

REVIEW

Reaching goal in hypercholesterolaemia: dual inhibition of cholesterol synthesis and absorption with simvastatin plus ezetimibe

Stella S. Daskalopoulou and Dimitri P. Mikhailidis

Department of Clinical Biochemistry, Royal Free Hospital, Royal Free and University College School of Medicine, London NW3 2QG, UK

Address for correspondence: Dr D. P. Mikhailidis, Academic Head of Department (Lipid Clinics), Royal Free Hospital, Royal Free and University College School of Medicine, University of London, Pond Street, London NW3 2QG, UK. Tel.: +44 20 7830 2258; Fax: +44 20 7830 2235. email: MIKHAILIDIS@aol.com

Key words: Coronary heart disease – Cholesterol – ‘Dual inhibition’ – Ezetimibe – Low-density lipoprotein – Simvastatin – Vascular disease

ABSTRACT

Lowering serum cholesterol levels reduces the risk of coronary heart disease (CHD)-related events. Statins are commonly prescribed as first-line treatment but many patients at high-risk for CHD still fail to reach their cholesterol or low-density lipoprotein cholesterol (LDL-C) goals with statin monotherapy.

National and international guidelines for the prevention of CHD recommend the modification of lipid profiles and particularly LDL-C [e.g. the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III; 2001) and Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice (2003) Guidelines]. Several recent clinical trials indicated an added benefit from aggressive lowering of LDL-C levels. Based on these findings, the NCEP ATP III revised the LDL-C target from < 100 mg/dL (2.6 mmol/L) to < 70 mg/dL (1.8 mmol/L) (optional target) for very high-risk patients and < 130 mg/dL (3.4 mmol/L) to < 100 mg/dL (2.6 mmol/L) for moderately high-risk patients.

For patients who fail to achieve their LDL-C target, inhibiting the two main sources of cholesterol – synthesis and uptake – can produce more effective lipid lowering, allowing more patients to reach their LDL-C goal. Ezetimibe is a highly-selective inhibitor of cholesterol absorption and simvastatin is an evidence-based inhibitor of cholesterol synthesis. The LDL-C-lowering efficacy of targeting both major sources of cholesterol with ezetimibe plus simvastatin was demonstrated in several multicentre, double-blind, placebo-controlled trials in patients with hypercholesterolaemia. For patients who do not reach their cholesterol goal with a statin, adding ezetimibe 10 mg significantly reduces LDL-C compared with statin monotherapy. Thus, this treatment option may help patients reach the new ‘stricter’ cholesterol goals.

This review, based on a Medline database search from January 2000 to August 2005, considers the LDL-C-lowering efficacy of ezetimibe and discusses the role of this agent for patients who fail to achieve guideline cholesterol goals with statin monotherapy.

Introduction

Coronary heart disease (CHD) is the leading cause of mortality and morbidity not only in the industrialised world but also in developing countries¹. Serum cholesterol levels are a major modifiable risk factor for

CHD and several primary and secondary prevention trials confirmed that lowering serum cholesterol reduces the risk of CHD-related events²⁻¹².

There are two main sources of cholesterol in the body: cholesterol synthesised by the liver and

peripheral tissues and cholesterol absorbed/reabsorbed by the intestine. Most of the cholesterol derived from the intestines originates from the reabsorption of cholesterol produced by the liver (approximately two-thirds), with a small contribution from the absorption of dietary cholesterol (approximately one-third), and also from the sloughing of intestinal cells¹³. The liver plays a central role in maintaining cholesterol homeostasis¹⁴. In addition to cholesterol synthesis, the liver receives most of the cholesterol that is absorbed through the intestine and is the site for degradation and excretion of cholesterol through the bile¹⁵. There is also evidence that the plasma cholesterol level is influenced by the efficiency of cholesterol absorption¹⁶. A negative correlation was observed between the amount of absorbed dietary cholesterol and cholesterol synthesis¹⁶. Thus, the efficiency of cholesterol absorption may have an important role in determining plasma cholesterol levels.

