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Incremental cholesterol reduction with ezetimibe/simvastatin, atorvastatin and rosuvastatin in UK General Practice (IN-PRACTICE): randomised controlled trial of achievement of Joint British Societies (JBS-2) cholesterol targets

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Incremental cholesterol reduction with ezetimibe/simvastatin, atorvastatin and rosuvastatin in UK General Practice (IN-PRACTICE): randomised controlled trial of achievement of Joint British Societies (JBS-2) cholesterol targets

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3 **Incremental cholesterol reduction with ezetimibe/simvastatin, atorvastatin and**
4 **rosuvastatin in UK General Practice (IN-PRACTICE): randomised controlled**
5 **trial of achievement of Joint British Societies (JBS-2) cholesterol targets**
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24
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ABSTRACT

Aim: To compare ezetimibe/simvastatin combination therapy with intensified statin monotherapy as alternative treatment strategies to achieve the JBS-2 and NICE low-density-lipoprotein cholesterol (LDL-C) target of < 2 mmol/l for secondary prevention or JBS-2 LDL-C target of < 2 mmol/l for primary prevention in high-risk patients who have failed to reach target with simvastatin 40 mg.

Methods: Prospective, double-blind study in 34 UK primary care centres; 1748 patients with established cardiovascular disease (CVD), diabetes or high risk of CVD who had been taking simvastatin 40 mg for ≥ 6 weeks were screened and 786 (45%) with fasting LDL-C ≥ 2.0 mmol/l (and < 4.2 mmol/l) at screening and after a further 6-week run-in period on simvastatin 40 mg were randomised to ezetimibe/simvastatin 10/40 mg (as a combination tablet; $n = 261$), atorvastatin 40 mg ($n = 263$) or rosuvastatin 5 mg ($n = 73$) or 10 mg ($n = 189$) once daily for 6 weeks. Rosuvastatin dose was based on UK prescribing instructions. The primary outcome measure was the proportion of patients achieving LDL-C < 2 mmol/l at the end of the study.

Results: The percentage of patients (adjusted for baseline differences) achieving LDL-C < 2 mmol/l was 69.4% with ezetimibe/simvastatin 10/40 mg, compared with 33.5% for atorvastatin 40 mg (odds ratio 4.5 [95% CI 3.0 to 6.8]; $p < 0.001$) and 14.3% for rosuvastatin 5 or 10 mg (odds ratio 13.6 [95% CI 8.6 to 21.6]; $p < 0.001$). Similar results were observed for achievement of total cholesterol < 4.0 mmol/l. All study treatments were well tolerated.

Conclusion: Approximately 45% of patients screened had not achieved LDL-C < 2 mmol/l after ≥ 12 weeks of treatment with simvastatin 40 mg. In this group, treatment with ezetimibe/simvastatin 10/40 mg achieved target LDL-C levels in a

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3 significantly higher proportion of patients during a 6-week period than switching to
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5 either atorvastatin 40 mg or rosuvastatin 5–10 mg.
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8 **Trial registration:** NCT 00462748 (www.clinicaltrials.gov)
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12 **Key words:** atorvastatin, cholesterol absorption inhibition, cardiovascular disease,
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14 ezetimibe/simvastatin, high risk, primary care, primary prevention, rosuvastatin
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20 **Running title:** Ezetimibe/simvastatin combination for LDL-C targets
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27 **WHAT THIS PAPER ADDS**

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31 What's known
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34 • Guidelines for the prevention of cardiovascular disease (CVD) from the Joint
35
36 British Societies (JBS-2) and National Institute for Health and Clinical Excellence
37
38 (NICE) recommend cholesterol-lowering treatment to achieve low-density-
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40 lipoprotein cholesterol (LDL-C) levels < 2 mmol/l and total cholesterol
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42 < 4 mmol/l for secondary prevention in patients with established CVD (and in the
43
44 case of NICE, in patients with diabetes).
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- 48 • Current NICE guidelines recommend initial treatment with simvastatin 40 mg,
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50 which is inexpensive and clinically proven to reduce CVD outcomes. However,
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52 simvastatin 40 mg fails to achieve recommended LDL-C targets in more than half
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54 of patients.
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- 57 • In patients for whom initial treatment with simvastatin 40 mg does not achieve
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59 LDL-C targets, alternative second-line options are to switch to a more potent
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3 statin, or to initiate combination therapy with the cholesterol absorption inhibitor
4 ezetimibe.
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10 What's new
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- 12 • This is the first randomised double-blind clinical trial conducted in UK primary
13 practice to compare second-line treatment strategies to reach LDL-C < 2 mmol/l
14 in patients for whom initial treatment with simvastatin 40 mg has failed to achieve
15 the guideline values.
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- 18 • During the screening and run-in periods of the trial, simvastatin 40 mg treatment
19 for ≥ 12 weeks failed to achieve the JBS-2 LDL-C target of < 2 mmol/l in nearly
20 half (786/1748; 45%) of patients who were screened.
21
22
- 23 • Treatment with ezetimibe/simvastatin 10/40 mg led to a significantly higher
24 proportion of patients achieving LDL-C < 2 mmol/l and total cholesterol
25 < 4 mmol/l than did intensifying statin therapy by switching to atorvastatin 40 mg
26 or rosuvastatin 5–10 mg.
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INTRODUCTION

Cardiovascular disease (CVD) remains a major health issue in the UK, and still accounts for more than one-third of deaths each year (1). It is widely accepted that lowering serum cholesterol levels, and in particular low-density-lipoprotein cholesterol (LDL-C), reduces the risk of CVD irrespective of the method used to do so (2, 3). Consequently, reduction of LDL-C is a key component of healthcare strategies for CVD prevention, as implemented in the National Services Framework (NSF) in the UK (4, 5). Current Joint British Societies guidelines (JBS-2) recommend target levels for LDL-C of < 2 mmol/l (< 77 mg/dl) and total cholesterol of < 4 mmol/l (< 155 mg/dl) for all individuals at high risk of CVD (whether for primary or secondary prevention) (6). These targets have recently been adopted in the latest National Institute for Health and Clinical Excellence (NICE) guidelines for secondary prevention in patients with established CVD and/or diabetes (7, 8). The NICE and JBS-2 guidelines differ for primary prevention in high-risk patients without diabetes, in that the NICE guidance recommends treatment with simvastatin 40 mg but does not specify a target cholesterol level.

Original NICE guidance on the use of statins published in 2006 recommended the use of low-cost generic statins as first-line therapy to achieve target LDL-C levels (9); more recent NICE guidelines specify the use of simvastatin 40 mg (7, 8). Simvastatin 40 mg was proven to be effective in preventing CVD outcomes in major clinical trials such as the UK Heart Protection Study (10). The average LDL-C level in the UK adult population is about 3.6 mmol/l (11); given that simvastatin 40 mg typically lowers LDL-C by approximately 40% or 1 mmol/l (10), fewer than half of patients

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3 requiring treatment are likely to reach LDL-C or total cholesterol targets with this
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5 first-line treatment (8). This raises the question of what the preferred second-line
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7 treatment option should be when simvastatin 40 mg has failed to achieve LDL-C <
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9 2 mmol/l (< 77 mg/dl). Potential therapeutic strategies include increasing the dose of
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11 simvastatin to 80 mg, switching to a higher-potency statin, or combining statin
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13 treatment with the cholesterol absorption inhibitor ezetimibe.
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20 We performed a randomised double-blind trial to compare three different treatment
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22 options for achieving LDL-C < 2 mmol/l (< 77 mg/dl) in primary and secondary
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24 prevention patients who had not attained target LDL-C with simvastatin 40 mg (the
25
26 most commonly used generic statin when the study was initiated). The strategies
27
28 tested were combination treatment with ezetimibe/simvastatin 10/40 mg, and
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30 intensifying statin monotherapy by switching to atorvastatin 40 mg or rosuvastatin 5–
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32 10 mg. As the majority of prescribing for cholesterol lowering in the UK takes place
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34 in primary care, the trial was conducted in this setting, including sites in England,
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36 Scotland, Wales and Northern Ireland. The proportion of patients reaching LDL-C <
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38 2 mmol/l (< 77 mg/dl) was the pre-specified primary endpoint for the study, and the
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40 JBS-2 target for total cholesterol (< 4 mmol/l [< 155 mg/dl]) was a secondary
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42 endpoint; both targets were adopted by NICE guidance for secondary prevention in
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44 patients with established CVD with or without diabetes, published after the study was
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46 initiated. The safety and tolerability of each treatment were also assessed.
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METHODS

Study design and patients

This was a randomised, double-blind, parallel-group study conducted at 34 primary care centres in the UK from March 2007 to May 2008, with full trial closure in November 2008. Patients eligible for inclusion were > 18 years of age, had established CVD or diabetes, or were at high risk of CVD (> 20% 10-year risk according to the Framingham scale), and had been taking simvastatin 40 mg for at least 6 weeks. Computer records at each study centre were searched to identify patients who were likely to fit the trial criteria, who were then invited for screening. Patients had to have a fasting LDL-C level between 2.0 and 4.2 mmol/l (77 and 162 mg/dl) at screening (visit 1) and at the end of the 6-week simvastatin 40 mg run-in period (visit 2). Patients also had to have a fasting triglyceride level < 3.7 mmol/l (< 328 mg/dl) and, for those with diabetes, haemoglobin A_{1C} ≤ 9% at visit 1, and show ≥ 75% compliance with simvastatin medication (assessed by tablet count) during the run-in period.

Major exclusion criteria included known hypersensitivity to study medications, a history of liver disease, severe renal impairment (estimated creatinine clearance < 30 ml/min), uncontrolled endocrine or metabolic disease known to affect serum lipids or lipoproteins, previous or current alcohol abuse, elevated creatine kinase (> 10x upper limit of normal). Female patients were also excluded if they were pregnant, breastfeeding or not using adequate contraception. The study was conducted in accordance with Good Clinical Practice (GCP) standards and the Declaration of Helsinki, and was approved by the South-West Multi-centre Research Ethics

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3 Committee. All patients gave written informed consent before participation in the
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5 study.
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10 ***Interventions***

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12 Following screening, eligible patients entered a 6-week run-in period during which
13 they received once-daily open-label simvastatin 40 mg. At the end of the run-in period
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15 (visit 2), blood samples were taken to assess lipid levels, and up to 7 days later
16
17 eligible patients were randomised equally to once-daily treatment for 6 weeks with
18
19 either ezetimibe/simvastatin 10/40 mg, atorvastatin 40 mg, or rosuvastatin 5 or 10 mg.
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21 The rosuvastatin dose was chosen on the basis of recommendations in the UK
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23 Summary of Product Characteristics that 5 mg should be the starting dose for patients
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25 over 70 years of age; for patients with creatinine clearance < 60 ml/min; and for
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27 patients of Asian ancestry or with other pre-disposing factors to myopathy switching
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29 from another statin.
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39 ***Randomisation and blinding***

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41 To achieve balance between the treatment groups, patients were stratified according to
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43 their baseline fasting LDL-C levels (≥ 2.0 to < 2.5 mmol/l; ≥ 2.5 to < 3.0 mmol/l; and
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45 ≥ 3.0 to ≤ 4.2 mmol/l [77 to < 97 mg/dl; 97 to ≤ 116 mg/dl; and ≥ 116 to
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47 ≤ 162 mg/dl]), and by the clinical criteria that determine rosuvastatin dose.
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51 Randomisation was done centrally using an external Interactive Voice Response
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53 System, which assigned an allocation number to each patient, and patients were
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55 randomised equally to one of the three treatment arms within their stratification
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57 groups. Following treatment allocation, patients received active study medication and
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59 matching placebo tablets to ensure blinding. All patients and investigators remained
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blinded to treatment allocation until the completion of the study.

Measurement of blood lipids

Blood samples for the measurement of fasting lipid levels (LDL-C, high-density-lipoprotein cholesterol [HDL-C], total cholesterol, triglycerides, and apoprotein [Apo] A1 and B) were taken following an 8- to 12-hour fast at screening, baseline and the end of the study (visits 1, 2 and 3, respectively). All blood samples were sent to a central laboratory for analysis (Quest Diagnostics, Heston, UK). LDL-C was estimated using the Friedewald equation.

Safety and tolerability assessments included monitoring for adverse experiences (which was performed throughout the study and included a follow-up telephone call 2 weeks after the study end), physical examination, measurement of vital signs, and laboratory assessments for haematology and blood chemistry.

