood sample needed to be drawn at the local lab within 48 h. Furthermore, by protocol, patients were withdrawn from the study and all study medication was stopped if (1) they required chronic (2 weeks) treatment with corticosteroids or immunosuppressants including ciclosporin, or (2) they required any other treatment that was specified in the exclusion criteria, (3) they were women and became pregnant during the study, and (4) they had any condition that exposed patients to significant risk by continuing in the trial or did not allow the patients to adhere to protocol requirements.

**Laboratory methods**

All analyses were conducted on fasting blood samples at a certified central laboratory (Erasmus MC, University Medical Center Rotterdam). The investigator remained blinded to lipid values. The investigator received alerts from the central laboratory as appropriate, based on laboratory findings. Lipids, lipoproteins, blood chemistry and HbA1c (in patients with diabetes only) were measured before randomization and at the end of the treatment period (Week 12). LDL-C was measured by the direct homogeneous method on a Hitachi autoanalyzer (Roche, Basel, Switzerland). LDL subfractions were isolated by a non-equilibrium density-gradient ultracentrifugation method. The occurrence of a change in LDL-C subtype profile was tested by Wilcoxon matched pairs test. Cholesterol in the subfractions was analyzed using a commercially available assay (WAKO, USA) on the Cobas Mira autoanalyzer (Roche, Basel). LDL subfractions were isolated by a non-equilibrium density-gradient. Twenty 500 µL aliquots were collected, by upward displacement from the tube, after centrifugation in a Beckman SW40 rotor for 24 h, 40000 rpm at 4°C as described by Griffin. The isolated fractions were frozen immediately at −80°C for subsequent duplicate cholesterol measurement. Major LDL subfractions were identified according to their density and divided into three LDL categories: 1.023–1.036 g/mL (LDL1), 1.037–1.045 g/mL (LDL2), and 1.046–1.063 g/mL (LDL3).

**Statistical analysis**

For the primary hypothesis comparing EZE/SIMVA and double-dose statin treatment with respect to percentage of patients reaching LDL-C targets, a treatment difference of 23 percentage points was anticipated in the percentage of patients reaching goal, i.e., assuming 35% at goal in the doubling statin group and 58% in EZE/SIMVA group. With 230 patients in each group (total sample size of 460 patients) this anticipated difference can be detected with power > 95% (α = 0.05, 2-sided).

The primary efficacy analysis was based on an intention-to-treat (ITT) approach, including all randomized patients. In addition to the overall comparison of the effect of doubling the statin dose with switching to EZE/SIMVA on the proportion of patients attaining LDL-C goals, treatment comparisons within the following two strata were also performed. Stratum I: (patients with simvastatin 20 mg at entry): comparison between simvastatin 40 mg and EZE/SIMVA. Stratum II: (patients with atorvastatin 10 mg at entry): comparison between atorvastatin 20 mg and EZE/SIMVA. The primary endpoint, the percentage of patients reaching the LDL-C target of < 2.5 mmol/L, was analyzed using a logistic regression model with terms for treatment, stratum and baseline LDL-C. The secondary endpoint, percentage reduction from baseline in LDL-C and total cholesterol, was assessed by ANOVA using a linear model. This model includes terms for treatment and stratum. As for the primary endpoint, treatment comparisons for the secondary endpoint were performed within each stratum separately using analysis of variance with treatment as a factor in the model. These analyses within stratum are supportive of the overall pooled analysis across strata.

In the substudy, the percentage reduction from baseline in cholesterol concentration in the lipoprotein subfractions was assessed by ANOVA using a linear model. The occurrence of a change in LDL-C subtype profile was tested by Wilcoxon matched pairs test.

**Results**

**Patient characteristics and baseline lipid concentrations**

A total of 367 patients were randomized in the study; 189 patients to the doubling statin group and 178 patients to the EZE/SIMVA group. Treatment groups were well balanced with respect to patient demographics and baseline variables. There were no significant differences (p > 0.2) between the groups (Table 1). Before randomization 225 (61%) patients
were on simvastatin 20 mg (stratum I) and 142 (39%) were on atorvastatin 10 mg (stratum II).