Approximately 60–70% of the total serum cholesterol is in the form of low-density lipoprotein cholesterol (LDL-C)¹⁷. Studies have shown that the development and recurrence of CHD is related to high plasma LDL-C levels¹⁸. Plasma concentrations of LDL-C can be influenced by the amount of cholesterol that is synthesised, the amount that is excreted and/or the amount absorbed through the intestine¹⁹.

Statins are the most widely used lipid-lowering drugs and for patients who achieve target LDL-C levels with statin monotherapy no further intervention is required. These drugs partially inhibit the synthesis of cholesterol in the liver by inhibiting hydroxymethylglutaryl-coenzyme A reductase (HMG-CoA), a key enzyme involved in the synthesis of cholesterol²⁰. Reduced cholesterol synthesis leads to an increase in LDL-receptor expression in the liver and reduced LDL-C levels in the circulation. The efficacy of statins in lowering LDL-C and reducing morbidity and mortality in patients with and without CHD is well

established^{2-12,21}. In primary or secondary prevention trials, statin monotherapy was shown to reduce the incidence of CHD-related events by 25–60% and the risk of death from any cause by up to 30%^{6,8,9,11,12}. Most recently, the results of a prospective meta-analysis of data from over 90 000 individuals who took part in one of 14 clinical trials of statin therapy, supports the need to consider long-term statin therapy aiming to achieve substantial reductions in LDL-C levels²². The authors reported a reduction in the 5-year incidence of vascular events such as major coronary event and stroke of approximately 20% for each 1.0 mmol/L (40 mg/dL) reduction in LDL-C²².

Despite their reported efficacy, approximately 60% of patients taking statins do not achieve their cholesterol goals (see Table 1 for current recommended cholesterol treatment goals)²³. This was confirmed in the Return on Expenditure Achieved for Lipid Therapy (REALITY) programme and in the European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) studies, which demonstrated that in clinical practice across Europe, there is a lack of adequate lipid management^{24,25}. Under-treatment is discussed in greater detail below. Thus, many patients do not fully benefit from the reduced risk of CHD resulting from lipid-lowering treatment. The significant gap between guideline recommended treatment goals and the lipid levels actually achieved in clinical practice highlights the urgent need for new management strategies, particularly for high-risk patients.

As blood cholesterol levels are maintained through cholesterol synthesis and intestinal absorption, a 'dual inhibition' strategy using two different LDL-C-lowering drugs, a cholesterol absorption inhibitor plus a statin in a single tablet, is an approach that is expected to effectively lower cholesterol levels, particularly in patients who fail to achieve their target levels with statin monotherapy.

Table 1. Current recommended cholesterol treatment goals^{32,33} and recommended modifications based on recent clinical trial evidence (adapted from Grundy et al. 2004¹⁸)

| Risk category | LDL-C goal |
|--|--|
| NCEP ATP III 2004 | |
| High risk: CHD or risk-equivalents (10-year risk > 20%) | < 100 mg/dL (2.6 mmol/L) (optional goal: < 70 mg/dL, 1.8 mmol/L)* |
| Moderately high risk: 2+ risk factors (10-year risk 10–20%) | < 130 mg/dL (3.4 mmol/L) (optional goal: < 100 mg/dL, 2.6 mmol/L)* |
| Moderate risk: 2+ risk factors (10-year risk < 10%) | < 130 mg/dL (3.4 mmol/L) |
| Lower risk: 0–1 risk factors | < 160 mg/dL (4.2 mmol/L) |
| Third joint task force of European and other societies on cardiovascular disease prevention in clinical practice | |
| < 5% 10-year risk of cardiovascular death | < 115 mg/dL (3.0 mmol/L) |
| ≥ 5% 10-year risk of cardiovascular death | < 100 mg/dL (2.6 mmol/L) |

*Recommended modification

Aims and literature search methodology

This review considers the evidence-base supporting the LDL-C-lowering efficacy of ezetimibe and discusses the current and potential role of this agent for patients who fail to achieve guideline cholesterol goals with statin monotherapy. Clinical trials were identified through a search of the Medline database using the terms 'ezetimibe' and 'clinical trial' for the period January 2000–August 2005.