Outcome measures

The primary efficacy variable was the overall percentage of patients (primary and secondary prevention) who attained the target fasting LDL-C level of < 2 mmol/l (< 77 mg/dl) at study end (defined as the last post-baseline assessment during the double-blind treatment period, regardless of whether the patient was receiving study medication at the time). Secondary efficacy endpoints were the percentage change from baseline to study end in LDL-C, total cholesterol and triglyceride levels, and the proportion of patients achieving total cholesterol < 4 mmol/l (< 155 mg/dl) at study end. Pre-specified exploratory efficacy variables included the percentage change from baseline in HDL-C, non-HDL-C, Apo-A1, Apo-B, total cholesterol:HDL-C ratio and

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3 Apo-B:Apo-A1 ratio, and the proportions of patients achieving LDL-C levels
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5 ≤ 1.8 mmol/l (< 70 mg/dl) and < 2.5 mmol/l (< 97 mg/dl) at study end.
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10 *Statistical analysis*

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12 The target sample size was 720 patients completing the study (240 patients per
13 treatment group). This provided 85% power to detect a 15% difference in the primary
14 endpoint between the ezetimibe/simvastatin group and the two comparator groups,
15 using a two-sided 5% test and allowing for multiplicity. For the secondary endpoints
16 of percentage change from baseline in fasting LDL-C and total cholesterol, 240
17 patients per treatment group gave more than 99% power to detect a difference
18 between treatment groups of 10% (assuming a standard deviation for the reduction
19 from baseline of 20%), using a two-sided 5% test and allowing for multiplicity.
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34 Efficacy data were analysed using the Full Analysis Set population, which included
35 all randomised patients who took at least one dose of double-blind study medication
36 and had both baseline and post-baseline efficacy measurements. Safety data were
37 analysed using the All-Patients-as-Treated (APaT) population, which included all
38 randomised participants who received at least one dose of double-blind study
39 medication.
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51 For the primary efficacy outcome measure, the percentage of patients reaching the
52 LDL-C target of < 2 mmol/l (< 77 mg/dl) was analysed using a logistic regression
53 model with terms for treatment and stratum (in order to adjust for differences between
54 treatment groups in baseline fasting LDL-C and in the clinical criteria determining
55 rosuvastatin dose). Odds ratio estimates and 95% confidence intervals (CIs) derived
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3 from the logistic regression model were used to quantify the treatment effect.
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5 Analysis of Variance (ANOVA) was used to investigate the percentage reduction in
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7 lipid parameters between baseline and post-baseline assessments, with terms for
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9 stratum and treatment group included in the model. Within- and between-treatment
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11 group least-squares means and 95% CIs were estimated from the models. The
12
13 proportion of patients achieving other targets, and primary and secondary prevention
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15 patient subgroups, were also analysed using logistic regression with treatment and
16
17 stratum included in the model. Multiplicity was addressed using a false discovery rate
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19 for the comparison of each treatment with the ezetimibe/simvastatin group, and using
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21 an ordered closed testing procedure for the secondary efficacy endpoints, undertaken
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23 only if the primary endpoint showed a significant effect. The percentage change in
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25 triglycerides was non-normally distributed, and was transformed to Tukey's
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27 normalised ranks. The data were analysed using ANOVA with treatment and strata as
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29 factors. Hodges–Lehmann methodology was used to derive estimates of the pairwise
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31 differences in medians between the treatment groups and corresponding 95% CI. All
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33 statistical analyses were performed using SAS version 8.2.
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RESULTS

Patient disposition and baseline characteristics

We screened a total of 1748 patients for the study (Figure 1). After the 6-week simvastatin run-in period, 786 patients (45%) met the eligibility criteria and were randomised to ezetimibe/simvastatin 10/40 mg (n = 261), atorvastatin 40 mg (n = 263) or rosuvastatin 5–10 mg (n = 262) for 6 weeks. In the rosuvastatin group, 73 patients (27.9%) received the 5 mg dose. The main reason for non-randomisation was LDL-C \leq 2.0 mmol/l (\leq 77 mg/dl).

Six randomised patients did not take any study medication so were excluded from the APaT population used for the safety analyses (Figure 1). A further eight patients were excluded from the Full Analysis Set population because they had no post-baseline LDL-C or other lipid measurement. Hence a total of 772 patients were included in the efficacy analyses. Two patients with LDL-C level $<$ 2.0 mmol/l at baseline were randomised to study medication in error (1.9 mmol/l [atorvastatin 40 mg] and 1.6 mmol/l [rosuvastatin 10 mg]).

Overall, 95.7% of patients completed the study. The number of treatment discontinuations was similar between treatment groups; adverse experiences were the main reason for treatment discontinuation. Average compliance with study medication was above 95%.

Treatment groups were well matched for patient baseline and demographic characteristics (Table 1). Overall, randomised patients had a mean age of 64.3 years;

two-thirds were male (66.5%) and the majority were Caucasian (98.6%).

Efficacy

Primary efficacy outcome

The primary outcome measure (primary efficacy variable) was the proportion of primary and secondary prevention patients achieving LDL-C < 2 mmol/l (< 77 mg/dl). The adjusted proportion of patients in the ezetimibe/simvastatin 10/40 mg group who achieved LDL-C < 2 mmol/l was 69.4%, compared with 33.5% in the atorvastatin 40 mg group (Figure 2). The corresponding odds ratio was 4.5 (95% CI: 3.0 to 6.8; $p < 0.001$) in favour of ezetimibe/simvastatin. Similarly, a significantly greater proportion of patients in the ezetimibe/simvastatin group achieved LDL-C < 2 mmol/l (< 77 mg/dl) compared with the rosuvastatin 5–10 mg group (69.4% vs 14.3%). The corresponding odds ratio was 13.6 (95% CI: 8.6 to 21.6; $p < 0.001$) in favour of ezetimibe/simvastatin. The unadjusted proportions of patients achieving LDL-C < 2 mmol/l (< 77 mg/dl) were 172/255 (67.5%) for ezetimibe/simvastatin, 94/259 (36.3%) for atorvastatin and 45/258 (17.4%) for rosuvastatin.

Results consistent with the full population were observed for achievement of LDL-C < 2 mmol/l (< 77 mg/dl) in each of the predefined baseline LDL-C strata (Figure 3), in the subset of patients who had clinical criteria qualifying for rosuvastatin 5 mg, for patients being treated for secondary prevention (i.e. with known CVD) and those treated for high-risk primary prevention (data not shown). A *post hoc* analysis of the primary efficacy variable by primary and secondary prevention subgroups yielded essentially identical results to the predefined analysis based on the overall population

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3 (Figure 3). There were no significant differences between primary and secondary
4 prevention subgroups in the proportions of patients achieving LDL-C < 2 mmol/l in
5 each treatment arm whether primary and secondary prevention were defined
6 according to JBS-2 (subgroup effect $p = 0.750$) or NICE guidance (subgroup effect p
7 = 0.666). The proportions of patients achieving LDL-C levels of ≤ 1.8 mmol/l
8 (< 70 mg/dl) and < 2.5 mmol/l (< 97 mg/dl) were also significantly higher with
9 ezetimibe/simvastatin 10/40 mg than with atorvastatin 40 mg or rosuvastatin 5–
10 10 mg.
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25 *Secondary efficacy outcomes*

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27 The adjusted proportion of primary and secondary prevention patients achieving total
28 cholesterol < 4 mmol/l (< 155 mg/dl) was also significantly greater with
29 ezetimibe/simvastatin 10/40 mg (57.7%) than with either atorvastatin 40 mg (31.8%;
30 $p < 0.001$) or rosuvastatin 5–10 mg (14.5%; $p < 0.001$; Figure 2). The odds ratio for
31 achievement of total cholesterol < 4 mmol/l was 2.9 (95% CI: 2.0 to 4.3; $p < 0.001$) in
32 favour of ezetimibe/simvastatin over atorvastatin 40 mg, and 8.0 (95% CI: 5.2 to 12.4;
33 $p < 0.001$) in favour of ezetimibe/simvastatin over rosuvastatin 5–10 mg.
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46 Average percentage reductions from baseline in LDL-C and total cholesterol were
47 significantly larger in patients receiving ezetimibe/simvastatin 10/40 mg than in those
48 receiving either atorvastatin 40 mg or rosuvastatin 5–10 mg (Table 2). There were no
49 significant between-treatment differences in changes in HDL-C or triglyceride levels
50 (Table 2).
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57 *Exploratory analyses*

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3 Exploratory analyses showed significantly greater mean reductions from baseline in
4 non-HDL-C, total cholesterol:HDL-C ratio, Apo B, and Apo B:Apo A1 ratio with
5 ezetimibe/simvastatin 10/40 mg than with atorvastatin 40 mg or rosuvastatin 5–10 mg
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10 (Table 2).

15 ***Tolerability***

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17 All treatments were generally well tolerated. The proportion of patients reporting
18 adverse experiences was similar in the three treatment groups, and consistent with the
19 known safety profile of the treatments. The only individual adverse experience
20 recorded in more than 3% of patients was diarrhoea with rosuvastatin (3.1%). The
21 majority of events were not considered to be related to study medication (Table 3).

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There were few discontinuations due to adverse experiences (n = 21) or serious
adverse experiences (n = 11) during double-blind treatment, and there were no notable
differences in laboratory values or vital signs between treatment groups.

DISCUSSION

We designed this study to address a question of specific clinical relevance to UK general practice: when treatment with simvastatin 40 mg (the most commonly prescribed low acquisition cost statin) fails to bring high-risk patients to LDL-C < 2 mmol/l (< 77 mg/dl), what is the best next step to reach the target? This has become a more relevant question since recent NICE guidance warned that fewer than half of patients with CVD are likely to reach LDL-C or total cholesterol targets (< 2 mmol/l [< 77 mg/dl] and < 4 mmol/l [< 155 mg/dl], respectively) with simvastatin 40 mg (8). Our study confirms this guidance by showing that simvastatin 40 mg treatment for ≥ 12 weeks failed to achieve LDL-C < 2 mmol/l in nearly half (45%) of the high-risk primary and secondary prevention patients who were screened. In this group, a significantly higher proportion of patients reached LDL-C < 2 mmol/l (< 77 mg/dl) or total cholesterol < 4 mmol/l (< 155 mg/dl) with ezetimibe/simvastatin 10/40 mg than with either atorvastatin 40 mg or rosuvastatin 5–10 mg. Average percentage reductions from baseline in LDL-C and total cholesterol were significantly larger with ezetimibe/simvastatin 10/40 mg than either atorvastatin 40 mg or rosuvastatin 5–10 mg. All treatments were similarly well tolerated.

Findings in relation to other studies

Our study design encompasses a number of elements with specific relevance to current UK clinical practice: (i) we evaluated patients treated in the primary care setting who were receiving simvastatin 40 mg prior to study entry (a dose subsequently recommended by NICE guidance published after our study had started) (7, 8); (ii) the second-line options that we compared are those commonly used in current UK practice; that is, combination of simvastatin with inhibition of cholesterol

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3 absorption by ezetimibe, and titration to two different statins considered by NICE to
4 be of higher potency than simvastatin (atorvastatin and rosuvastatin); (iii) the primary
5 endpoint of the JBS-2 target for LDL-C (< 2 mmol/l [< 77 mg/dl]) (6), which was
6 selected to reflect the 'target-oriented' approach followed in UK clinical practice (8),
7 has subsequently been adopted by NICE guidance for secondary prevention in
8 patients with established CVD and/or diabetes (although not for primary prevention in
9 patients without established CVD or diabetes) (7, 8).

