Familial hypercholesterolemia: the Dutch approach
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Colesevelam added to combination therapy with a statin and ezetimibe in patients with familial hypercholesterolemia: a 12-week, multicenter, randomized double-blind controlled trial

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Chapter 20

ABSTRACT

Background: Familial hypercholesterolemia (FH) has been associated with increased cardiovascular risk when untreated or when normal LDL-C concentrations are not reached. Some patients with FH do not reach LDL-C goals despite intensive combination therapy. This study assessed the efficacy and tolerability of colesevelam added to maximally-tolerated stable-dose combination treatment with a statin and ezetimibe.

Methods: This Phase IV, multicenter, randomized, double-blind, placebo-controlled trial enrolled patients aged 18 to 75 years with FH and an LDL-C concentration >2.5 mmol/L who were receiving a maximally tolerated and stable regimen of a statin and ezetimibe. Patients were randomly assigned to receive Colesevelam 3.75 g/d or placebo added to the statin and ezetimibe for 12 weeks. The primary efficacy outcome was the difference in LDL-C between the colesevelam and placebo groups after 6 weeks. Secondary efficacy outcomes were between-group differences in LDL-C, total cholesterol (TC), HDL-C, triglyceride, apolipoprotein (apo) B, and apoA-I concentrations, as well as apoB/apoA-I ratio after 12 weeks. Tolerability was assessed based on the prevalences of adverse events by organ system class in each treatment group.

Results: Eighty-six patients were randomized (45 colesevelam, 41 placebo) of whom 84 (44 colesevelam, 40 placebo) were included in the primary analysis. The mean (SD) age of the participants was 52.8 ± 10.8 years and 51 (59%) were men. The difference (95% CI) in LDL-C between colesevelam and placebo after 6 weeks, was -18.5% (-25.3 to -11.8). Between-group differences in LDL-C, TC, HDL-C, triglyceride and apoB/apo A-I ratio after 12 weeks were -12.0% (-17.8 to -6.3), -7.3% (-12.0 to -2.6), +3.3% (-2.4 to +9.0), +2.8% (-10.4 to +15.9) and -12.2% (-20.2 to -4.2), respectively. Colesevelam was generally well-tolerated with gastrointestinal side effects in 12 of the 45 patients (27%) versus 7 of the 40 (18%) in the placebo group (p=0.43).

Conclusion: In these patients with FH, colesevelam added to a combination of a statin and ezetimibe was associated with a significantly improved LDL-C concentrations compared with placebo during a 12-week study period and was generally well-tolerated.
INTRODUCTION

Familial hypercholesterolemia (FH) is an autosomal co-dominant disorder with a prevalence of 1:500 in Western countries. Defects in the genes that code for proteins involved in the hepatic clearance of low-density lipoprotein cholesterol (LDL-C) underlie the FH phenotype. Mutations in the genes that code for the LDL-receptor (LDLR), apolipoprotein (apo) B, and proprotein convertase subtilisin/kexin type 9 are known to cause FH. This disorder has been associated with elevated serum LDL-C concentrations and an increased risk for premature ischemic heart disease (IHD) (mean age at onset of the first IHD event, ~47 years). Left undiagnosed and untreated, the cumulative risk for IHD at age 60 years in European patients is 60% to 85% among men and 30% to 50% among women.

Reducing the LDL-C concentration is the cornerstone of prevention of cardiovascular (CV) disease in FH. Based on findings from a literature search, no intervention trials with CV-related end points in patients with FH have been published. However, treatment with statins has been reported to reduce IHD risk robustly in FH cohorts, as suggested by standardized mortality ratios in a cohort of patients with FH in the United Kingdom and a Cox proportional hazards model for a Dutch cohort of patients with clinically diagnosed FH. Based on the known morbidity and mortality of untreated FH and the beneficial effects of treatment, current guidelines advise pharmacologic treatment of FH. Although in some countries no clear treatment goals have been defined in the FH population, LDL-C targets can be extrapolated from European guidelines and the National Cholesterol Education Program (NCEP) in the United States. In patients at high risk for IHD, European guidelines advocate an LDL-C target ≤ 2.5 mmol/L (≤96.7 mg/dL(conversion equation for total, LDL and HDL cholesterol: multiply level in mmol/L by 38.7 to obtain that level in mg/dL)). The American Heart Association advocates an LDL-C target < 2.6 mmol/L (≤100 mg/dL). In some countries, guidelines advocate LDL-C targets specifically in the FH population. The Dutch guidelines stipulate a LDL-C target ≤ 2.5 mmol/L in patients with FH, and the National Institute for Health and Clinical Excellence (NICE) guidelines from the United Kingdom advocate a ≥ 50% reduction in LDL-C concentration.