Treatment goals

Indications that patients were not reaching their cholesterol treatment goals came from the EUROASPIRE I and II studies²⁵. These studies assessed almost 7000 patients with established CHD for the prevalence of modifiable risk factors. EUROASPIRE II showed that, although the proportion of patients treated and controlled with lipid-lowering drugs increased since EUROASPIRE I, most patients with CHD treated in specialist centres were still not reaching their cholesterol goal.

To assess the level of goal attainment in patients receiving lipid-lowering therapy in usual clinical practice, the REALITY programme initiated a series of observational studies²⁴. These included almost 60 000 patients in nine European countries, with treatment goals defined according to national and international guidelines. Results indicated that only 30% of all treated patients achieved their cholesterol plasma level goal in the first year of treatment²⁴. In the Spanish arm of the study > 70% of patients did not achieve their LDL-C goal. REALITY confirmed that there is a lack of adequate up-titration of statin dosage in lipid management and that patients are failing to reach their cholesterol goals across Europe²⁶. Similar observations have been reported in smaller studies across North America^{27–31}.

The threshold serum total cholesterol and LDL-C concentrations above which diet and drug therapy should be initiated have been defined by the National Cholesterol Education Program (NCEP)³². In 2001 the NCEP Adult Treatment Panel III (NCEP ATP III) issued an evidence-based set of guidelines on cholesterol management. These 2001 guidelines recommended a target of < 100 mg/dL (2.6 mmol/L) for very high-risk patients, < 130 mg/dL (3.4 mmol/L) for moderately high-risk patients and < 160 mg/dL (4.2 mmol/L) for low-risk patients³². Other, more recent, guidelines, including those published by the Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice³³ and the British Hypertension Society (BHS IV) advocate broadly

similar targets for LDL-C levels³⁴. The European guidelines recommend a target of 2.5 mmol/L (96 mg/dL) for patients with established cardiovascular disease or diabetes³³ while the British Hypertension Society advocates an LDL-C target of < 2.0 mmol/L (78 mg/dL)³⁴.

Since the publication of NCEP ATP III report³² in 2001, five major statin trials have been published – Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial – Lipid Lowering Trial (ALLHAT-LLT), Heart Protection Study (HPS), Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA), and Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction (PROVE-IT) – that addressed issues which had not been examined in previous clinical trials^{6,7,35–37}. These studies suggested that reducing LDL-C to targets below those recommended at the time might be necessary to obtain greater clinical benefit. PROVE-IT concluded that in patients who have recently had an acute coronary syndrome, intensive lipid-lowering treatment (with atorvastatin 80 mg) provides greater protection against death or major cardiovascular events when compared with a standard regimen (with pravastatin 40 mg)³⁷. In light of these new data, in 2004, the NCEP ATP III updated their guidelines¹⁸ and recommended that for very high-risk and moderately high-risk patients there should be a therapeutic option for physicians to reduce target LDL-C goals to < 70 mg/dL (1.8 mmol/L) and < 100 mg/dL (2.6 mmol/L), respectively. For patients in lower-risk categories there were no changes in treatment goals¹⁸. The current NCEP ATP III cholesterol treatment goals and their recommended modifications based on recent clinical evidence are shown in Table 1. The NCEP ATP III goals have been supported by results from the Treating New Target (TNT) study³⁸. This trial compared the efficacy of atorvastatin 80 mg (aimed at reducing LDL-C ≤ 75 mg/dL [1.9 mmol/L]) and atorvastatin 10 mg (with a target LDL-C of ≤ 100 mg/dL [2.6 mmol/L]) in 10 001 patients with stable CHD followed up for 5 years. Patients with the lower goal had a significantly reduced incidence of major cardiovascular events compared with patients with the higher LDL-C goal as their target³⁸. Thus, there is substantial evidence supporting the concept that for circulating cholesterol levels 'lower is better'³⁹. There is also evidence from two trials (the Greek Atorvastatin and Coronary-Heart-Evaluation study [GREACE] and the Aggressive Lipid Lowering Initiation Abates New Cardiac Events study [ALLIANCE]) that treating to target by forced titration with atorvastatin results in significant reduction in clinically relevant vascular events^{3,4,40}. In the GREACE

trial, patients in the atorvastatin and 'usual care' groups had comparable LDL-C levels at baseline [180 mg/dL (4.6 mmol/L) and 179 mg/dL (4.6 mmol/L), respectively], but those in the atorvastatin group achieved a significant reduction in LDL-C from baseline (46%; $p < 0.001$) during treatment compared with a mean reduction of 5% in the 'usual care' group. Moreover, in the GREACE trial, 95% of patients treated with atorvastatin achieved the NCEP ATP III LDL-C goal of < 100 mg/dL (2.6 mmol/L) and the lower the LDL-C, the better was the outcome in terms of clinical event reduction^{3,40}.