10
11
12 Overall, we found that 69% of patients (primary and secondary prevention) achieved
13 LDL-C < 2 mmol/l (< 77 mg/dl) with ezetimibe/simvastatin 10/40 mg, which was
14 significantly greater than the proportion of patients reaching the target with
15 atorvastatin 40 mg (34%) or rosuvastatin 5–10 mg (14%). Virtually identical findings
16 were obtained when primary and secondary prevention subgroups were considered
17 separately, irrespective of whether these were defined according to JBS-2 or NICE
18 guidance (7, 8). This was by necessity a *post hoc* analysis as the NICE guidance was
19 published after this study was initiated. Our findings were also robust across different
20 baseline LDL-C strata and different LDL-C treatment targets (specifically, the
21 ≤ 1.8 mmol/l [< 70 mg/dl] target recommended by the US National Cholesterol
22 Education Program (12) and the < 2.5 mmol/l [< 97 mg/dl] target recommended in
23 European guidelines (13)). LDL-C levels were reduced by approximately 26% from
24 baseline with ezetimibe/simvastatin (compared with 11% for atorvastatin and 3% for
25 rosuvastatin), and there were also significant reductions in total cholesterol and Apo-
26 B. The cholesterol-lowering effects of combining ezetimibe and simvastatin relative
27 to statin monotherapy observed in our study are broadly consistent with the results of
28 a large number of ezetimibe clinical studies, as analysed in recent systematic
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3 reviews/meta-analyses (14, 15). Our results are also congruent with those of the
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5 INFORCE study, a multicentre, randomised, open-label study in 424 patients
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7 hospitalised for an acute coronary event and taking a stable dose of a statin (≥ 6
8
9 weeks) (16). In that study, combination treatment with ezetimibe 10 mg plus
10
11 simvastatin 40 mg over 12 weeks was associated with a mean 27% reduction from
12
13 baseline in LDL-C; 70.1% of patients achieved LDL-C < 2.0 mmol/l (< 77 mg/dl).
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15 This suggests that the 6-week randomized treatment period used in this and previous
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17 studies (17) is sufficient to observe the full effects of lipid-lowering treatment on
18
19 cholesterol levels. Indeed, a meta-analysis of ezetimibe clinical trials has shown that
20
21 the cholesterol-lowering effects of ezetimibe/statin combinations and statin
22
23 monotherapy observed over short-term treatment (6–8 weeks) are maintained at a
24
25 similar level during long-term follow-up (up to 48 weeks) (15). A meta-analysis of 18
26
27 randomised clinical trials of ezetimibe involving more than 14,000 patients generally
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29 showed no significant safety issues with the addition of ezetimibe to statin therapy
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31 over up to 48 weeks (18).
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41 Our study design selected patients who had not reached an LDL-C of < 2 mmol/l
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43 (< 77 mg/dl) despite at least 12 weeks' treatment with simvastatin 40 mg. Other
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45 studies have addressed similar 'non-responder' groups, albeit with different treatment
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47 strategies (17). This patient group may simply represent those with a very high
48
49 baseline LDL-C who are therefore unlikely to reach target with simvastatin
50
51 monotherapy, or may represent relatively poor responders to statin therapy (19).
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53 Unfortunately, no reliable diagnostic for the latter group exists; an early hypothesis
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55 that indices of cholesterol absorption (e.g. campesterol/total cholesterol ratio) might
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57 be useful to predict which patients would respond better to statin therapy as compared
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3 with ezetimibe has been refuted by recent clinical trials (20, 21). Nevertheless,
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6 irrespective of the underlying reason for the inadequate response to simvastatin, the
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8 practising physician is faced with a high-risk patient who has not achieved target
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10 LDL-C levels, and has to make a decision regarding the best next step to bring their
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12 patient to goal. Our study suggests that ezetimibe/simvastatin treatment is more
13
14 effective than switching such a patient to a different, higher potency statin at the doses
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16 investigated. Unlike many studies that use percentage reduction in LDL-C as the
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18 primary endpoint, we believe that our pre-specified endpoint – percentage of patients
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20 achieving LDL-C target – is appropriate in the current target-driven clinical setting in
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22 the UK.
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29 *Limitations of the study*

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31 The primary endpoint of this study was achievement of LDL-C targets; whether the
32
33 observed efficacy of ezetimibe/simvastatin translates into long-term reductions in
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35 morbidity and mortality that are superior to the proven benefits of statins such as
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37 atorvastatin and rosuvastatin is not answered by this study. Studies to assess whether
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39 LDL-C reduction with ezetimibe/statin combination translates into a reduction in
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41 clinical events are underway, including trials such as IMPROVE-IT, which will
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43 compare the effects of ezetimibe/simvastatin and simvastatin in patients with acute
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45 coronary syndromes (22). Pending endpoint data, the available evidence from meta-
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47 analyses of clinical outcome trials indicates that LDL-C reduction reduces CVD risk
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49 regardless of the method by which this is achieved (2, 3). The current study included
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51 clinical trial sites spread across the UK and we had intended to recruit a broadly
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53 representative population. The proportion of women was approximately one-third,
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58 and Asian and Black patients were relatively under-represented compared with the
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3 UK population as a whole (Asian 4%; Black 2%) (23). Further studies in specific
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5 ethnic groups may be desirable.
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10 The need to administer rosuvastatin in accordance with the UK Summary of Product
11 Characteristics and the lack of an up-titration step in the study design meant that the
12 doses used (5 or 10 mg) would be expected *a priori* to exert a smaller effect on LDL-
13 C than, for example, atorvastatin 40 mg. Previous studies would indicate that
14 rosuvastatin 20 mg would be a more appropriate comparator for atorvastatin 40 mg
15 (24). Indeed, higher doses of any of the statins employed in our study (e.g.
16 atorvastatin 80 mg, rosuvastatin 20–40 mg or simvastatin 80 mg) would have
17 provided larger reductions in LDL-C, although these tend to be of the order of only 6–
18 8% for each doubling of the statin dose (24). Firm conclusions as to the efficacy of
19 rosuvastatin compared with ezetimibe/simvastatin therefore cannot be drawn from the
20 results of the present study. It should be noted, however, that current prescribing data
21 from UK primary practice (IMS Disease Analyzer Mediplus, September 2009)
22 indicates that the doses of rosuvastatin and atorvastatin used in this study are an
23 accurate reflection of current prescribing patterns for patients switched between
24 statins in UK primary practice (although the reasons for switching from simvastatin
25 were not ascertained in the analysis of the IMS dataset). Thus, the vast majority (86%)
26 of patients switched to rosuvastatin from a different statin are receiving the 5 or
27 10 mg doses (28% on 5 mg, 58% on 10 mg, 14% on 20 mg and 2% on 40 mg), and
28 the majority (87%) of patients switched to atorvastatin from a different statin are
29 receiving the 40 mg dose or lower (36% on 10 mg, 24% on 20 mg, 27% on 40 mg and
30 13% on 80 mg). Whether the safety and tolerability of maximum-dose statin
31 monotherapy would have been similar to that of the ezetimibe/simvastatin
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3 combination remains open to question and needs to be investigated in future studies. It
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5 should also be noted that the study did not assess the effects of combining ezetimibe
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7 with atorvastatin or rosuvastatin in patients not achieving target LDL-C goal with
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9 these drugs; further studies would be required to investigate the relative efficacy of
10
11 this treatment approach.
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14 15 16 17 *Potential implications and unanswered questions*

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19 Our study shows that for high-risk patients who do not achieve desired targets for
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21 LDL-C with simvastatin 40 mg, a higher proportion will achieve LDL-C and total
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23 cholesterol targets with ezetimibe/simvastatin 10/40 mg than by switching to
24
25 atorvastatin 40 mg or rosuvastatin 5–10 mg. A 2008 NICE Health Technology
26
27 Assessment found that addition of ezetimibe to statin therapy was cost-effective
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29 compared with statin titration under specific scenarios, one of which was
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31 ezetimibe/simvastatin compared with switching to atorvastatin (14). Health economic
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33 studies are required to evaluate the budget implications for the NHS of routine
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35 prescribing of ezetimibe to achieve specified target LDL-C levels, given that NICE
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37 recommendations are not based solely on clinical efficacy, but also on cost-
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39 effectiveness and budget impact. Ultimately, data from clinical studies reporting
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41 cardiovascular events and mortality data associated with the addition of ezetimibe to
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43 statin treatment will be required to confirm the clinical benefits and safety profile of
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45 this therapeutic option.
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AUTHOR CONTRIBUTIONS

TM is the guarantor; he was involved in discussions regarding the protocol, he was an investigator, he administrated the independent analysis and he was the Lead author of the writing committee. PH and RG were investigators and members of the writing committee. VA conducted the independent statistical analysis and was a member of the writing committee. RC and PR were involved in protocol design and clinical research operations and PR also contributed to the interpretation of the analysis. All authors had full access to all data and take responsibility for the integrity of the data and the accuracy of the data analysis, and approved the final version of the manuscript for publication.

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2
3 Statistician) and Clare Mellon (Clinical Project Manager).
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11
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13 analysis. The writing committee undertook an independent statistical analysis (VA)
14 and were responsible for the interpretation of the data, the writing of the article and
15 the decision to submit.
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REFERENCES

1. Allender S, Peto V, Scarborough P, Kaur A, Rayner M. Coronary heart disease statistics 2008. London: BHF; 2008.
2. Gould AL, Davies GM, Alemao E, Yin DD, Cook JR. Cholesterol reduction yields clinical benefits: meta-analysis including recent trials. *Clin Ther* 2007; **29**: 778-94.
3. Robinson JG, Smith B, Maheshwari N, Schrott H. Pleiotropic effects of statins: benefit beyond cholesterol reduction? A meta-regression analysis. *J Am Coll Cardiol* 2005; **46**: 1855-62.
4. Department of Health. National Service Framework for Coronary Heart Disease (2000). Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4094275. Accessed 1 June 2009.
5. Boyle R. DoH explains thinking behind national service framework for coronary heart disease. *BMJ* 2000; **321**: 1083.
6. Joint British Societies. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 2005; **91 Suppl 5**: v1-52.
7. National Institute for Health and Clinical Excellence. Type 2 diabetes - the management of type 2 diabetes (partial update) (2009). *Clinical guidelines CG87* available at <http://guidance.nice.org.uk/CG87>. Accessed 11 June 2009.
8. National Institute for Health and Clinical Excellence. Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease (2008). *Clinical guidelines CG67* available at <http://www.nice.org.uk/CG067>. Accessed 1 June 2009.
9. National Institute for Health and Clinical Excellence. Statins for the prevention of cardiovascular events: NICE technology appraisal 94. In: ISBN

1
2
3 1846291410; 2006.

4
5
6 10. Heart Protection Study Investigators. MRC/BHF Heart Protection Study of
7
8 cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised
9
10 placebo-controlled trial. *Lancet* 2002; **360**: 7-22.

11
12
13 11. National Institute for Health and Clinical Excellence. Ezetimibe for the
14
15 treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia:
16
17 NICE technology appraisal guidance 132. In; 2007.

18
19
20 12. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials
21
22 for the National Cholesterol Education Program Adult Treatment Panel III
23
24 Guidelines. *J Am Coll Cardiol* 2004; **44**: 720-32.

25
26
27 13. De Backer G, Ambrosioni E, Borch-Johnsen K, et al. European guidelines on
28
29 cardiovascular disease prevention in clinical practice. Third Joint Task Force of
30
31 European and Other Societies on Cardiovascular Disease Prevention in Clinical
32
33 Practice. *Eur Heart J* 2003; **24**: 1601-10.

34
35
36 14. Ara R, Tumur I, Pandor A, et al. Ezetimibe for the treatment of
37
38 hypercholesterolaemia: a systematic review and economic evaluation. *Health Technol*
39
40 *Assess* 2008; **12**: iii, xi-xiii, 1-212.

41
42
43 15. Mikhailidis DP, Sibbring GC, Ballantyne CM, Davies GM, Catapano AL.
44
45 Meta-analysis of the cholesterol-lowering effect of ezetimibe added to ongoing statin
46
47 therapy. *Curr Med Res Opin* 2007; **23**: 2009-26.

48
49
50 16. Reckless JP, Henry P, Pomykaj T, et al. Lipid-altering efficacy of
51
52 ezetimibe/simvastatin 10/40 mg compared with doubling the statin dose in patients
53
54 admitted to the hospital for a recent coronary event: the INFORCE study. *Int J Clin*
55
56 *Pract* 2008; **62**: 539-54.