Despite receiving combinations of lipid-lowering drugs, >70% of patients with FH did not achieve LDL-C targets during follow-up in outpatient clinics of 733 patients in the United Kingdom and of 1249 patients in the Netherlands, with targets defined as ≤ 3.0 mmol/L in the United Kingdom in 2003 and ≤ 2.5 mmol/L in the Netherlands in 2008. Therefore, treatments that further reduce LDL-C when added to
combination treatment with a statin at maximally-tolerated dose plus ezetimibe are of interest. Theoretically, an adjuvant third-line therapy with good tolerability might be of benefit in refractory FH. Colesevelam hydrochloride is a well-tolerated bile acid sequestrant (BAS) that is not absorbed. The availability of an effective BAS, with fewer associated adverse events (AEs) and better palatability than cholestyramine might enhance the convenience of combination therapy with statins. Bile acid binding resins combine with bile acids in the intestine, decreasing their absorption. As such, they interfere with the enterohepatic circulation of bile acids and bile acid salts, and increase the clearance of LDL-C and very low-density lipoprotein (VLDL) remnants from the circulation, decreasing serum LDL-C concentrations.

This study was conducted to assess the efficacy and tolerability of the addition of colesevelam to combination treatment with a maximally tolerated and stable regimen of a statin and ezetimibe in decreasing LDL-C concentrations in patients with refractory FH.

METHODS

This Phase IV study, named Triple, had 2 parts. Part 1 was a 12-week, randomized, double-blind, placebocontrolled phase; part 2 was an open-label extension period of 40 weeks. The results of only the double-blind phase, conducted at eight lipid clinics in France, Germany, the Netherlands, Sweden, and the United Kingdom, are reported here. The study protocol was approved by the respective ethics committees applicable for the institutions and the applicable regulatory body per country. Written informed consent was obtained from all participants before any study procedures were conducted.

Patient Selection
Men and women aged 18 to 75 years were eligible for inclusion if they had FH confirmed on genotyping or as defined using one of the diagnostic criteria described by van Aalst-Cohen and Jansen (based on a combination of criteria from the United Kingdom [Simon Broome Register Criteria], the Netherlands [Dutch Lipid Clinic Network Criteria], and the United States [Make Early Diagnosis to Prevent Early Death (MEDPED)]). A diagnosis of FH was defined as the presence of a documented LDL receptor mutation, or as a history of untreated LDL-C concentration above the 95th percentile for sex and age, in combination with at least one of the following: (1) presence of typical tendon xanthomas in the patient or in a first-degree relative; (2) an LDL-C concentration above the 95th percentile in a first-degree relative; and
(3) coronary artery disease in the patient or in a first-degree relative aged <60 years. Additional eligibility criteria were refractory FH, defined as an LDL-C concentration >2.5 mmol/L despite combination treatment with a maximally tolerated and stable regimen of a combination of a statin + ezetimibe for ≥12 consecutive weeks preceding the screening visit. Patients with a fasting triglyceride concentration >3.4 mmol/L (300 mg/dL); a known allergy to any of the components used in colesevelam or placebo, bowel, or biliary obstruction; and/or secondary causes of hypercholesterolemia and poorly controlled diabetes (ie, hemoglobin [Hb] A1c >9%) at screening were excluded.

Study Design
The first patient was screened in August 2007 and the last patient was randomized in September 2008. A patient was considered to be enrolled after having provided informed consent.