When considering the results of the statin studies described above it should be noted that comparable studies have not yet been reported for other lipid-lowering agents and the option of a lower LDL-C goal for high-risk patients is optional at present in the NCEP ATP III guidelines.

Inhibiting the two sources of cholesterol

To date, statin monotherapy has been the leading treatment for hypercholesterolaemia and remains the first-line choice for the majority of patients. However, reductions in plasma cholesterol levels obtained with statin monotherapy may have limits as a deficiency in the supply of cholesterol from one major source may be compensated for by increased activity of the other pathway^{14,15}. The increase in side effects such as liver abnormalities associated with the higher doses of statins needed to achieve greater LDL-C reductions may limit their clinical utility in a large proportion of patients^{37,38}. In addition to inhibiting cholesterol synthesis, hepatic cholesterol levels can be lowered by reducing the intestinal absorption of cholesterol. It follows that when both production and absorption are inhibited simultaneously plasma LDL-C levels fall more markedly^{23,41-43}. In many therapeutic areas (e.g. hypertension, diabetes, cancer, severe infections and asthma) it is common practice to use a combination of two (or more) agents that affect different physiological pathways to achieve adequate control. This is why several formulations include two drugs in one tablet. This approach may also help with compliance, since many high-risk patients need to take several drugs.

Ezetimibe, the first selective cholesterol absorption inhibitor, is a potent inhibitor of dietary, intestinal and biliary cholesterol absorption^{44,45}. Several studies suggest that ezetimibe binds to the brush border of the small intestine. More specifically, ezetimibe binds to the Niemann Pick C1-Like 1 (NPC1L1) protein, which is believed to be involved in cholesterol absorption⁴⁶⁻⁴⁹.

Ezetimibe was shown to inhibit > 50 – 55% of cholesterol absorption in patients with mild-to-moderate hypercholesterolaemia⁴⁵. Unlike pancreatic lipase inhibitors, ezetimibe does not affect the absorption of triglycerides and unlike bile-acid sequestrants, it does not affect the absorption of fat-soluble vitamins or bile acids⁵⁰. Ezetimibe is not principally metabolised by the CYP-450 pathway and, therefore, has a low potential for clinically relevant drug interactions with commonly prescribed drugs, including oral contraceptives⁵¹, glipizide⁵², fenofibrate^{53,54} or fluvastatin⁵⁵. However, there is a report suggesting that a lower dose of ezetimibe may be necessary in patients taking ciclosporin⁵⁶. This is an important consideration for patients with co-morbidities^{57,58}. As a large proportion of the cholesterol in the intestine is derived from biliary secretion¹⁴, ezetimibe can be very effective in lowering cholesterol, even in patients on low-cholesterol diets.

A 'dual inhibition' strategy of inhibiting both synthesis and absorption using ezetimibe and a statin has the advantage of influencing both major sources of cholesterol gain (Figure 1)⁵⁹. The benefits of 'dual inhibition' have been demonstrated with ezetimibe plus a statin in several large multicentre, double-blind, placebo-controlled trials in patients with hypercholesterolaemia. In a recent study⁴³, 788 patients with primary hypercholesterolaemia were randomised to ezetimibe 10 mg plus simvastatin 10, 20, 40 or 80 mg or atorvastatin monotherapy 10, 20, 40 or 80 mg over a 6-week period. After 6 weeks, the mean decrease in LDL-C was significantly greater for ezetimibe 10 mg plus simvastatin 10 mg compared with atorvastatin 10 mg alone (-46.1% vs. -37.2% , respectively; $p \leq 0.001$). After 4 weeks of therapy, ezetimibe 10 mg plus simvastatin 80 mg was significantly superior to atorvastatin 80 mg for LDL-C decrease (-59.4% vs. -52.5% , respectively; $p < 0.001$). All treatments were well tolerated⁴³ (Figure 2). Furthermore, a significant improvement in vascular function during statin–ezetimibe combination therapy compared with statin monotherapy has recently been reported⁶⁰, suggesting a more effective restoration of endothelial function.