57
58
59 17. Farnier M, Averna M, Missault L, et al. Lipid-altering efficacy of
60

- 1
2
3 ezetimibe/simvastatin 10/20 mg compared with rosuvastatin 10 mg in high-risk
4
5 hypercholesterolaemic patients inadequately controlled with prior statin monotherapy
6
7
8 - The IN-CROSS study. *Int J Clin Pract* 2009; **63**: 547-59.
9
- 10 18. Kashani A, Sallam T, Bheemreddy S, Mann DL, Wang Y, Foody JM. Review
11
12 of side-effect profile of combination ezetimibe and statin therapy in randomized
13
14 clinical trials. *Am J Cardiol* 2008; **101**: 1606-13.
15
- 16 19. Reynolds T. Sleight of hand in trial design: average behaviour is not average,
17
18 not all new information is really new. *Int J Clin Pract* 2009; **63**: 534-5.
19
- 20 20. Jakulj L, Vissers MN, Groen AK, et al. Baseline cholesterol absorption and
21
22 the response to ezetimibe/simvastatin therapy; a post-hoc analysis of the ENHANCE
23
24 trial. *J Lipid Res* 2009.
25
26
- 27 21. Lakoski SG, Xu F, Vega GL, et al. Indices of Cholesterol Metabolism and
28
29 Relative Responsiveness to Ezetimibe and Simvastatin. *J Clin Endocrinol Metab*
30
31 2009.
32
33
- 34 22. Cannon CP, Giugliano RP, Blazing MA, et al. Rationale and design of
35
36 IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International
37
38 Trial): comparison of ezetimibe/simvastatin versus simvastatin monotherapy on
39
40 cardiovascular outcomes in patients with acute coronary syndromes. *Am Heart J*
41
42 2008; **156**: 826-32.
43
44
- 45 23. Bosveld K, Connolly H. Chapter 2: Population. In: Dobbs J, Green H, Zealey
46
47 L, editors. Focus on Ethnicity and Religion. London: Office for National Statistics;
48
49 2006. p. 20-41.
50
51
- 52 24. Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and
53
54 safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses
55
56 (STELLAR* Trial). *Am J Cardiol* 2003; **92**: 152-60.
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TABLES

Table 1 Subject baseline and demographic characteristics (randomised population, $n = 786$)

	Ezetimibe/simvastatin 10/40 mg	Atorvastatin 40 mg	Rosuvastatin 5–10 mg
	($n = 261$)	($n = 263$)	($n = 262$)
Age, years	64.7 ± 8.7	64.2 ± 8.4	63.9 ± 8.6
≥ 70 years, n (%)	76 (29.1%)	76 (28.9%)	67 (25.6%)
Male, n (%)	160 (61.3%)	185 (70.3%)	178 (67.9%)
Race, n (%)			
Caucasian	254 (97.3%)	261 (99.2%)	257 (98.1%)
Asian	3 (1.1%)	0	2 (0.8%)
Black	4 (1.5%)	0	2 (0.8%)
Other	0	2 (0.8%)	1 (0.4%)
Current smoker, n (%)	44 (16.9%)	55 (20.9%)	47 (17.9%)

Cardiovascular disease

Current CVD/diabetes, <i>n</i> (%)	138 (52.9%)	131 (49.8%)	136 (51.9%)
High-risk CVD, <i>n</i> (%)	123 (47.1%)	131 (49.8%)	126 (48.1%)
Mean 10-year CVD risk ^a	36.3% ± 15.0%	37.4% ± 15.6%	33.5% ± 13.6%

Diabetes

Type 1, <i>n</i> (%)	2 (0.8%)	1 (0.4%)	1 (0.4%)
Type 2, <i>n</i> (%)	40 (15.3%)	26 (9.9%)	32 (12.2%)

Fasting lipid levels, mmol/l

LDL-C	2.6 ± 0.4	2.6 ± 0.4	2.5 ± 0.4
HDL-C	1.4 ± 0.3	1.4 ± 0.3	1.4 ± 0.3
Total cholesterol	4.7 ± 0.5	4.7 ± 0.6	4.7 ± 0.6
Triglycerides, median (range)	1.6 (0.7 to 3.8)	1.5 (0.7 to 4.0)	1.6 (0.7 to 4.3)

Values are mean ± SD unless otherwise stated.

^aExcluding secondary prevention.

CVD, cardiovascular disease; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol.

Table 2 Summary of secondary and exploratory efficacy outcome measures (Full Analysis Set, $n = 772$)

	Ezetimibe/simvastatin 10/40 mg ($n = 255$)	Atorvastatin 40 mg ($n = 259$)	Rosuvastatin 5–10 mg ($n = 258$)
<i>Percentage change from baseline</i>			
LDL-C	–26.2 (–29.1 to –23.2)	–11.1(–14.0 to –8.2)**	–3.0 (–5.9 to –0.1)**
Total cholesterol	–16.3 (–18.2 to –14.5)	–8.3 (–10.2 to –6.5)**	–2.5 (–4.4 to –0.7)**
Triglycerides	–9.5 (–12.5 to –6.7)	–8.1 (–11.8 to –2.9)	–4.3 (–7.0 to 0.0)
HDL-C	–1.4 (–2.9 to 0.0)	–2.3 (–3.7 to –0.9)	–0.1 (–1.5 to +1.3)
Non-HDL-C	–22.2 (–24.7 to –19.6)	–10.5 (–13.0 to –8.0)**	–3.1 (–5.6 to –0.6)**
Total cholesterol:HDL-C ratio	–14.4 (–16.4 to –12.4)	–5.5 (–7.5 to –3.4)**	–2.0 (–4.0 to 0.0) **
Apo A1	–1.6 (–3.1 to –0.2)	–4.5 (–5.9 to –3.1)*	+0.6 (–0.8 to +2.1)*
Apo B	–17.5 (–19.7 to –15.4)	–9.0 (–11.1 to –6.9)**	–3.2 (–5.3 to –1.1) **
Apo B:Apo A1 ratio	–15.4 (–17.8 to –12.9)	–3.8 (–6.2 to –1.4)**	–3.1 (–5.5 to –0.7) **

* $p < 0.05$, ** $p < 0.001$ vs ezetimibe/simvastatin 10/40 mg.

Data are least-squares mean (95% CI) percentage change from baseline, except for triglycerides which are median percent change (ANOVA

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3 with treatment and strata as factors).

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5 ANOVA, analysis of variance; Apo, apolipoprotein; CI, confidence interval; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-
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8 lipoprotein cholesterol.
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Table 3. Tolerability of study treatments (All-Patients-as-Treated population, $n = 780$)

	Ezetimibe/simvastatin	Atorvastatin	Rosuvastatin
	10/40 mg	40 mg	5–10 mg
	($n = 259$)	($n = 260$)	($n = 261$)
Any AE	89 (34.4)	93 (35.8)	103 (39.5)
Drug-related AE	23 (8.9)	22 (8.5)	27 (10.3)
AE leading to study discontinuation	7 (2.7)	5 (1.9)	9 (3.4)
Serious AE	4 (1.5)	2 (0.8)	5 (1.9)
Laboratory AE	5 (1.9)	3 (1.2)	1 (0.4)

Values are the number (%) of patients with at least one adverse experience (AE).

AEs reported were those occurring or worsening after the first dose of double-blind study medication and up to 14 days following the last dose of study medication (or 30 days for serious AEs).

FIGURE LEGENDS**Figure 1.** Patient flow through study

†Patients could have more than one reason for randomisation failure. ‡No further details recorded. Randomised population (demographic and baseline characteristics); APaT, All-Patients-as-Treated (APaT) population (safety analyses); Full Analysis Set (efficacy analyses). ALT/AST, alanine aminotransferase/aspartate aminotransferase; LDL-C, low-density-lipoprotein cholesterol; ULN, upper limit of normal.

Figure 2. Proportion of patients achieving low-density-lipoprotein cholesterol (LDL-C) < 2 mmol/l (< 77 mg/dl) and total cholesterol < 4 mmol/l (< 155 mg/dl) for ezetimibe/simvastatin 10/40 mg compared with atorvastatin 40 mg and with rosuvastatin 5–10 mg (Full Analysis Set).

Data are presented as adjusted proportions (95% confidence interval [CI]). ** indicates ** $p < 0.001$ vs ezetimibe/simvastatin 10/40 mg in a logistic regression model with treatment and LDL-C stratum as factors.

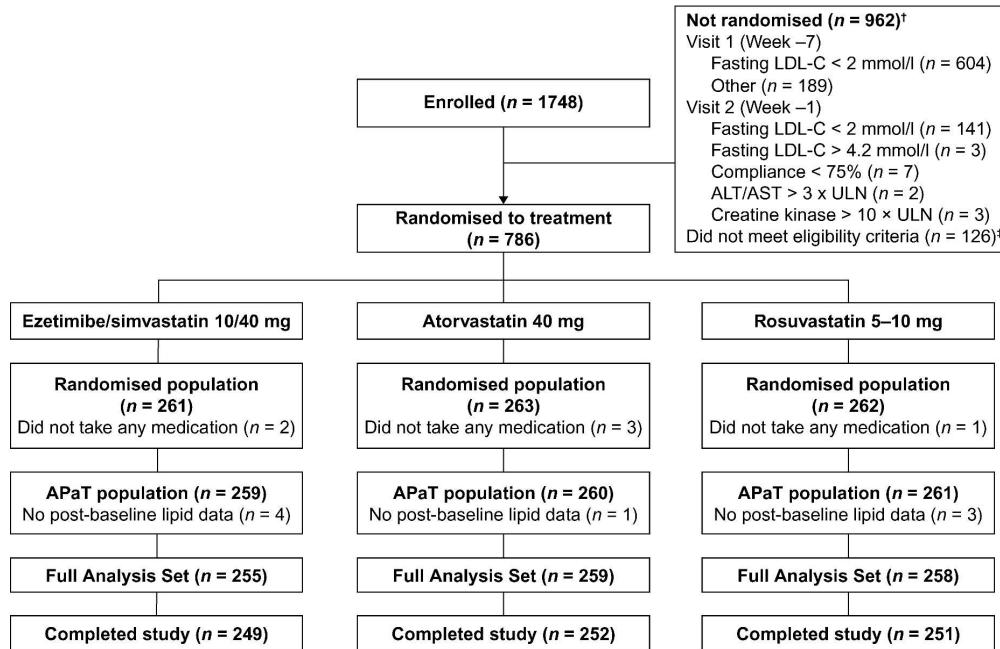
Figure 3. Subgroup analysis of proportion of patients achieving low-density-lipoprotein cholesterol LDL-C treatment goals for ezetimibe/simvastatin 10/40 mg compared with atorvastatin 40 mg and with rosuvastatin 5–10 mg (Full Analysis Set)

Data are adjusted proportion (95% CI), using logistic regression analysis with treatment and strata as factors. ^aJBS-2 definition of secondary prevention for patients with existing CVD or CVD and diabetes; primary prevention for high-risk patients or patients with diabetes but no CVD. ^bNICE definition of secondary prevention for patients with existing CVD and/or diabetes; primary prevention for high-risk patients without diabetes. Analysis was *post hoc*

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3 because NICE treatment guidelines were published after the study was initiated. ^cPredefined
4 baseline LDL-C strata were ≥ 2.0 to < 2.5 mmol/l; ≥ 2.5 to < 3.0 mmol/l; and ≥ 3.0 to \leq
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8 4.2 mmol/l; the upper two strata were combined because there were too few patients in the
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10 highest stratum for analysis.

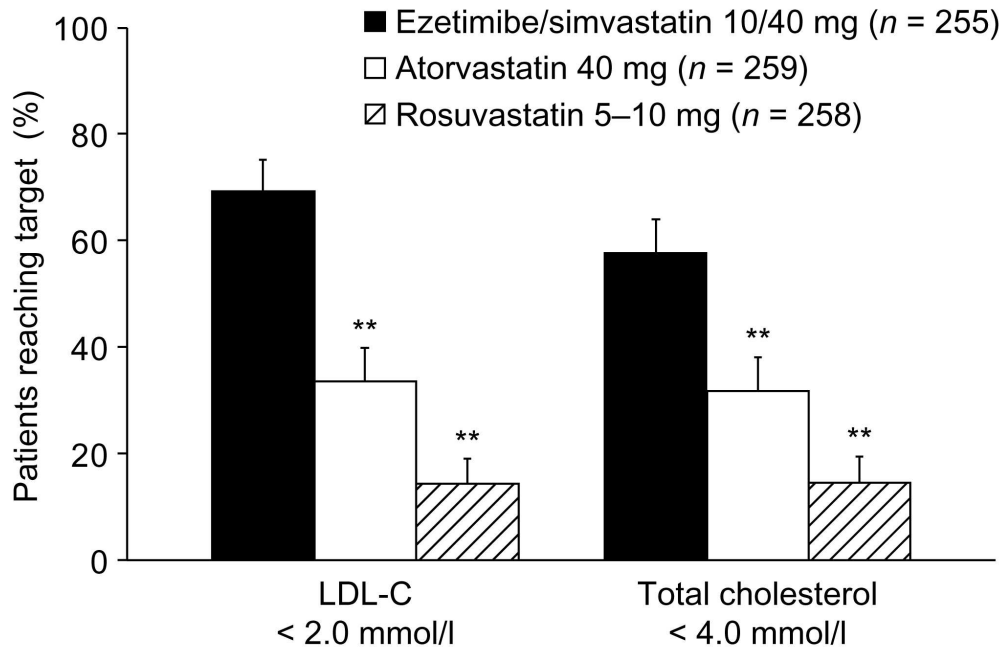
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12 CI, confidence interval; JBS, Joint British Societies; LDL-C, low-density-lipoprotein
13 cholesterol; NICE, National Institute for Health and Clinical Excellence.