The screening period comprised a 4-week run-in period to assess the stability of the lipid-lowering effect of combination treatment with the statin + ezetimibe. At the baseline visit, participants who met the inclusion criterion of ≤10% variability in LDL-C compared with screening were randomly assigned in a 1:1 ratio, using a computer-generated table of random numbers per study center, to receive colesevelam or placebo. Participants were instructed to continue to use their regimen of a statin + ezetimibe. The investigational product consisted of a daily dose of 6 tablets of colesevelam (625 mg per tablet) or matching placebo tablets. The study medication was administered with a meal and beverage according to the patient’s preference, either as 6 tablets once daily (QD) or 3 tablets twice a day (BID). Efficacy and tolerability assessments were conducted at week 6 (± 1 week) and at week 12 (± 1 week).

Outcome Measures
The primary efficacy outcome was the difference in the percentage change from baseline to week 6 in LDL-C concentration between colesevelam and placebo. This time point was chosen because the effects on LDL-C lowering with colesevelam are detectable 2 weeks after the start of treatment. The week-6 visit was the earliest planned time point at which LDL-C was measured.

The predefined secondary end points were the percentage changes in concentrations of HDL-C, total cholesterol (TC), triglyceride, apoA-I, and APOB, as well as apoB/apoA-I ratio, from baseline to weeks 6 and 12, and the between-group differences in these parameters; the percentage change in LDL-C at week 12 compared with baseline and the between-group difference in this parameter; the proportions of patients who
reached an LDL-C target ≤2.5 mmol/L at weeks 6 and 12; the proportions of patients with a decrease from baseline in LDL-C ≥15% at weeks 6 and 12 (responders); and absolute changes in fasting glucose, HbA1c, and highly sensitive C-reactive protein (hsCRP) concentrations at weeks 6 and 12.

Serum lipid concentrations were measured by a central laboratory (Quintiles Laboratories Europe, Livingston, United Kingdom) using Roche BMD methodology. ApoA-I and APOB were measured using immunoturbidimetric methodology. Quality-control procedures were applied in line with the calibration and control requirements specified for each assessment and executed according to Good Laboratory Practice, and the central laboratory was certified by the College of American Pathologists.

Tolerability was assessed by recording the prevalence and severity of AEs that were discovered during patient interview and physical examination at each study visit or based on laboratory analysis of hematology and blood chemistry, including creatine phosphokinase, liver and kidney function tests, and discontinuation due to AEs with the use of colesevelam and placebo at the end of 12 weeks. The proportions of patients whose Tg concentrations were elevated to >1.7 mmol/L (150 mg/dL) - considered a clinically important threshold according to the European Guidelines on CV Disease Prevention in Clinical Practice - were calculated.

Sample Size Calculation and Statistical Analyses
Statistical assumptions for detecting a between-group difference in LDL-C decrease were based on an estimated between-group difference of ≥6% (being just clinically relevant like the reduction expected on doubling the dose of a statin) to a maximum of 15% (as an anticipated maximal added effect in combination therapy), with an anticipated SD of 10% to 16%. Assuming a between-group difference in the decrease of LDL-C of 9% and an SD of 12%, and using a 2-sided α level of 0.05 at 90% power, a sample size of 37 patients was calculated. Forty patients per group were randomized to allow for a sufficient sample size in the primary analysis. Patients who were withdrawn before week 6 were replaced, to a maximum of ~90 randomized patients.

For the primary efficacy end point, ANCOVA, with study drug and center as covariates, was used to compare data from the colesevelam and placebo groups. Least squares means (LSMs), differences in LSMs, and P values were determined. A P value <0.05 was considered statistically significant. Similarly, ANCOVA was conducted for continuous secondary end-point data and in the intent-to-treat population, defined as
Colesevelam added to statin and ezetimibe in FH

all randomized patients who received at least one dose of study medication who had evaluable data available from baseline and at least one postbaseline lipid assessment (last observation carried forward). Due to skewness of change from baseline in triglycerides, secondary endpoints related to triglycerides were also analyzed non-parametrically, as a confirmative measure, using the Wilcoxon rank sum test with the Hodges-Lehmann estimate of the shift parameter. Secondary endpoint analyses for goal rate and responder rate were conducted using the Fisher exact test. All results were calculated using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Study Population
Of the 138 participants who were screened, 52 were excluded before randomization due to LDL-C variability of > 10% compared with baseline (n=30), not meeting inclusion criteria (n = 9), meeting exclusion criteria (n=6), personal reasons (n = 6), and an AE (n = 1). The remaining 86 participants were assigned to receive colesevelam (n = 45) or placebo (n = 41). Three patients per study group, were withdrawn prematurely leaving 42 and 38 patients who completed the double-blind phase in the colesevelam and placebo groups, respectively (Figure 1).