Reaching treatment goals

The introduction of the new lower treatment goals recommended by the NCEP ATP III¹⁸, will result in an increased number of patients not on target. This group will include patients on statin monotherapy, those who cannot tolerate higher doses of a statin and patients who cannot tolerate any statin.

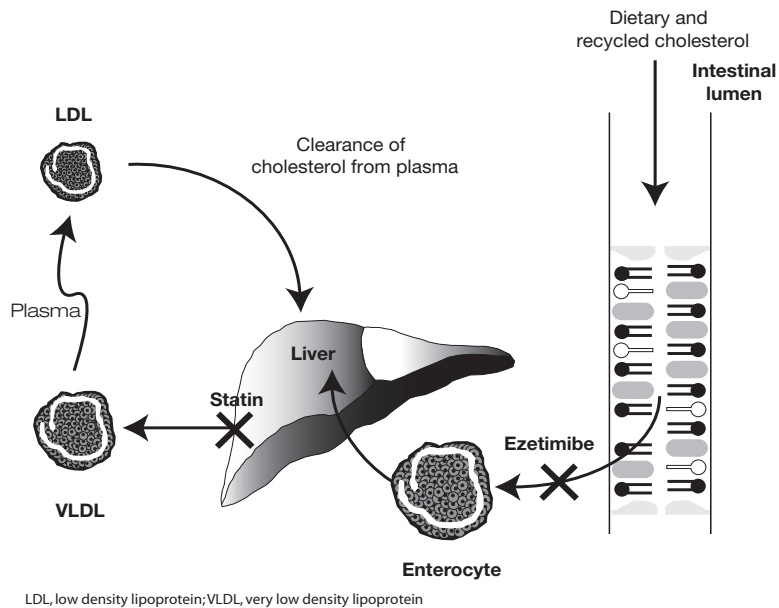
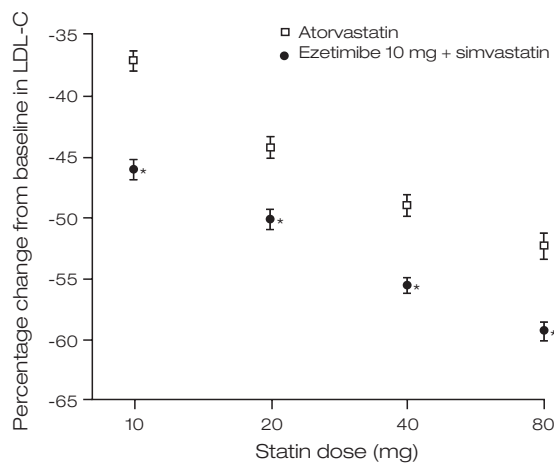
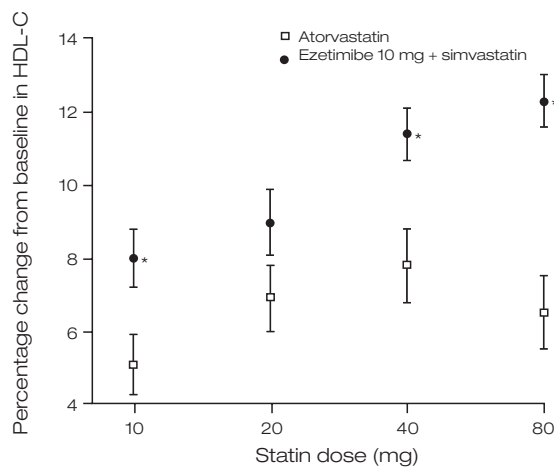


Figure 1. Dual lipid-lowering action: mechanism of action for statins and ezetimibe



(A)



(B)

* $p < 0.05$ for differences between specified doses of atorvastatin and 10 mg of ezetimibe + simvastatin (\pm robust SE = [interquartile range/1.075/n])

Figure 2. Efficacy and safety of ezetimibe co-administered with simvastatin compared with atorvastatin in adults with hypercholesterolaemia. Mean change in low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) for ezetimibe plus simvastatin versus atorvastatin, (a) decrease in LDL-C, (b) increase in HDL-C⁴³. (Reprinted from Ref. 43. ©2004 with permission from Excerpta Medica, Inc.)