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17 ** indicates ** $p < 0.001$ vs ezetimibe/simvastatin 10/40 mg in a logistic regression model
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19 with treatment and LDL-C stratum as factors.
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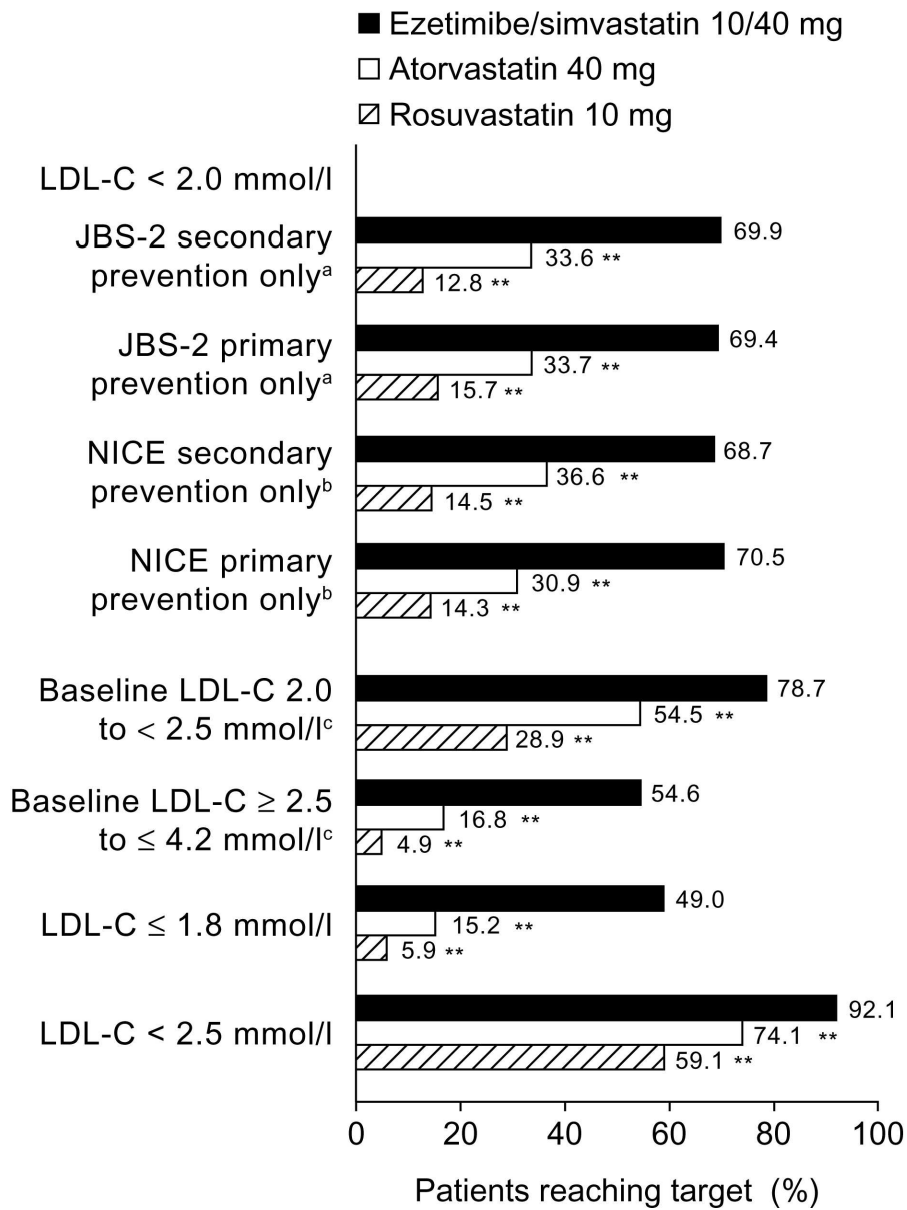
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Incremental cholesterol reduction with ezetimibe/simvastatin, atorvastatin and rosuvastatin in UK General Practice (IN-PRACTICE): randomised controlled trial of achievement of Joint British Societies (JBS-2) cholesterol targets

Authors

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10 *Disclosures*

11
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17 Dohme. RC is an employee of Schering-Plough. PR is an employee of Merck Sharp &
18 Dohme. VA has no potential conflicts of interest to declare.
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ABSTRACT

Aim: To compare ezetimibe/simvastatin combination therapy with intensified statin monotherapy as alternative treatment strategies to achieve the JBS-2 and NICE low-density-lipoprotein cholesterol (LDL-C) target of < 2 mmol/l for secondary prevention or JBS-2 LDL-C target of < 2 mmol/l for primary prevention in high-risk patients who have failed to reach target with simvastatin 40 mg.

Methods: Prospective, double-blind study in 34 UK primary care centres; 1748 patients with established cardiovascular disease (CVD), diabetes or high risk of CVD who had been taking simvastatin 40 mg for ≥ 6 weeks were screened and 786 (45%) with fasting LDL-C ≥ 2.0 mmol/l (and < 4.2 mmol/l) at screening and after a further 6-week run-in period on simvastatin 40 mg were randomised to ezetimibe/simvastatin 10/40 mg (as a combination tablet; $n = 261$), atorvastatin 40 mg ($n = 263$) or rosuvastatin 5 mg ($n = 73$) or 10 mg ($n = 189$) once daily for 6 weeks. Rosuvastatin dose was based on UK prescribing instructions. The primary outcome measure was the proportion of patients achieving LDL-C < 2 mmol/l at the end of the study.

Results: The percentage of patients (adjusted for baseline differences) achieving LDL-C < 2 mmol/l was 69.4% with ezetimibe/simvastatin 10/40 mg, compared with 33.5% for atorvastatin 40 mg (odds ratio 4.5 [95% CI 3.0 to 6.8]; $p < 0.001$) and 14.3% for rosuvastatin 5 or 10 mg (odds ratio 13.6 [95% CI 8.6 to 21.6]; $p < 0.001$). Similar results were observed for achievement of total cholesterol < 4.0 mmol/l. All study treatments were well tolerated.

Conclusion: Approximately 45% of patients screened had not achieved LDL-C < 2 mmol/l after ≥ 12 weeks of treatment with simvastatin 40 mg. In this group, treatment with ezetimibe/simvastatin 10/40 mg achieved target LDL-C levels in a

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4 either atorvastatin 40 mg or rosuvastatin 5–10 mg.

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6 **Trial registration:** NCT 00462748 (www.clinicaltrials.gov)
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10 **Key words:** atorvastatin, cholesterol absorption inhibition, cardiovascular disease,
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12 ezetimibe/simvastatin, high risk, primary care, primary prevention, rosuvastatin
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16 **Running title:** Ezetimibe/simvastatin combination for LDL-C targets
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18 **Word count:** 3768
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20 21 22 **WHAT THIS PAPER ADDS** 23

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26 What's known
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- 28 • Guidelines for the prevention of cardiovascular disease (CVD) from the Joint
29 British Societies (JBS-2) and National Institute for Health and Clinical Excellence
30 (NICE) recommend cholesterol-lowering treatment to achieve low-density-
31 lipoprotein cholesterol (LDL-C) levels < 2 mmol/l and total cholesterol
32 < 4 mmol/l for secondary prevention in patients with established CVD (and in the
33 case of NICE, in patients with diabetes).
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- 36 • Current NICE guidelines recommend initial treatment with simvastatin 40 mg,
37 which is inexpensive and clinically proven to reduce CVD outcomes. However,
38 simvastatin 40 mg fails to achieve recommended LDL-C targets in more than half
39 of patients.
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- 41 • In patients for whom initial treatment with simvastatin 40 mg does not achieve
42 LDL-C targets, alternative second-line options are to switch to a more potent
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statin, or to initiate combination therapy with the cholesterol absorption inhibitor ezetimibe.

What's new

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- This is the first randomised double-blind clinical trial conducted in UK primary practice to compare second-line treatment strategies to reach LDL-C < 2 mmol/l in patients for whom initial treatment with simvastatin 40 mg has failed to achieve the guideline values.
- During the screening and run-in periods of the trial, simvastatin 40 mg treatment for ≥ 12 weeks failed to achieve the JBS-2 LDL-C target of < 2 mmol/l in nearly half (786/1748; 45%) of patients who were screened.
- Treatment with ezetimibe/simvastatin 10/40 mg led to a significantly higher proportion of patients achieving LDL-C < 2 mmol/l and total cholesterol < 4 mmol/l than did intensifying statin therapy by switching to atorvastatin 40 mg or rosuvastatin 5–10 mg.

INTRODUCTION

Cardiovascular disease (CVD) remains a major health issue in the UK, and still accounts for more than one-third of deaths each year (1). It is widely accepted that lowering serum cholesterol levels, and in particular low-density-lipoprotein cholesterol (LDL-C), reduces the risk of CVD irrespective of the method used to do so (2, 3). Consequently, reduction of LDL-C is a key component of healthcare strategies for CVD prevention, as implemented in the National Services Framework (NSF) in the UK (4, 5). Current Joint British Societies guidelines (JBS-2) recommend target levels for LDL-C of < 2 mmol/l (< 77 mg/dl) and total cholesterol of < 4 mmol/l (< 155 mg/dl) for all individuals at high risk of CVD [\(whether for primary or secondary prevention\)](#) (6). These [targets](#) have recently been adopted in the latest National Institute for Health and Clinical Excellence (NICE) guidelines for secondary prevention in patients with established CVD and/or diabetes (7, 8). [The NICE and JBS-2 guidelines differ for primary prevention in high-risk patients without diabetes, in that the NICE guidance recommends treatment with simvastatin 40 mg but does not specify a target cholesterol level.](#)

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Original NICE guidance on the use of statins published in 2006 recommended the use of low-cost generic statins as first-line therapy to achieve target LDL-C levels (9); more recent NICE guidelines specify the use of simvastatin 40 mg (7, 8). Simvastatin 40 mg was proven to be effective in preventing CVD outcomes in major clinical trials such as the UK Heart Protection Study (10). The average LDL-C level in the UK adult population is about 3.6 mmol/l (11); given that simvastatin 40 mg typically lowers LDL-C by approximately 40% or 1 mmol/l (10), fewer than half of patients

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2 requiring treatment are likely to reach LDL-C or total cholesterol targets with this
3 first-line treatment (8). This raises the question of what the preferred second-line
4 treatment option should be when simvastatin 40 mg has failed to achieve LDL-C <
5 2 mmol/l (< 77 mg/dl). Potential therapeutic strategies include increasing the dose of
6 simvastatin to 80 mg, switching to a higher-potency statin, or combining statin
7 treatment with the cholesterol absorption inhibitor ezetimibe.
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16 We performed a randomised double-blind trial to compare three different treatment
17 options for achieving LDL-C < 2 mmol/l (< 77 mg/dl) in primary and secondary
18 prevention patients who had not attained target LDL-C with simvastatin 40 mg (the
19 most commonly used generic statin when the study was initiated). The strategies
20 tested were combination treatment with ezetimibe/simvastatin 10/40 mg, and
21 intensifying statin monotherapy by switching to atorvastatin 40 mg or rosuvastatin 5–
22 10 mg. As the majority of prescribing for cholesterol lowering in the UK takes place
23 in primary care, the trial was conducted in this setting, including sites in England,
24 Scotland, Wales and Northern Ireland. The proportion of patients reaching LDL-C <
25 2 mmol/l (< 77 mg/dl) was the pre-specified primary endpoint for the study, and the
26 JBS-2 target for total cholesterol (< 4 mmol/l [< 155 mg/dl]) was a secondary
27 endpoint; both targets were adopted by NICE guidance for secondary prevention in
28 patients with established CVD with or without diabetes, published after the study was
29 initiated. The safety and tolerability of each treatment were also assessed.
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METHODS

Study design and patients

This was a randomised, double-blind, parallel-group study conducted at 34 primary care centres in the UK from March 2007 to May 2008, with full trial closure in November 2008. Patients eligible for inclusion were > 18 years of age, had established CVD or diabetes, or were at high risk of CVD (> 20% 10-year risk according to the Framingham scale), and had been taking simvastatin 40 mg for at least 6 weeks. Computer records at each study centre were searched to identify patients who were likely to fit the trial criteria, who were then invited for screening. Patients had to have a fasting LDL-C level between 2.0 and 4.2 mmol/l (77 and 162 mg/dl) at screening (visit 1) and at the end of the 6-week simvastatin 40 mg run-in period (visit 2). Patients also had to have a fasting triglyceride level < 3.7 mmol/l (< 328 mg/dl) and, for those with diabetes, haemoglobin A_{1C} ≤ 9% at visit 1, and show ≥ 75% compliance with simvastatin medication (assessed by tablet count) during the run-in period.

Major exclusion criteria included known hypersensitivity to study medications, a history of liver disease, severe renal impairment (estimated creatinine clearance < 30 ml/min), uncontrolled endocrine or metabolic disease known to affect serum lipids or lipoproteins, previous or current alcohol abuse, elevated creatine kinase (> 10x upper limit of normal). Female patients were also excluded if they were pregnant, breastfeeding or not using adequate contraception. The study was conducted in accordance with Good Clinical Practice (GCP) standards and the Declaration of Helsinki, and was approved by the South-West Multi-centre Research Ethics

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Committee. All patients gave written informed consent before participation in the study.