The baseline demographic and clinical characteristics were not significantly different between the 2 study groups (51% male; mean [SD] age, 52.8 [10.8] years; weight, 83.8 [17.4] kg; and race, 100% white in the colesevelam group and 98% white and 2% black in the placebo group) (Table 1).

Efficacy
At baseline, LDL-C and other lipoprotein concentrations were not significantly different between the 2 study arms (Table 2). Changes from baseline in study parameters are shown in Table 3. The between-group difference in change from baseline LDL-C was significant at week 6, with an LSM change (95% CI) of –18.5% (–25.3 to –11.8). The difference in the proportions of patients who achieved the target LDL-C concentration (≤2.5 mmol/L) between the colesevelam and placebo groups was not significant (4 [9%] vs 1 [3%]). However, the proportion of responders (decrease in LDL-C concentration ≥15%) at week 6 was significantly higher in the colesevelam group than in the placebo group (14/44 [32%] vs 0/40; P < 0.001). This difference remained significant at week 12 (13/44 [30%] vs 3/40 [8%]; P = 0.012). Between-group differences (95% CI) in LDL-C, TC, HDL-C, Tg, and apoB/apoA-I
ratio after 12 weeks were –12.0% (–17.8 to –6.3), –7.3% (–12.0 to –2.6), +3.3% 
(–2.4 to +9.0), +2.8% (–10.4 to +15.9), and –12.2% (–20.2 to –4.2), respectively. 
Mean TC concentrations were significantly reduced with colestevam compared with 
placebo at weeks 6 and 12 (LSM between-group differences, –11.1% and –7.3%, 
respectively; P < 0.001 and P < 0.003). On average, triglyceride levels increased 
in the colestevam treatment group from baseline to weeks 6 and 12 (Tables 2 and 3). The median triglyceride concentration increased from 1.14 mmol/L at baseline 
to 1.27 and 1.26 mmol/L at weeks 6 and 12, respectively. The mean increase in 
triglyceride concentrations with colestevam compared with placebo was significant 
at week 6, according to the Wilcoxon rank sum test (Hodges-Lehmann shift, 12.8; 
P = 0.045), although triglyceride concentrations were not significantly different at 
week 12, likely due to an increase over time in triglyceride concentrations in the 
placebo group. At baseline, 11 of 44 patients (25%) in the Colesevelam group had a 
Tg concentration above the threshold9 of >1.7 mmol/L (150 mg/dL); these numbers 
were 14 of 43 (33%) at week 6, and 12 of 44 (27%) at week 12. In the placebo group, 
8 of 40 (20%), 6 of 40 (15%), and 14 of 40 (35%) had a triglyceride concentration 
>1.7 mmol/L at those time points. The between-group differences between the 
proportions of patients with a triglyceride concentration >1.7 mmol/L at baseline 
and weeks 6 and 12 did not reach statistical significance at any of those time points. 
LSM between-group differences from baseline to weeks 6 and 12 in apoB/apoA-I ratio 
were significantly improved with colestevam compared with placebo (–14.2% and 
–12.2% at weeks 6 and 12; P < 0.001 and P = 0.003). This improvement in apoB/ 
apoA-I ratio was likely based on a reduction in APOB concentration. 