Patients who do not reach their cholesterol goal with statin monotherapy

The success of statin dose titration is limited, as most LDL-C reduction is achieved with the starting dose. In fact, doubling the dose of a statin only provides an approximate 6% additional reduction in LDL-C – the ‘rule of six’⁶¹. In a prospective study by Foley *et al.*, patients with CHD were treated with a statin, followed by dose titration to achieve an LDL-C goal of < 100 mg/dL (2.6 mmol/L); only 31% achieved their goal within 6 months of starting treatment⁶². While statins are well tolerated and adverse events are rare, the potential for side effects such as myotoxicity rises with the increase in dose used⁶³.

A marked increase in adverse events and discontinuations because of them during high-dose statin therapy was recently reported in the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) study in almost 9000 adults with a history of acute myocardial infarction⁶⁴. In this study patients received either high-dose atorvastatin (80 mg/day) or ‘usual dose’ simvastatin (20 mg/day). Some patients in this trial were taking atorvastatin 40 mg or simvastatin 40 mg. There was no difference between the treatment groups with respect to the primary endpoint of the study – occurrence of a major coronary event – although mean LDL-C levels were markedly lower in the high-dose statin group (81 mg/dL [2.1 mmol/L] in the atorvastatin group vs. 104 mg/dL [2.7 mmol/L] in the simvastatin group) but there were significant differences in favour of the more aggressive treatment on a number of the secondary endpoints including the occurrence of non-fatal myocardial infarction⁶⁴. However, significantly more patients in the atorvastatin group discontinued treatment due to non-serious adverse events; transaminase elevations alone accounted for withdrawal of 43 patients from the atorvastatin arm compared with 5 patients in the simvastatin arm ($p < 0.001$)⁶⁴.

So far, there is no convincing evidence showing that ezetimibe monotherapy can cause rhabdomyolysis. However, some cases have been reported in patients receiving combined statin and ezetimibe therapy and rarely among patients receiving ezetimibe monotherapy; as with all recently introduced drugs caution must be exercised^{65,66}.

Combining other lipid-lowering agents such as bile acid sequestrants, fibric acid derivatives and niacin with statin therapy is an additional strategy for further reducing LDL-C levels. Bile acid sequestrants and niacin, when combined with statins, have been reported to reduce LDL-C by an additional 7–20% and 42% (in one study), respectively^{67–69}. In a review of clinical trials, where fibrates were co-administered with

statins, LDL-C was lowered by an average of 30% from baseline⁷⁰. However, the efficacy of these combinations is limited by increased potential for non-adherence, adverse events and drug–drug interactions^{71,72}.