In stratum I 115 (51%) patients were randomized to simvastatin 40 mg and 110 (49%) were randomized to EZE/SIMVA. In stratum II 74 (52%) patients were randomized to atorvastatin 20 mg and 68 (48%) were randomized to EZE/SIMVA.

For three patients (two in the doubling statin group and one in the EZE/SIMVA group) no measurements were available after start of treatment. In the primary endpoint analysis these patients are considered as a failure. Only patients with an LDL-C value of ≥ 2.5 mmol/L at entry and an LDL-C value < 2.5 mmol/L at completion of the trial were considered a success. Every other combination of values was considered a failure for the primary endpoint. As a consequence, 12 patients with an LDL-C value below 2.5 mmol/L at entry of the trial (three patients in the doubling statin group and nine patients in the EZE/SIMVA group) were considered a failure as well, irrespective of their LDL-C values at the end of the study. In total 331 (90%) patients of the randomized cohort completed the 12 week treatment period without protocol deviation (Per Protocol Set). Analyses with respect to the secondary endpoints were carried out on this population. Study patient allocation is shown in Figure 2.

A total of 91 patients were included in the substudy of which 78 were available for the per-protocol analyses of the compositional change in lipoprotein subfractions.

### Efficacy

The primary endpoint, an LDL-C target of < 2.5 mmol/L, was reached in 119 (67%) of the patients in the EZE/SIMVA group and 49 (26%) of the patients in the doubling statin group. In logistic regression analysis the association between treatment and the odds ratio of a success (i.e., a patient who attains a LDL-C < 2.5 mmol/L) was highly significant \((p < 0.0001)\). The odds ratio of success was 5.7 (95% CI: 3.7–9.0) for EZE/SIMVA versus doubling statin treatment.

In stratum I, after doubling the simvastatin dose from 20 to 40 mg, 28 of 115 patients (24%) attained LDL-C < 2.5 mmol/L. After a switch to EZE/SIMVA, 80 of 110 patients (73%) reached LDL-C < 2.5 mmol/L \((p < 0.0001)\). In Stratum I patients on EZE/SIMVA had an odds ratio (OR) of 8.2 (95% CI: 4.6–15.1) for achieving LDL-C < 2.5 mmol/L compared with the patients who had doubled their simvastatin dose to 40 mg.

In stratum II, after doubling the atorvastatin dose from 10 to 20 mg, 21 of 74 patients (28%) reached LDL-C < 2.5 mmol/L. After switching to EZE/SIMVA 39 of 68 (57%) of the patients attained LDL-C ≤ 2.5 mmol/L \((p < 0.0004)\). In Stratum II the OR

### Table 1. Baseline characteristics for all randomized patients

<table>
<thead>
<tr>
<th></th>
<th>Doubling statin n = 189</th>
<th>EZE/SIMVA n = 178</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Previous treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin (%)</td>
<td>115 (51%)</td>
<td>110 (49%)</td>
</tr>
<tr>
<td>Atorvastatin (%)</td>
<td>74 (52%)</td>
<td>68 (48%)</td>
</tr>
<tr>
<td>Mean age years (SD)</td>
<td>65 (10)</td>
<td>64 (10)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>45 (24%)</td>
<td>44 (25%)</td>
</tr>
<tr>
<td><strong>History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD (%)</td>
<td>184 (97%)</td>
<td>173 (97%)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>89 (47%)</td>
<td>69 (39%)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>25 (13%)</td>
<td>20 (11%)</td>
</tr>
<tr>
<td><strong>Baseline lipid values:</strong></td>
<td><strong>mean (SD)</strong></td>
<td></td>
</tr>
<tr>
<td>TC mmol/L</td>
<td>5.0 (0.6)</td>
<td>5.0 (0.6)</td>
</tr>
<tr>
<td>HDL-C mmol/L</td>
<td>1.3 (0.3)</td>
<td>1.3 (0.3)</td>
</tr>
<tr>
<td>TG mmol/L</td>
<td>1.6 (0.7)</td>
<td>1.5 (0.6)</td>
</tr>
<tr>
<td>LDL-C mmol/L</td>
<td>3.2 (0.5)</td>
<td>3.1 (0.5)</td>
</tr>
<tr>
<td>TC/HDL-C ratio</td>
<td>4.0 (0.9)</td>
<td>3.9 (0.9)</td>
</tr>
<tr>
<td>Apo-B g/L</td>
<td>1.1 (0.2)</td>
<td>1.1 (0.2)</td>
</tr>
</tbody>
</table>