Although not significant at week 6 (–0.06%), the LSM between-group difference 
in change from baseline to week 12 in mean HbA1c concentration was significant 
(–0.12%; P = 0.027). There were no significant between-group differences in HDL-C, 
fasting glucose, or hsCRP concentrations at week 6 or 12.
Table 1: Characteristics of all randomized patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (N=41)</th>
<th>Colesevelam (N=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.8 ± 11.3</td>
<td>53.7 ± 10.3</td>
</tr>
<tr>
<td>Male sex – n (%)</td>
<td>28 (68)</td>
<td>23 (51)</td>
</tr>
<tr>
<td>Caucasian – n (%)</td>
<td>40 (98)</td>
<td>45 (100)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.8 ± 4.7</td>
<td>28.5 ± 5.0</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>84.5 ± 17.7</td>
<td>83.2 ± 17.4</td>
</tr>
<tr>
<td>History of symptomatic atherosclerotic cardiovascular disease – n (%)</td>
<td>22 (54)</td>
<td>21 (47)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>6 (15)</td>
<td>13 (29)</td>
</tr>
<tr>
<td>Ischaemic angina</td>
<td>11 (27)</td>
<td>12 (27)</td>
</tr>
<tr>
<td>PCI</td>
<td>8 (20)</td>
<td>10 (22)</td>
</tr>
<tr>
<td>CABG</td>
<td>7 (17)</td>
<td>9 (20)</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>2 (5)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>CVA or TIA</td>
<td>1 (2)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>History of diabetes – n (%)</td>
<td>1 (2)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>History of hypertension – n (%)</td>
<td>9 (22)</td>
<td>14 (31)</td>
</tr>
<tr>
<td>Current smoker – n (%)</td>
<td>4 (10)</td>
<td>8 (18)</td>
</tr>
<tr>
<td>Former smoker – n (%)</td>
<td>20 (49)</td>
<td>21 (47)</td>
</tr>
<tr>
<td>Current statin use – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>22 (54)</td>
<td>22 (49)</td>
</tr>
<tr>
<td>Use of maximum dose (80 mg)</td>
<td>10 (24)</td>
<td>12 (27)</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>9 (22)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Use of maximum dose (80 mg)</td>
<td>5 (12)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>9 (22)</td>
<td>20 (44)</td>
</tr>
<tr>
<td>Use of maximum dose (40 mg)</td>
<td>6 (15)</td>
<td>15 (33)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>1 (2)</td>
<td>-</td>
</tr>
<tr>
<td>Use of maximum dose (80 mg)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ezetimibe 10 mg – n (%)</td>
<td>41 (100)</td>
<td>44 (98)</td>
</tr>
<tr>
<td>Ezetimibe 20 mg – n (%)</td>
<td>-</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Baseline blood pressure (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>130 ± 16 a</td>
<td>128 ± 16</td>
</tr>
<tr>
<td>Diastolic</td>
<td>79 ± 10 b</td>
<td>79 ± 10</td>
</tr>
<tr>
<td>Initial untreated LDL-C (mmol/L)</td>
<td>8.4 ± 2.1 b</td>
<td>7.9 ± 1.9</td>
</tr>
</tbody>
</table>

Data are presented as number (percentage) or mean ± SD. Where indicated, due to unavailable patient data, the following numbers of patients were included in the analysis: ** n=40; * n=16; † n=12. CABG= coronary artery bypass graft, CVA= cerebrovascular accident, LDL-C= low-density lipoprotein cholesterol, PCI= percutaneous coronary intervention, SD= standard deviation, TIA= transient ischaemic attack. Initial untreated LDL-C is the highest LDL-C level measured without medication in the medical history of the participant, which was known for only 28/86 (33%) participants.
Figure 1. Patient enrolment and disposition

**Screened**
N=138

Excluded (N=52)
- Did not meet LDL-C variability criterion (30)
- Did not meet inclusion criteria (9)
- Met exclusion criteria (6)
- Personal reasons (6)
- Adverse event (1)

**Randomized**
N=86

**Colesvelam**
N=45
- Withdrawn before week 6 (N=2)
  - Adverse event (2)*
- Withdrawn before week 6 (N=1)
  - Adverse event (1)†

**Placebo**
N=41
- Withdrawn before week 6 (N=2)
  - Adverse event (1)‖
- Withdrawn before week 6 (N=1)
  - Adverse event (1)‡