Interventions

Following screening, eligible patients entered a 6-week run-in period during which they received once-daily open-label simvastatin 40 mg. At the end of the run-in period (visit 2), blood samples were taken to assess lipid levels, and up to 7 days later eligible patients were randomised equally to once-daily treatment for 6 weeks with either ezetimibe/simvastatin 10/40 mg, atorvastatin 40 mg, or rosuvastatin 5 or 10 mg. The rosuvastatin dose was chosen on the basis of recommendations in the UK Summary of Product Characteristics that 5 mg should be the starting dose for patients over 70 years of age; for patients with creatinine clearance < 60 ml/min; and for patients of Asian ancestry or with other pre-disposing factors to myopathy switching from another statin.

Randomisation and blinding

To achieve balance between the treatment groups, patients were stratified according to their baseline fasting LDL-C levels (≥ 2.0 to < 2.5 mmol/l; ≥ 2.5 to < 3.0 mmol/l; and ≥ 3.0 to ≤ 4.2 mmol/l [77 to < 97 mg/dl; 97 to ≤ 116 mg/dl; and ≥ 116 to ≤ 162 mg/dl]), and by the clinical criteria that determine rosuvastatin dose.

Randomisation was done centrally using an external Interactive Voice Response System, which assigned an allocation number to each patient, and patients were randomised equally to one of the three treatment arms within their stratification groups. Following treatment allocation, patients received active study medication and matching placebo tablets to ensure blinding. All patients and investigators remained

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2 blinded to treatment allocation until the completion of the study.
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6 ***Measurement of blood lipids***
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8 Blood samples for the measurement of fasting lipid levels (LDL-C, high-density-
9 lipoprotein cholesterol [HDL-C], total cholesterol, triglycerides, and apoprotein [Apo]
10 A1 and B) were taken following an 8- to 12-hour fast at screening, baseline and the
11 end of the study (visits 1, 2 and 3, respectively). All blood samples were sent to a
12 central laboratory for analysis (Quest Diagnostics, Heston, UK). LDL-C was
13 estimated using the Friedewald equation.
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22 Safety and tolerability assessments included monitoring for adverse experiences
23 (which was performed throughout the study and included a follow-up telephone call 2
24 weeks after the study end), physical examination, measurement of vital signs, and
25 laboratory assessments for haematology and blood chemistry.
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32 ***Outcome measures***
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34 The primary efficacy variable was the overall percentage of patients (primary and
35 secondary prevention) who attained the target fasting LDL-C level of < 2 mmol/l
36 (< 77 mg/dl) at study end (defined as the last post-baseline assessment during the
37 double-blind treatment period, regardless of whether the patient was receiving study
38 medication at the time). Secondary efficacy endpoints were the percentage change
39 from baseline to study end in LDL-C, total cholesterol and triglyceride levels, and the
40 proportion of patients achieving total cholesterol < 4 mmol/l (< 155 mg/dl) at study
41 end. Pre-specified exploratory efficacy variables included the percentage change from
42 baseline in HDL-C, non-HDL-C, Apo-A1, Apo-B, total cholesterol:HDL-C ratio and
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2 Apo-B:Apo-A1 ratio, and the proportions of patients achieving LDL-C levels
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4 ≤ 1.8 mmol/l (< 70 mg/dl) and < 2.5 mmol/l (< 97 mg/dl) at study end.
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8 *Statistical analysis*

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10 The target sample size was 720 patients completing the study (240 patients per
11 treatment group). This provided 85% power to detect a 15% difference in the primary
12 endpoint between the ezetimibe/simvastatin group and the two comparator groups,
13 using a two-sided 5% test and allowing for multiplicity. For the secondary endpoints
14 of percentage change from baseline in fasting LDL-C and total cholesterol, 240
15 patients per treatment group gave more than 99% power to detect a difference
16 between treatment groups of 10% (assuming a standard deviation for the reduction
17 from baseline of 20%), using a two-sided 5% test and allowing for multiplicity.
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28 Efficacy data were analysed using the Full Analysis Set population, which included
29 all randomised patients who took at least one dose of double-blind study medication
30 and had both baseline and post-baseline efficacy measurements. Safety data were
31 analysed using the All-Patients-as-Treated (APaT) population, which included all
32 randomised participants who received at least one dose of double-blind study
33 medication.
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43 For the primary efficacy outcome measure, the percentage of patients reaching the
44 LDL-C target of < 2 mmol/l (< 77 mg/dl) was analysed using a logistic regression
45 model with terms for treatment and stratum (in order to adjust for differences between
46 treatment groups in baseline fasting LDL-C and in the clinical criteria determining
47 rosuvastatin dose). Odds ratio estimates and 95% confidence intervals (CIs) derived
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2 from the logistic regression model were used to quantify the treatment effect.
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4 Analysis of Variance (ANOVA) was used to investigate the percentage reduction in
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6 lipid parameters between baseline and post-baseline assessments, with terms for
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8 stratum and treatment group included in the model. Within- and between-treatment
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10 group least-squares means and 95% CIs were estimated from the models. The
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12 proportion of patients achieving other targets, and primary and secondary prevention
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14 patient subgroups, were also analysed using logistic regression with treatment and
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16 stratum included in the model. Multiplicity was addressed using a false discovery rate
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18 for the comparison of each treatment with the ezetimibe/simvastatin group, and using
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20 an ordered closed testing procedure for the secondary efficacy endpoints, undertaken
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22 only if the primary endpoint showed a significant effect. The percentage change in
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24 triglycerides was non-normally distributed, and was transformed to Tukey's
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26 normalised ranks. The data were analysed using ANOVA with treatment and strata as
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28 factors. Hodges–Lehmann methodology was used to derive estimates of the pairwise
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30 differences in medians between the treatment groups and corresponding 95% CI. All
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32 statistical analyses were performed using SAS version 8.2.
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RESULTS

Patient disposition and baseline characteristics

We screened a total of 1748 patients for the study (Figure 1). After the 6-week simvastatin run-in period, 786 patients (45%) met the eligibility criteria and were randomised to ezetimibe/simvastatin 10/40 mg (n = 261), atorvastatin 40 mg (n = 263) or rosuvastatin 5–10 mg (n = 262) for 6 weeks. In the rosuvastatin group, 73 patients (27.9%) received the 5 mg dose. The main reason for non-randomisation was LDL-C \leq 2.0 mmol/l (\leq 77 mg/dl).

Six randomised patients did not take any study medication so were excluded from the APaT population used for the safety analyses (Figure 1). A further eight patients were excluded from the Full Analysis Set population because they had no post-baseline LDL-C or other lipid measurement. Hence a total of 772 patients were included in the efficacy analyses. Two patients with LDL-C level $<$ 2.0 mmol/l at baseline were randomised to study medication in error (1.9 mmol/l [atorvastatin 40 mg] and 1.6 mmol/l [rosuvastatin 10 mg]).

Overall, 95.7% of patients completed the study. The number of treatment discontinuations was similar between treatment groups; adverse experiences were the main reason for treatment discontinuation. Average compliance with study medication was above 95%.

Treatment groups were well matched for patient baseline and demographic characteristics (Table 1). Overall, randomised patients had a mean age of 64.3 years;

two-thirds were male (66.5%) and the majority were Caucasian (98.6%).

Efficacy

Primary efficacy outcome

The primary outcome measure (primary efficacy variable) was the proportion of

primary and secondary prevention patients achieving LDL-C < 2 mmol/l

(< 77 mg/dl). The adjusted proportion of patients in the ezetimibe/simvastatin

10/40 mg group who achieved LDL-C < 2 mmol/l was 69.4%, compared with 33.5%

in the atorvastatin 40 mg group (Figure 2). The corresponding odds ratio was 4.5

(95% CI: 3.0 to 6.8; $p < 0.001$) in favour of ezetimibe/simvastatin. Similarly, a

significantly greater proportion of patients in the ezetimibe/simvastatin group

achieved LDL-C < 2 mmol/l (< 77 mg/dl) compared with the rosuvastatin 5–10 mg

group (69.4% vs 14.3%). The corresponding odds ratio was 13.6 (95% CI: 8.6 to 21.6;

$p < 0.001$) in favour of ezetimibe/simvastatin. The unadjusted proportions of patients

achieving LDL-C < 2 mmol/l (< 77 mg/dl) were 172/255 (67.5%) for

ezetimibe/simvastatin, 94/259 (36.3%) for atorvastatin and 45/258 (17.4%) for

rosuvastatin.

Results consistent with the full population were observed for achievement of LDL-C

< 2 mmol/l (< 77 mg/dl) in each of the predefined baseline LDL-C strata (Figure 3),

in the subset of patients who had clinical criteria qualifying for rosuvastatin 5 mg, for

patients being treated for secondary prevention (i.e. with known CVD) and those

treated for high-risk primary prevention (data not shown). A *post hoc* analysis of the

primary efficacy variable by primary and secondary prevention subgroups yielded

essentially identical results to the predefined analysis based on the overall population

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(Figure 3). There were no significant differences between primary and secondary prevention subgroups in the proportions of patients achieving LDL-C < 2 mmol/l in each treatment arm whether primary and secondary prevention were defined according to JBS-2 (subgroup effect $p = 0.750$) or NICE guidance (subgroup effect $p = 0.666$). The proportions of patients achieving LDL-C levels of ≤ 1.8 mmol/l (< 70 mg/dl) and < 2.5 mmol/l (< 97 mg/dl) were also significantly higher with ezetimibe/simvastatin 10/40 mg than with atorvastatin 40 mg or rosuvastatin 5–10 mg.

Secondary efficacy outcomes

The adjusted proportion of primary and secondary prevention patients achieving total cholesterol < 4 mmol/l (< 155 mg/dl) was also significantly greater with ezetimibe/simvastatin 10/40 mg (57.7%) than with either atorvastatin 40 mg (31.8%; $p < 0.001$) or rosuvastatin 5–10 mg (14.5%; $p < 0.001$; Figure 2). The odds ratio for achievement of total cholesterol < 4 mmol/l was 2.9 (95% CI: 2.0 to 4.3; $p < 0.001$) in favour of ezetimibe/simvastatin over atorvastatin 40 mg, and 8.0 (95% CI: 5.2 to 12.4; $p < 0.001$) in favour of ezetimibe/simvastatin over rosuvastatin 5–10 mg.

Average percentage reductions from baseline in LDL-C and total cholesterol were significantly larger in patients receiving ezetimibe/simvastatin 10/40 mg than in those receiving either atorvastatin 40 mg or rosuvastatin 5–10 mg (Table 2). There were no significant between-treatment differences in changes in HDL-C or triglyceride levels (Table 2).

Exploratory analyses

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2 Exploratory analyses showed significantly greater mean reductions from baseline in
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4 non-HDL-C, total cholesterol:HDL-C ratio, Apo B, and Apo B:Apo A1 ratio with
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6 ezetimibe/simvastatin 10/40 mg than with atorvastatin 40 mg or rosuvastatin 5–10 mg
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8 (Table 2).

Deleted: . The proportions of patients achieving LDL-C levels of ≤ 1.8 mmol/l (< 70 mg/dl) and < 2.5 mmol/l (< 97 mg/dl) were also significantly higher with ezetimibe/simvastatin 10/40 mg than with atorvastatin 40 mg or rosuvastatin 5–10 mg

12 *Tolerability*

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14 All treatments were generally well tolerated. The proportion of patients reporting
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16 adverse experiences was similar in the three treatment groups, and consistent with the
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18 known safety profile of the treatments. The only individual adverse experience
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20 recorded in more than 3% of patients was diarrhoea with rosuvastatin (3.1%). The
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22 majority of events were not considered to be related to study medication (Table 3).
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24 There were few discontinuations due to adverse experiences (n = 21) or serious
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26 adverse experiences (n = 11) during double-blind treatment, and there were no notable
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28 differences in laboratory values or vital signs between treatment groups.
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DISCUSSION

We designed this study to address a question of specific clinical relevance to UK general practice: when treatment with simvastatin 40 mg (the most commonly prescribed low acquisition cost statin) fails to bring high-risk patients to LDL-C < 2 mmol/l (< 77 mg/dl), what is the best next step to reach the target? This has become a more relevant question since recent NICE guidance warned that fewer than half of patients with CVD are likely to reach LDL-C or total cholesterol targets (< 2 mmol/l [< 77 mg/dl] and < 4 mmol/l [< 155 mg/dl], respectively) with simvastatin 40 mg (8). Our study confirms this guidance by showing that simvastatin 40 mg treatment for ≥ 12 weeks failed to achieve LDL-C < 2 mmol/l in nearly half (45%) of the high-risk primary and secondary prevention patients who were screened. In this group, a significantly higher proportion of patients reached LDL-C < 2 mmol/l (< 77 mg/dl) or total cholesterol < 4 mmol/l (< 155 mg/dl) with ezetimibe/simvastatin 10/40 mg than with either atorvastatin 40 mg or rosuvastatin 5–10 mg. Average percentage reductions from baseline in LDL-C and total cholesterol were significantly larger with ezetimibe/simvastatin 10/40 mg than either atorvastatin 40 mg or rosuvastatin 5–10 mg. All treatments were similarly well tolerated.