Doubling statin = simvastatin 40 mg or atorvastatin 20 mg; EZE/SIMVA = ezetimibe/simvastatin 10/20 mg; CHD = coronary heart disease; TC = total cholesterol; TG = triglycerides; HDL-C = high density lipoprotein; LDL-C = low density lipoprotein; Apo-B = apolipoprotein B.
was 3.4 (95% CI: 1.7–6.8). LDL-C < 2.0 mmol/L was reached in 3% of patients in the doubling statin group, and in 30% of the patients of the EZE/SIMVA group (OR 12.9; 95% CI: 5.4–31.0) (Table 2).

With regard to percentage change from baseline to follow-up an additional LDL-C reduction of 29.1% was observed in the switching to EZE/SIMVA group, compared to a 11.5% reduction in the doubling statin group (p < 0.001 between treatment comparisons).

Similar changes were noted in TC, TC/HDL-C ratio and apo-B and these reductions were significantly more pronounced in the EZE/SIMVA group as compared with the doubling statin group, as depicted in Figure 3. A slight rise of HDL-C was observed, in the doubling group (Figure 2).

**Table 2.** Number of patients and odds-ratio (OR) by treatment in patients with LDL-C value ≥ 2.5 mmol/L at study entry and LDL-C values < 2.5 and < 2.0 mmol/L respectively at completion of the trial

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Doubling statin</th>
<th>EZE/SIMVA</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n = 367)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects (n)</td>
<td>189</td>
<td>178</td>
<td></td>
</tr>
<tr>
<td>LDL-C &lt; 2.5 mmol/L (%)</td>
<td>49 (26%)</td>
<td>119 (67%)</td>
<td>5.7 (95% CI: 3.7–9.0)</td>
</tr>
<tr>
<td>Strata by statin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin at baseline (n)</td>
<td>115</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>LDL-C &lt; 2.5 mmol/L (%)</td>
<td>28 (24%)</td>
<td>80 (73%)</td>
<td>8.2 (95% CI: 4.6–15.1)</td>
</tr>
<tr>
<td>Atorvastatin at baseline (n)</td>
<td>74</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>LDL-C &lt; 2.5 mmol/L (%)</td>
<td>21 (28%)</td>
<td>39 (57%)</td>
<td>3.4 (95% CI: 1.7–6.8)</td>
</tr>
<tr>
<td>All (n = 367)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects (n)</td>
<td>189</td>
<td>178</td>
<td></td>
</tr>
<tr>
<td>LDL-C &lt; 2.0 mmol/L (%)*</td>
<td>6 (3%)</td>
<td>53 (30%)</td>
<td>12.9 (95% CI: 5.4–31.0)</td>
</tr>
</tbody>
</table>

*According to 2007 ESC guidelines (LDL-C goal of < 2.0 mmol/L if feasible)

Doubling statin = simvastatin 40 mg or atorvastatin 20 mg; EZE/SIMVA = ezetimibe/simvastatin 10/20 mg; OR = odds ratio; LDL-C = low density lipoprotein
statin group, whereas in the EZE/SIMVA group HDL-C was slightly lowered. This difference was significant \( p < 0.02 \). Changes in plasma TG were not significant.