**Completed double-blind phase**
N=42
N=38

Adverse events: * Balance disorder, dizziness, nausea (1 patient) and hyperchloridia (1 patient); † nausea, myalgia; ‡ myalgia; ‖ dyspepsia.
Table 2: Effects on laboratory parameters of Colesevelam (n=44) or placebo (n=40) added to the combination treatment with a statin and ezetimibe in patients with familial hypercholesterolemia.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
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<th>Week 6</th>
<th></th>
<th>Week 12</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Colesevelam</td>
<td>Placebo</td>
<td>Colesevelam</td>
<td>Placebo</td>
<td>Colesevelam</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Cholesterol (mmol/L)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5.6 ± 1.1</td>
<td>5.8 ± 1.2</td>
<td>5.9 ± 1.3†</td>
<td>5.5 ± 1.2*</td>
<td>5.7 ± 1.3</td>
<td>5.4 ± 1.1</td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>3.7 ± 1.0</td>
<td>3.9 ± 1.0</td>
<td>3.9 ± 1.1†</td>
<td>3.3 ± 0.8§</td>
<td>3.8 ± 1.0</td>
<td>3.4 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>1.3 ± 0.3</td>
<td>1.3 ± 0.4</td>
<td>1.3 ± 0.3†</td>
<td>1.3 ± 0.4†</td>
<td>1.2 ± 0.3</td>
<td>1.3 ± 0.4</td>
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<tr>
<td><strong>Triglycerides (mmol/L)</strong></td>
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<td></td>
<td>1.3 ± 0.6</td>
<td>1.4 ± 0.8</td>
<td>1.3 ± 0.5†</td>
<td>1.6 ± 1.0*</td>
<td>1.5 ± 0.6</td>
<td>1.6 ± 1.1</td>
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<tr>
<td><strong>Apolipoprotein (mmol/L)</strong></td>
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<tr>
<td>Apo B</td>
<td>1.0 ± 0.3†</td>
<td>1.1 ± 0.3*</td>
<td>1.1 ± 0.3†</td>
<td>1.0 ± 0.2</td>
<td>1.1 ± 0.3†</td>
<td>1.0 ± 0.2†</td>
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<tr>
<td>Apo A-I</td>
<td>1.3 ± 0.2†</td>
<td>1.4 ± 0.3*</td>
<td>1.4 ± 0.2†</td>
<td>1.4 ± 0.3</td>
<td>1.4 ± 0.3†</td>
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<tr>
<td>Apo B/A-I ratio</td>
<td>0.8 ± 0.2†</td>
<td>0.8 ± 0.3†</td>
<td>0.8 ± 0.2†</td>
<td>0.7 ± 0.2</td>
<td>0.8 ± 0.2†</td>
<td>0.7 ± 0.2†</td>
<td></td>
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<tr>
<td><strong>hsCRP (mg/L)</strong></td>
<td>1.3 ± 2.4</td>
<td>2.0 ± 2.5</td>
<td>1.5 ± 1.8†</td>
<td>2.3 ± 3.1</td>
<td>1.4 ± 1.7</td>
<td>1.9 ± 3.2</td>
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<tr>
<td><strong>Fasting glucose (mmol/L)</strong></td>
<td></td>
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<tr>
<td></td>
<td>5.2 ± 0.6</td>
<td>5.4 ± 0.9</td>
<td>5.3 ± 0.6†</td>
<td>5.3 ± 0.8</td>
<td>5.4 ± 0.9</td>
<td>5.4 ± 0.7</td>
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</tr>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td>5.7 ± 0.3</td>
<td>5.8 ± 0.5</td>
<td>5.7 ± 0.3†</td>
<td>5.8 ± 0.5</td>
<td>5.8 ± 0.3</td>
<td>5.8 ± 0.5</td>
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</tbody>
</table>