Findings in relation to other studies

Our study design encompasses a number of elements with specific relevance to current UK clinical practice: (i) we evaluated patients treated in the primary care setting who were receiving simvastatin 40 mg prior to study entry (a dose subsequently recommended by NICE guidance published after our study had started) (7, 8); (ii) the second-line options that we compared are those commonly used in current UK practice; that is, combination of simvastatin with inhibition of cholesterol

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absorption by ezetimibe, and titration to two different statins considered by NICE to be of higher potency than simvastatin (atorvastatin and rosuvastatin); (iii) the primary endpoint of the JBS-2 target for LDL-C (< 2 mmol/l [< 77 mg/dl]) (6), which was selected to reflect the 'target-oriented' approach followed in UK clinical practice (8), has subsequently been adopted by NICE guidance for secondary prevention in patients with established CVD and/or diabetes (although not for primary prevention in patients without established CVD or diabetes) (7, 8).

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Overall, we found that 69% of patients (primary and secondary prevention) achieved LDL-C < 2 mmol/l (< 77 mg/dl) with ezetimibe/simvastatin 10/40 mg, which was significantly greater than the proportion of patients reaching the target with atorvastatin 40 mg (34%) or rosuvastatin 5–10 mg (14%). Virtually identical findings were obtained when primary and secondary prevention subgroups were considered separately, irrespective of whether these were defined according to JBS-2 or NICE guidance (7, 8). This was by necessity a *post hoc* analysis as the NICE guidance was published after this study was initiated. Our findings were also robust across different baseline LDL-C strata and different LDL-C treatment targets (specifically, the ≤ 1.8 mmol/l [< 70 mg/dl] target recommended by the US National Cholesterol Education Program (12) and the < 2.5 mmol/l [< 97 mg/dl] target recommended in European guidelines (13)). LDL-C levels were reduced by approximately 26% from baseline with ezetimibe/simvastatin (compared with 11% for atorvastatin and 3% for rosuvastatin), and there were also significant reductions in total cholesterol and Apo-B. The cholesterol-lowering effects of combining ezetimibe and simvastatin relative to statin monotherapy observed in our study are broadly consistent with the results of a large number of ezetimibe clinical studies, as analysed in recent systematic

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3 reviews/meta-analyses (14, 15). Our results are also congruent with those of the
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5 INFORCE study, a multicentre, randomised, open-label study in 424 patients
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7 hospitalised for an acute coronary event and taking a stable dose of a statin (≥ 6
8
9 weeks) (16). In that study, combination treatment with ezetimibe 10 mg plus
10
11 simvastatin 40 mg over 12 weeks was associated with a mean 27% reduction from
12
13 baseline in LDL-C; 70.1% of patients achieved LDL-C < 2.0 mmol/l (< 77 mg/dl).

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15 This suggests that the 6-week randomized treatment period used in this and previous
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17 studies (17) is sufficient to observe the full effects of lipid-lowering treatment on
18
19 cholesterol levels. Indeed, a meta-analysis of ezetimibe clinical trials has shown that
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21 the cholesterol-lowering effects of ezetimibe/statin combinations and statin
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23 monotherapy observed over short-term treatment (6–8 weeks) are maintained at a
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25 similar level during long-term follow-up (up to 48 weeks) (15). A meta-analysis of 18
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27 randomised clinical trials of ezetimibe involving more than 14,000 patients generally
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29 showed no significant safety issues with the addition of ezetimibe to statin therapy
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31 over up to 48 weeks (18).

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34 Our study design selected patients who had not reached an LDL-C of < 2 mmol/l
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36 (< 77 mg/dl) despite at least 12 weeks' treatment with simvastatin 40 mg. Other
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38 studies have addressed similar 'non-responder' groups, albeit with different treatment
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40 strategies (17). This patient group may simply represent those with a very high
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42 baseline LDL-C who are therefore unlikely to reach target with simvastatin
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44 monotherapy, or may represent relatively poor responders to statin therapy (19).

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46 Unfortunately, no reliable diagnostic for the latter group exists; an early hypothesis
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48 that indices of cholesterol absorption (e.g. campesterol/total cholesterol ratio) might
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50 be useful to predict which patients would respond better to statin therapy as compared
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3 with ezetimibe has been refuted by recent clinical trials (20, 21). Nevertheless,
4 irrespective of the underlying reason for the inadequate response to simvastatin, the
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6 practising physician is faced with a high-risk patient who has not achieved target
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8 LDL-C levels, and has to make a decision regarding the best next step to bring their
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10 patient to goal. Our study suggests that ezetimibe/simvastatin treatment is more
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12 effective than switching such a patient to a different, higher potency statin at the doses
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14 investigated. Unlike many studies that use percentage reduction in LDL-C as the
15
16 primary endpoint, we believe that our pre-specified endpoint – percentage of patients
17
18 achieving LDL-C target – is appropriate in the current target-driven clinical setting in
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20 the UK.
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22 23 24 *Limitations of the study*

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26 The primary endpoint of this study was achievement of LDL-C targets; whether the
27
28 observed efficacy of ezetimibe/simvastatin translates into long-term reductions in
29
30 morbidity and mortality that are superior to the proven benefits of statins such as
31
32 atorvastatin and rosuvastatin is not answered by this study. Studies to assess whether
33
34 LDL-C reduction with ezetimibe/statin combination translates into a reduction in
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36 clinical events are underway, including trials such as IMPROVE-IT, which will
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38 compare the effects of ezetimibe/simvastatin and simvastatin in patients with acute
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40 coronary syndromes (22). Pending endpoint data, the available evidence from meta-
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42 analyses of clinical outcome trials indicates that LDL-C reduction reduces CVD risk
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44 regardless of the method by which this is achieved (2, 3). The current study included
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46 clinical trial sites spread across the UK and we had intended to recruit a broadly
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48 representative population. The proportion of women was approximately one-third,
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50 and Asian and Black patients were relatively under-represented compared with the
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UK population as a whole (Asian 4%; Black 2%) (23). Further studies in specific ethnic groups may be desirable.

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The need to administer rosuvastatin in accordance with the UK Summary of Product

Characteristics and the lack of an up-titration step in the study design meant that the doses used (5 or 10 mg) would be expected *a priori* to exert a smaller effect on LDL-

C than, for example, atorvastatin 40 mg. Previous studies would indicate that

rosuvastatin 20 mg would be a more appropriate comparator for atorvastatin 40 mg

(24). Indeed, higher doses of any of the statins employed in our study (e.g.

atorvastatin 80 mg, rosuvastatin 20–40 mg or simvastatin 80 mg) would have

provided larger reductions in LDL-C, although these tend to be of the order of only 6–

8% for each doubling of the statin dose (24). Firm conclusions as to the efficacy of

rosuvastatin compared with ezetimibe/simvastatin therefore cannot be drawn from the

results of the present study. It should be noted, however, that current prescribing data

from UK primary practice (IMS Disease Analyzer Mediplus, September 2009)

indicates that the doses of rosuvastatin and atorvastatin used in this study are an

accurate reflection of current prescribing patterns for patients switched between

statins in UK primary practice (although the reasons for switching from simvastatin

were not ascertained in the analysis of the IMS dataset). Thus, the vast majority (86%)

of patients switched to rosuvastatin from a different statin are receiving the 5 or

10 mg doses (28% on 5 mg, 58% on 10 mg, 14% on 20 mg and 2% on 40 mg), and

the majority (87%) of patients switched to atorvastatin from a different statin are

receiving the 40 mg dose or lower (36% on 10 mg, 24% on 20 mg, 27% on 40 mg and

13% on 80 mg). Whether the safety and tolerability of maximum-dose statin

monotherapy would have been similar to that of the ezetimibe/simvastatin

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3 combination remains open to question and needs to be investigated in future studies. It
4 should also be noted that the study did not assess the effects of combining ezetimibe
5 with atorvastatin or rosuvastatin in patients not achieving target LDL-C goal with
6 these drugs; further studies would be required to investigate the relative efficacy of
7 this treatment approach.
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12 13 14 15 *Potential implications and unanswered questions*

16 Our study shows that for high-risk patients who do not achieve desired targets for
17 LDL-C with simvastatin 40 mg, a higher proportion will achieve LDL-C and total
18 cholesterol targets with ezetimibe/simvastatin 10/40 mg than by switching to
19 atorvastatin 40 mg or rosuvastatin 5–10 mg. A 2008 NICE Health Technology
20 Assessment found that addition of ezetimibe to statin therapy was cost-effective
21 compared with statin titration under specific scenarios, one of which was
22 ezetimibe/simvastatin compared with switching to atorvastatin (14). Health economic
23 studies are required to evaluate the budget implications for the NHS of routine
24 prescribing of ezetimibe to achieve specified target LDL-C levels, given that NICE
25 recommendations are not based solely on clinical efficacy, but also on cost-
26 effectiveness and budget impact. Ultimately, data from clinical studies reporting
27 cardiovascular events and mortality data associated with the addition of ezetimibe to
28 statin treatment will be required to confirm the clinical benefits and safety profile of
29 this therapeutic option.
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AUTHOR CONTRIBUTIONS

TM is the guarantor; he was involved in discussions regarding the protocol, he was an investigator, he administrated the independent analysis and he was the Lead author of the writing committee. PH and RG were investigators and members of the writing committee. VA conducted the independent statistical analysis and was a member of the writing committee. RC and PR were involved in protocol design and clinical research operations and PR also contributed to the interpretation of the analysis. All authors had full access to all data and take responsibility for the integrity of the data and the accuracy of the data analysis, and approved the final version of the manuscript for publication.

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2 Statistician) and Clare Mellon (Clinical Project Manager).
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11 analysis. The writing committee undertook an independent statistical analysis (VA)
12 and were responsible for the interpretation of the data, the writing of the article and
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16 the decision to submit.
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REFERENCES

1. Allender S, Peto V, Scarborough P, Kaur A, Rayner M. Coronary heart disease statistics 2008. London: BHF; 2008.
2. Gould AL, Davies GM, Alemao E, Yin DD, Cook JR. Cholesterol reduction yields clinical benefits: meta-analysis including recent trials. *Clin Ther* 2007; **29**: 778-94.
3. Robinson JG, Smith B, Maheshwari N, Schrott H. Pleiotropic effects of statins: benefit beyond cholesterol reduction? A meta-regression analysis. *J Am Coll Cardiol* 2005; **46**: 1855-62.
4. Department of Health. National Service Framework for Coronary Heart Disease (2000). Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4094275. Accessed 1 June 2009.
5. Boyle R. DoH explains thinking behind national service framework for coronary heart disease. *BMJ* 2000; **321**: 1083.
6. Joint British Societies. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 2005; **91 Suppl 5**: v1-52.
7. National Institute for Health and Clinical Excellence. Type 2 diabetes - the management of type 2 diabetes (partial update) (2009). *Clinical guidelines CG87 available at <http://guidance.nice.org.uk/CG87>*. Accessed 11 June 2009.
8. National Institute for Health and Clinical Excellence. Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease (2008). *Clinical guidelines CG67 available at <http://www.nice.org.uk/CG067>*. Accessed 1 June 2009.
9. National Institute for Health and Clinical Excellence. Statins for the prevention of cardiovascular events: NICE technology appraisal 94. In: ISBN

1
2 1846291410; 2006.

3
4 10. Heart Protection Study Investigators. MRC/BHF Heart Protection Study of
5 cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised
6 placebo-controlled trial. *Lancet* 2002; **360**: 7-22.

7
8
9
10 11. National Institute for Health and Clinical Excellence. Ezetimibe for the
11 treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia:
12 NICE technology appraisal guidance 132. In; 2007.

13
14
15 12. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials
16 for the National Cholesterol Education Program Adult Treatment Panel III
17 Guidelines. *J Am Coll Cardiol* 2004; **44**: 720-32.

18
19
20 13. De Backer G, Ambrosioni E, Borch-Johnsen K, et al. European guidelines on
21 cardiovascular disease prevention in clinical practice. Third Joint Task Force of
22 European and Other Societies on Cardiovascular Disease Prevention in Clinical
23 Practice. *Eur Heart J* 2003; **24**: 1601-10.