As stated, lipoprotein subfractions were determined according to protocol in a subset of 78 patients, of which 54 patients were in the doubling statin group and 24 in the EZE/SIMVA group. Results are depicted in Figure 4. In this subgroup analysis no significant differences were detected when comparing the switch to EZE/SIMVA with doubling statin with regard to IDL-C, HDL-C and VLDL-C. Furthermore significant reductions in median concentrations of cholesterol LDL-1, LDL-2 and LDL-3 were seen in both the doubling statin as well as the EZE/SIMVA groups. However, the pattern of LDL subfractions did not change towards the presence of more buoyant LDL particles, not in the doubling statin group nor in the EZE/SIMVA group (data not shown). Also a subanalysis looking at the effect of EZE/SIMVA versus doubling statin did not reveal significant differences between the patients with baseline TG levels < 1.7 mmol/L versus patients with baseline TG levels > 1.7 mmol/L. (all interaction \( p \) values > 0.19).

**Adverse events**

During the study 210 adverse events in 130 patients were recorded. There were no significant differences between the 2 treatment groups. In the doubling statin group 66 patients experienced 105 AEs. Of these 66 patients, 7 experienced 10 SAEs. In the

![Figure 3](image-url)

**Figure 3.** Mean percentage change from treated baseline (mean [SE]) in lipid parameters following 12 weeks of treatment with ezetimibe/simvastatin 10/20 mg or doubling the statin dose (simvastatin 40 mg or atorvastatin 20 mg). (*\( p < 0.001 \), and \#\( p = 0.02 \) for between-treatment comparison between EZE/SIMVA and doubling statin)

![Figure 4](image-url)

**Figure 4.** Substudy results: mean percentage change from treated baseline (mean [SE]) in lipid fractions following 12 weeks of treatment with ezetimibe/simvastatin 10/20 mg or doubling the statin dose (simvastatin 40 mg or atorvastatin 20 mg) in a substudy of 78 cases. (*\( p < 0.001 \) for between-treatment comparison between EZE/SIMVA and doubling statin, other comparison \( p = \) not significant, VLDL = very-low-density lipoprotein; IDL = intermediate-density lipoprotein)
EZE/SIMVA group 64 patients experienced 105 AEs and 9 of the 64 patients experienced 9 SAEs. Musculoskeletal complaints (myalgia, joint pain or swelling, musculoskeletal stiffness, osteoarthritis, pain in extremity, intervertebral disc protrusion) were somewhat more frequent in the EZE/SIMVA group than in the doubling statin group: 10.9 versus 7.4 %, but this difference was not significant.

Seventeen patients discontinued study treatment due to an AE: 7 patients in the doubling statin group and 10 patients in the EZE/SIMVA group. No patient died during the study and no patient discontinued the study because of CK or liver enzymes elevation. No significant differences were found between the treatment groups (Table 3).

### Discussion

The results of the EASEGO study demonstrate that in patients with CHD and/or DM2 with LDL-C levels ≥ 2.5 mmol/L despite treatment with simvastatin 20mg or atorvastatin 10 mg, switching to a EZE/SIMVA is a considerably more effective treatment option than doubling the dose of the statin used, in order to reach the LDL-C target of < 2.5 mmol/L as recommended in ESC guidelines. The odds ratio of a success of switching to EZE/SIMVA compared with doubling the statin dose is 5.7 (95% CI: 3.7–9.0, p < 0.0001).

LDL-C rose by 1% in the doubling statin group and fell by 2.6% in the EZE/SIMVA group. This HDL-C decrease has not been observed in other studies. In a recent study it was reported that ezetimibe alone has a favorable effect on the distribution of LDL subfractions as measured by automated gel electrophoresis. In the current study, we have used ezetimibe in combination with statin therapy. Under these circumstances we could not replicate this observation in our study: in a subset of 78 patients the distribution of the LDL subfraction pattern, provided as cholesterol distribution among a density gradient, was not influenced by doubling the statin dose or EZE/SIMVA treatment, irrespective of baseline TG.

Thus, combining a statin with ezetimibe mainly impacts LDL-C parameters and is in essence a totally different combination than for example combining a statin with a fibrate or other TG lowering drugs, since these combinations often do (profoundly) influence TG levels.