Data are presented as mean ± SD for the intent-to-treat population. Week 12 means are based on last observation carried forward. Where indicated, due to unavailable patient data, the following numbers of patients were included in the analysis: † Placebo: N=39; * Colesevelam: N=43; † Colesevelam: N=42; § Placebo: N=37. ApoA-I = apolipoprotein A-I, APOB = apolipoprotein B, HDL = high-density lipoprotein, hsCRP = high sensitivity C-reactive protein, LDL = low-density lipoprotein.
Table 3. Changes from baseline in laboratory parameters with colesevelam or placebo.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo n=44</th>
<th>Colesevelam n=40</th>
<th>Difference</th>
<th>Placebo n=44</th>
<th>Colesevelam n=40</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage changes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>4.9 †</td>
<td>-6.3 *</td>
<td>-11.1</td>
<td>0.7</td>
<td>-6.6</td>
<td>-7.3</td>
</tr>
<tr>
<td>LDL-C</td>
<td>6.8 †</td>
<td>-11.7 §</td>
<td>-18.5</td>
<td>0.6</td>
<td>-11.4</td>
<td>-12.0</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.3 †</td>
<td>0.5 *</td>
<td>-0.8</td>
<td>-3.5</td>
<td>-0.2</td>
<td>3.3</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>4.3 †</td>
<td>16.3 †</td>
<td>12.0</td>
<td>11.7</td>
<td>14.4</td>
<td>2.8</td>
</tr>
<tr>
<td>Apolipoprotein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>5.7 †</td>
<td>-8.3 *</td>
<td>-14.0</td>
<td>4.6 †</td>
<td>-6.0 *</td>
<td>-10.6</td>
</tr>
<tr>
<td>Apolipoprotein A-1</td>
<td>2.3 †</td>
<td>3.2 *</td>
<td>0.9</td>
<td>3.8 †</td>
<td>5.3 *</td>
<td>1.6</td>
</tr>
<tr>
<td>Apo B/A-I ratio</td>
<td>4.2 †</td>
<td>-10.0 *</td>
<td>-14.2</td>
<td>2.6 †</td>
<td>-9.6 *</td>
<td>-12.2</td>
</tr>
<tr>
<td>Absolute changes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>0.2 †</td>
<td>0.4</td>
<td>0.3</td>
<td>0.2 *</td>
<td>0.1</td>
<td>-0.1</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>0.1 †</td>
<td>-0.1 *</td>
<td>-0.2</td>
<td>0.2 *</td>
<td>0.0</td>
<td>-0.2</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>0.0 †</td>
<td>-0.1</td>
<td>-0.06</td>
<td>0.1 †</td>
<td>-0.0</td>
<td>-0.12</td>
</tr>
</tbody>
</table>

Data are presented as least squares mean change from baseline for the Intent-to-Treat population. Placebo: N = 40; Colesevelam: N = 44. P-values are calculated by analysis of covariance. 5Week-12 means were based on last observation carried forward.

Where indicated, due to unavailable patient data, the following numbers of patients were included in the analysis: Placebo: N = 39; Colesevelam: N = 43; Placebo: n = 36; Placebo: N = 40.

ApoA-I = apolipoprotein A-I, APOB = apolipoprotein B, HDL = high-density lipoprotein, hsCRP = high sensitivity C-reactive protein, LDL = low-density lipoprotein.
Safety Profile
The overall frequency of treatment-emergent AEs (TEAEs) over the 12-week study period was not significantly different between the colesevelam and placebo groups (27/45 [60%] and 21/40 [53%], respectively). The most commonly reported TEAEs were gastrointestinal (12/45 [27%] and 7/40 [18%], respectively; P = NS). In total, 6 patients reported constipation (4/45 [9%] and 2/40 [5%]; P = NS). The second largest category of TEAEs was infections and infestations, with 5 patients with nasopharyngitis (2/45 [4%] and 3/40 [8%]; P = NS). The majority of TEAEs were mild or moderate, and the frequencies of TEAEs that were considered related to study drug were not significantly different between the 2 groups (13/45 [29%] and 9/40 [23%]).

During 12-week double-blind phase 5 patients discontinued due to an AE (3/45 [7%] and 2/40 [5%] with colesevelam and placebo, respectively) (Figure 1). One treatment-emergent serious adverse event (TSAE) - 2 episodes of unstable angina that led to a percutaneous coronary intervention - was reported in a patient in the placebo group and was considered by the investigator to be unrelated to the study drug. The patient continued to use the study drug and completed the 12-week study period.

DISCUSSION
This 12-week study assessed the efficacy and tolerability of colesevelam added to an intensive lipid-lowering regimen of a statin + ezetimibe. The findings suggest that colesevelam used as add-on therapy significantly reduced LDL-C concentrations. The safety profile of colesevelam given as combination treatment with a statin + ezetimibe did not reveal any new concerns during this 12-week period. The majority of AEs that occurred in the colesevelam group were considered by the investigator to be mild or moderate in severity and were observed in studies of colesevelam monotherapy. The most frequently reported AE in the colesevelam group was constipation (9%), which might be expected with BAS treatment. This frequency was lower than that observed in the Lipid Research Clinics trial in 3806 patients, in which 39% of patients who received cholestyramine 24 g/d reported moderate to severe constipation over a period of 12 months. Even so, the 12-week period of the double-blind phase of the Triple study was short, and the results from the 40-week open-label phase may be more informative.