24
25
26 14. Ara R, Tumur I, Pandor A, et al. Ezetimibe for the treatment of
27 hypercholesterolaemia: a systematic review and economic evaluation. *Health Technol*
28 *Assess* 2008; **12**: iii, xi-xiii, 1-212.

29
30
31 15. Mikhailidis DP, Sibbring GC, Ballantyne CM, Davies GM, Catapano AL.
32 Meta-analysis of the cholesterol-lowering effect of ezetimibe added to ongoing statin
33 therapy. *Curr Med Res Opin* 2007; **23**: 2009-26.

34
35
36 16. Reckless JP, Henry P, Pomykaj T, et al. Lipid-altering efficacy of
37 ezetimibe/simvastatin 10/40 mg compared with doubling the statin dose in patients
38 admitted to the hospital for a recent coronary event: the INFORCE study. *Int J Clin*
39 *Pract* 2008; **62**: 539-54.

40
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42 17. Farnier M, Averna M, Missault L, et al. Lipid-altering efficacy of

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ezetimibe/simvastatin 10/20 mg compared with rosuvastatin 10 mg in high-risk hypercholesterolaemic patients inadequately controlled with prior statin monotherapy - The IN-CROSS study. *Int J Clin Pract* 2009; **63**: 547-59.

18. Kashani A, Sallam T, Bheemreddy S, Mann DL, Wang Y, Foody JM. Review of side-effect profile of combination ezetimibe and statin therapy in randomized clinical trials. *Am J Cardiol* 2008; **101**: 1606-13.

19. Reynolds T. Sleight of hand in trial design: average behaviour is not average, not all new information is really new. *Int J Clin Pract* 2009; **63**: 534-5.

20. Jakulj L, Vissers MN, Groen AK, et al. Baseline cholesterol absorption and the response to ezetimibe/simvastatin therapy; a post-hoc analysis of the ENHANCE trial. *J Lipid Res* 2009.

21. Lakoski SG, Xu F, Vega GL, et al. Indices of Cholesterol Metabolism and Relative Responsiveness to Ezetimibe and Simvastatin. *J Clin Endocrinol Metab* 2009.

22. Cannon CP, Giugliano RP, Blazing MA, et al. Rationale and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimibe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. *Am Heart J* 2008; **156**: 826-32.

23. Bosveld K, Connolly H. Chapter 2: Population. In: Dobbs J, Green H, Zealey L, editors. Focus on Ethnicity and Religion. London: Office for National Statistics; 2006. p. 20-41.

24. Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). *Am J Cardiol* 2003; **92**: 152-60.

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TABLES

Table 1 Subject baseline and demographic characteristics (randomised population, *n* = 786)

	Ezetimibe/simvastatin 10/40 mg	Atorvastatin 40 mg	Rosuvastatin 5–10 mg
	(<i>n</i> = 261)	(<i>n</i> = 263)	(<i>n</i> = 262)
Age, years	64.7 ± 8.7	64.2 ± 8.4	63.9 ± 8.6
≥ 70 years, <i>n</i> (%)	76 (29.1%)	76 (28.9%)	67 (25.6%)
Male, <i>n</i> (%)	160 (61.3%)	185 (70.3%)	178 (67.9%)
Race, <i>n</i> (%)			
Caucasian	254 (97.3%)	261 (99.2%)	257 (98.1%)
Asian	3 (1.1%)	0	2 (0.8%)
Black	4 (1.5%)	0	2 (0.8%)
Other	0	2 (0.8%)	1 (0.4%)
Current smoker, <i>n</i> (%)	44 (16.9%)	55 (20.9%)	47 (17.9%)

Cardiovascular disease

Current CVD/diabetes, <i>n</i> (%)	138 (52.9%)	131 (49.8%)	136 (51.9%)
High-risk CVD, <i>n</i> (%)	123 (47.1%)	131 (49.8%)	126 (48.1%)
Mean 10-year CVD risk ^a	36.3% ± 15.0%	37.4% ± 15.6%	33.5% ± 13.6%
Diabetes			
Type 1, <i>n</i> (%)	2 (0.8%)	1 (0.4%)	1 (0.4%)
Type 2, <i>n</i> (%)	40 (15.3%)	26 (9.9%)	32 (12.2%)
Fasting lipid levels, mmol/l			
LDL-C	2.6 ± 0.4	2.6 ± 0.4	2.5 ± 0.4
HDL-C	1.4 ± 0.3	1.4 ± 0.3	1.4 ± 0.3
Total cholesterol	4.7 ± 0.5	4.7 ± 0.6	4.7 ± 0.6
Triglycerides, median (range)	1.6 (0.7 to 3.8)	1.5 (0.7 to 4.0)	1.6 (0.7 to 4.3)

Values are mean ± SD unless otherwise stated.

^aExcluding secondary prevention.

CVD, cardiovascular disease; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol.

Table 2 Summary of secondary and exploratory efficacy outcome measures (Full Analysis Set, n = 772)

	Ezetimibe/simvastatin 10/40 mg (n = 255)	Atorvastatin 40 mg (n = 259)	Rosuvastatin 5–10 mg (n = 258)
<i>Percentage change from baseline</i>			
LDL-C	-26.2 (-29.1 to -23.2)	-11.1(-14.0 to -8.2)**	-3.0 (-5.9 to -0.1)**
Total cholesterol	-16.3 (-18.2 to -14.5)	-8.3 (-10.2 to -6.5)**	-2.5 (-4.4 to -0.7)**
Triglycerides	-9.5 (-12.5 to -6.7)	-8.1 (-11.8 to -2.9)	-4.3 (-7.0 to 0.0)
HDL-C	-1.4 (-2.9 to 0.0)	-2.3 (-3.7 to -0.9)	-0.1 (-1.5 to +1.3)
Non-HDL-C	-22.2 (-24.7 to -19.6)	-10.5 (-13.0 to -8.0)**	-3.1 (-5.6 to -0.6)**
Total cholesterol:HDL-C ratio	-14.4 (-16.4 to -12.4)	-5.5 (-7.5 to -3.4)**	-2.0 (-4.0 to 0.0) **
Apo A1	-1.6 (-3.1 to -0.2)	-4.5 (-5.9 to -3.1)*	+0.6 (-0.8 to +2.1)*
Apo B	-17.5 (-19.7 to -15.4)	-9.0 (-11.1 to -6.9)**	-3.2 (-5.3 to -1.1) **
Apo B:Apo A1 ratio	-15.4 (-17.8 to -12.9)	-3.8 (-6.2 to -1.4)**	-3.1 (-5.5 to -0.7) **

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*p < 0.05, **p < 0.001 vs ezetimibe/simvastatin 10/40 mg.

Data are least-squares mean (95% CI) percentage change from baseline, except for triglycerides which are median percent change (ANOVA

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with treatment and strata as factors).

ANOVA, analysis of variance; Apo, apolipoprotein; CI, confidence interval; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol

Deleted: ^bData are adjusted proportion (95% CI), using logistic regression analysis with treatment and strata as factors.¶

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Deleted: ^dJBS-2 definition of secondary prevention for patients with existing CVD or CVD and diabetes; primary prevention for high-risk patients or patients with diabetes but no CVD.¶

^eNICE definition of secondary prevention for patients with existing CVD and/or diabetes; primary prevention for high-risk patients without diabetes. Analysis was *post hoc* because NICE treatment guidelines were published after the study was initiated.¶

^fPredefined baseline LDL-C strata were ≥ 2.0 to < 2.5 mmol/l; ≥ 2.5 to < 3.0 mmol/l; and ≥ 3.0 to ≤ 4.2 mmol/l; the upper two strata were combined because there were too few patients in the highest stratum for analysis.

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^gBased on NICE guidance for treatment of patients with existing CVD and/or diabetes (analysis was *post hoc* because NICE treatment guidelines were published after the study was initiated).

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Table 3. Tolerability of study treatments (All-Patients-as-Treated population, $n = 780$)

	Ezetimibe/simvastatin	Atorvastatin	Rosuvastatin
	10/40 mg	40 mg	5–10 mg
	($n = 259$)	($n = 260$)	($n = 261$)
Any AE	89 (34.4)	93 (35.8)	103 (39.5)
Drug-related AE	23 (8.9)	22 (8.5)	27 (10.3)
AE leading to study discontinuation	7 (2.7)	5 (1.9)	9 (3.4)
Serious AE	4 (1.5)	2 (0.8)	5 (1.9)
Laboratory AE	5 (1.9)	3 (1.2)	1 (0.4)

Values are the number (%) of patients with at least one adverse experience (AE).

AEs reported were those occurring or worsening after the first dose of double-blind study medication and up to 14 days following the last dose of study medication (or 30 days for serious AEs).

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FIGURE LEGENDS

Figure 1. Patient flow through study

†Patients could have more than one reason for randomisation failure. ‡No further details recorded. Randomised population (demographic and baseline characteristics); APaT, All-Patients-as-Treated (APaT) population (safety analyses); Full Analysis Set (efficacy analyses). ALT/AST, alanine aminotransferase/aspartate aminotransferase; LDL-C, low-density-lipoprotein cholesterol; ULN, upper limit of normal.

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Figure 2. Proportion of patients achieving low-density-lipoprotein cholesterol (LDL-C) < 2 mmol/l (< 77 mg/dl) and total cholesterol < 4 mmol/l (< 155 mg/dl) for ezetimibe/simvastatin 10/40 mg compared with atorvastatin 40 mg and with rosuvastatin 5–10 mg (Full Analysis Set).

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Data are presented as adjusted proportions (95% confidence interval [CI]). ** indicates **p < 0.001 vs ezetimibe/simvastatin 10/40 mg in a logistic regression model with treatment and LDL-C stratum as factors.

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Figure 3. Subgroup analysis of proportion of patients achieving low-density-lipoprotein cholesterol LDL-C treatment goals for ezetimibe/simvastatin 10/40 mg compared with atorvastatin 40 mg and with rosuvastatin 5–10 mg (Full Analysis Set)

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Data are adjusted proportion (95% CI), using logistic regression analysis with treatment and strata as factors. ^aJBS-2 definition of secondary prevention for patients with existing CVD or CVD and diabetes; primary prevention for high-risk patients or patients with diabetes but no CVD. ^bNICE definition of secondary prevention for patients with existing CVD and/or diabetes; primary prevention for high-risk patients without diabetes. Analysis was *post hoc*

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2 because NICE treatment guidelines were published after the study was initiated. ^cPredefined
3 baseline LDL-C strata were ≥ 2.0 to < 2.5 mmol/l; ≥ 2.5 to < 3.0 mmol/l; and ≥ 3.0 to \leq
4 4.2 mmol/l; the upper two strata were combined because there were too few patients in the
5 highest stratum for analysis.
6
7 CI, confidence interval; JBS, Joint British Societies; LDL-C, low-density-lipoprotein
8 cholesterol; NICE, National Institute for Health and Clinical Excellence.
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10 ** indicates **p < 0.001 vs ezetimibe/simvastatin 10/40 mg in a logistic regression model
11 with treatment and LDL-C stratum as factors.
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Richard White

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Proportion of patients achieving LDL-C target^b

LDL-C < 2.0 mmol/l (JBS-2 criteria)	69.4 (62.9 to 75.2)	33.5 (27.6 to 39.9)**
All patients (primary efficacy variable)	69.4 (62.9 to 75.2)	33.5 (27.6 to 39.9)**
Baseline LDL-C \geq 2.5 to \leq 4.2 mmol/l ^c JBS-2 secondary prevention only ^c	69.9 (59.4 to 78.7) [n = 100]	33.6 (24.9 to 43.6)** [n = 109]
LDL-C < 2.0 mmol/l (NICE criteria) ^d JBS-2 primary prevention only ^c	69.4 (61.1 to 76.7) [n = 155]	33.7 (26.1 to 42.2)** [n = 150]
NICE secondary prevention only ^d	68.7 (59.5 to 76.7) [n = 131]	36.6 (28.1 to 46.0)** [n = 125]
NICE primary prevention only ^d	70.5 (61.2 to 78.3) [n = 124]	30.9 (23.2 to 39.7)** [n = 134]
Baseline LDL-C 2.0 to < 2.5 mmol/l ^e	78.7 (71.0 to 84.8) [n = 136]	54.5 (46.0 to 62.7)** [n = 134]
Baseline LDL-C \geq 2.5 to \leq 4.2 mmol/l ^e	54.6 (45.6 to 63.3) [n = 119]	16.8 (11.2 to 24.4)** [n = 125]
LDL-C \leq 1.8 mmol/l	49.0 (42.4 to 55.6)	15.2 (11.3 to 20.2)**
LDL-C < 2.5 mmol/l	92.1 (88.2 to 94.7)	74.1 (68.1 to 79.4)**