EZE/SIMVA was well tolerated in this study. There were no statistical differences in adverse events between the study groups and no patient in this study had to be withdrawn because of CK or liver enzyme elevations. There was no difference in the incidence of myalgia between the two groups.

Lipid lowering plays a crucial role in secondary prevention of cardiovascular risk. Guidelines recommend targeting plasma LDL-C concentrations to low (< 2.5 mmol/L) or in very-high-risk patients to very low (< 2.0 mmol/L) levels. In routine practice a large number of patients do not reach these target values if treated with statins at the recommended starting dose. Many factors may account for this, for example, lack of vigilance of the physician, poor patient compliance or insufficient potency of the statin used; all are obvious causes for not reaching desired target levels. Lack of responsiveness to a statin, caused by either high absorption of cholesterol, or induction of absorption caused by statin treatment, may also contribute to a lower response. Until recently there were two options for additional LDL-C lowering in patients not at target, for example, to increase the dose of the statin used, or to switch to a more potent statin. Patients are increasingly aware of side effects of statins, especially at higher doses. Under these circumstances, not having to change the dose and brand of statin may be attractive for both patients and doctors. An alternative avenue then to the desired LDL-C target is to leave the statin dose unchanged and to add a cholesterol absorption inhibitor.

In our short-term study, as in other published studies using ezetimibe treatment, reduction in mortality or a reduction in cardiovascular events was not evaluated. However, all lipid-lowering treatment trials show long-term positive results for

<table>
<thead>
<tr>
<th>Table 3. Safety profile, presented by pooled treatment groups</th>
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<tbody>
<tr>
<td><strong>Doubling statin n = 189</strong></td>
</tr>
<tr>
<td>All adverse events</td>
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<tr>
<td>Serious adverse events</td>
</tr>
<tr>
<td>Treatment-related adverse events</td>
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<tr>
<td>Gastrointestinal adverse events</td>
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<td>Musculoskeletal adverse events</td>
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<td>Laboratory adverse event</td>
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</tbody>
</table>

Doubling statin = simvastatin 40 mg or atorvastatin 20 mg; EZE/SIMVA = ezetimibe/simvastatin 10/20 mg

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cardiovascular events\textsuperscript{24}, if the following criteria were met: (1) sufficiently powered with respect to the risk profile of the patient population included; (2) the degree of LDL-C lowering induced was adequate, and (3) a sufficiently long treatment period. The same holds true for trials assessing regression or slowing down of the progression of coronary plaques\textsuperscript{33,34}. In addition, the magnitude of the effect is proportional to the LDL-C-lowering reached in these trials. Most of these are statin trials, because statins were the most potent LDL-C lowering agents available. However, non-statin trials meeting the above specified criteria, for example with diet\textsuperscript{27,28}, surgery\textsuperscript{29}, and resins\textsuperscript{30,31} also showed positive results with respect to major clinical events. Therefore, the secondary prevention challenge seems to be to lower LDL-C to target levels, seemingly irrespective by which treatment modality these levels are reached.

Studies to demonstrate the efficacy of EZE/SIMVA or ezetimibe in the prevention of complications of atherosclerosis have not been completed, but many studies with EZE/SIMVA are under way: for example, SEAS\textsuperscript{32} (patients with aortic sclerosis, primary endpoint major cardiovascular events), ENHANCE\textsuperscript{33} (patients with familial hypercholesterolemia, with change in carotid intima media thickness as primary endpoint), SHARP\textsuperscript{34} (patients with renal insufficiency, primary endpoint major vascular events) and IMPROVE-IT (patients with acute coronary syndrome, endpoint mortality and coronary events).

Conclusions

In the 367 CHD/DM2 patients examined, who were not at recommended LDL-C target levels despite treatment with the recommended starting dose of simvastatin or atorvastatin, a switch to EZE/SIMVA was significantly more effective in attaining LDL-C target levels of < 2.5 mmol/L than doubling of the statin dose.

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Trial registration: http://www.Clinicaltrials.gov : NCT00166530

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