An additional reduction in LDL-C concentration of 11% to 12% with colesevelam adjuvant treatment might be considered a meaningful treatment response when, in
comparison, each doubling of statin dose has been found to achieve a 6% decrease in LDL-C. Three meta-analyses specifically evaluated the effects of reductions in LDL-C concentrations on CV morbidity and mortality. According to those analyses, for each 1 mmol/L decrease in LDL-C achieved, there are reductions in overall mortality (15.4%), IHD-related mortality (28.0%) and any IHD event (26.6%). Overall, for each 1% decrease in LDL-C achieved, the estimated reduction in IHD risk is 1%.

Several means of LDL-C lowering have been reported to reduce CV risk. Findings from studies on the effects of BAS and ileal bypass surgery have supported the concept that decreasing LDL-C by depleting bile salt pools decreases CV disease risk. A meta-analysis on the intensity of statin therapy and clinical outcomes in patients with stable coronary artery disease provided support for the more beneficial effect of the intensive statin regimens. The ASAP (Effects of Atorvastatin versus Simvastatin on Atherosclerosis Progression) trial, a surrogate end-point study that used carotid intima-media thickness as an end point, reported that the more intensive lipid-lowering treatment (atorvastatin 80 mg vs simvastatin 40 mg) was associated with less progression of carotid atherosclerosis in patients with FH. The Triple study population had above target LDL-C concentrations despite maximally-tolerated combination treatment with statin + ezetimibe. In comparison with findings from another trial in patients with FH, the ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) trial the Triple population had more CV disease risk factors. The authors speculate that a cohort of patients with an FH phenotype, severely elevated LDL-C concentrations, established CV disease and/or other comorbidities, as in the Triple trial, might obtain greater benefit from lowering LDL-C with the addition of colesevelam to the therapeutic regimen.

The proportions of responders (reduction from baseline LDL-C ≥15%) were significantly higher with colesevelam than placebo (P < 0.001 at week 6 and P = 0.012 at week 12). However, the mean LDL-C concentration at randomization was 1.3 mmol/L above the LDL-C target of 2.5 mmol/L. A mean reduction in LDL-C concentration ≥ 33% would have been required to reach that target. It might have been expected that 4 participants (9%) achieved the target concentration after 12 weeks of treatment with add-on colesevelam.

Triglyceride concentrations have been reported to increase ~5% to 20% with colesevelam treatment based on the findings from a previously published clinical study. Although no triglyceride treatment goals are provided in the current European Guidelines on CV Disease Prevention in Clinical Practice, concentrations...
>1.7 mmol/L are considered to reflect increased CV risk. The changes in triglyceride concentrations in the present study are not considered clinically meaningful because the proportion of colesevelam-treated patients with a triglyceride concentration >1.7 mmol/L was not significantly different between baseline and week 12 (25% vs 27%, respectively).

The apoB/apoA-I ratio is considered an important indicator of CV risk and represents a balance between potentially atherogenic and anti-atherogenic lipoprotein components, particularly in patients receiving treatment. The decreased apoB/apoA-I ratio, which was attributed to a significant decrease in APOB concentration, observed in patients treated with colesevelam in this study, suggests a reduced risk for IHD events with this treatment.

Several limitations of the study design merit discussion. The selection criteria led to the exclusion of patients with risk factors, such as overt diabetes or high triglyceride concentrations. High LDL-C variability resulted in the exclusion of 22% of the screened patients. Such criteria limit the ability to extrapolate the findings to the general population of patients with FH.

The findings from the present study in patients with FH suggest that colesevelam was efficacious in decreasing LDL-C in those who did not reach target LDL-C concentrations with a maximally-tolerated and stable regimen of a statin + ezetimibe. Colesevelam was generally well tolerated in this patient population.
REFERENCES


Colesevelam added to statin and ezetimibe in FH