A large number of trials demonstrated the benefit of adding ezetimibe to other lipid-lowering drugs (Table 2). In a community-based, randomised clinical trial, the Ezetimibe Add-on to Statin for Effectiveness (EASE) trial, involving > 3000 patients with LDL-C above the NCEP ATP III target by risk category, the efficacy of ezetimibe 10 mg with a stable dose of five different statins was evaluated. Ezetimibe co-administered with any statin reduced LDL-C by an additional 23% ($p = 0.001$) compared with a statin plus placebo. Of the total population, ezetimibe co-administered with a statin allowed 71% of patients to reach their cholesterol goal versus 20.6% for statin plus placebo ($p = 0.001$). Of patients with ≥ 2 CHD risk factors, ezetimibe co-administered with a statin allowed 75.1% of patients to reach their cholesterol goal versus 32.2% for statin plus placebo ($p = 0.001$)⁷³. In a recent randomised study in patients with hypercholesterolaemia and CHD, the addition of ezetimibe 10 mg to ongoing atorvastatin therapy 10 mg or 20 mg led to a mean reduction in LDL-C from baseline of 31.1% compared with 4.2% for placebo ($p \leq 0.001$); in 81.3% of patients in the combination therapy group achieved an LDL-C goal of ≤ 2.6 mmol/L (100 mg/dL) compared with 21.8% of patients in the atorvastatin monotherapy group ($p \leq 0.001$)⁷⁴. In a similar study also conducted in patients with hypercholesterolaemia and CHD, ezetimibe 10 mg plus simvastatin 10 mg or 20 mg, resulted in a 27.1% mean reduction in LDL-C from baseline compared with 4.1% for placebo added to the statin ($p \leq 0.001$ for both doses)⁷⁵. In this study 80.4% of patients in the combination therapy group achieved an LDL-C goal of ≤ 2.6 mmol/L (100 mg/dL) compared with 17.4% of those receiving simvastatin monotherapy ($p \leq 0.001$)⁷⁵. In a randomised study in patients with hypercholesterolaemia with LDL-C ≥ 130 mg/dL (3.4 mmol/L), ezetimibe 10 mg co-administered with rosuvastatin 10 mg significantly reduced mean LDL-C compared with rosuvastatin alone after 2 weeks of treatment (–61.4% vs. –44.9%, respectively; $p < 0.01$)⁴¹. A similar study, in which ezetimibe 10 mg was added to the current statin regimen, showed that the addition of ezetimibe resulted in a further 21% reduction in LDL-C with 71.5% of patients achieving their LDL-C goal compared with 18.9% of those on statin only ($p < 0.001$), suggesting that equivalent effects can be produced regardless of the statin⁴². In a retrospective subgroup analysis of this trial, 83.6% and 71.8% of patients with diabetes mellitus or the metabolic syndrome, respectively, achieved their LDL-C goal ($p < 0.001$)⁷⁶. Most recently in a study

Table 2. Summary of trials demonstrating the benefits of adding ezetimibe to other lipid-lowering drugs

| Drug comparison | Patient population | Study type (reference) | Change in LDL-C (baseline to endpoint) |
|---|---|--|--|
| <i>Ezetimibe plus statins</i> | | | |
| SIM (10 or 20 mg, pooled analysis) | Documented CHD plus hypercholesterolaemia | Randomised double-blind trial evaluating safety and efficacy ¹³² | -25.2% (SIM + EZE), -0.9% (SIM + PBO), * <i>p</i> ≤ 0.001 |
| SIM (10 or 20 mg, pooled analysis) | Documented CHD plus hypercholesterolaemia | Randomised double-blind trial evaluating safety and efficacy ⁷⁵ | -27.1% (SIM + EZE), -4.1% (SIM + PBO) * <i>p</i> ≤ 0.001 |
| ATV (10 or 20 mg, pooled analysis) | Documented CHD plus hypercholesterolaemia | Randomised double-blind trial evaluating safety and efficacy ⁷⁴ | -31.1% (ATV + EZE), -4.2% (ATV + PBO), * <i>p</i> ≤ 0.001 |
| SIM (40 or 80 mg), ATV (40 or 80 mg) | Familial hypercholesterolaemia | Randomised double-blind trial evaluating safety and efficacy ¹⁰² | -20.7% (STA 40/80 mg + EZE), -6.7% (STA 80 mg), -27.5% (STA 80 mg + EZE), -7.0% (STA 80 mg) * <i>p</i> < 0.01 |
| ATV (10, 20, 40 or 80 mg) | Primary hypercholesterolaemia | Randomised double-blind trial evaluating safety and efficacy ¹⁰³ | -50.0% (ATV 10 mg + EZE), -35.0% (ATV 10 mg), -54.0% (ATV 20 mg + EZE), -40.0% (ATV 20 mg), -54.0% (ATV 40 mg + EZE), -43.0% (ATV 40 mg), -60.0% (ATV 80 mg + EZE), -51.0% (ATV 80 mg), <i>p</i> < 0.01 vs. corresponding statin dose alone for all comparisons |
| SIM (80 mg), ATV (80 mg) | Primary hypercholesterolaemia | Randomised double-blind trial evaluating safety and efficacy ⁴³ | -59.4% (SIM + EZE), -52.5% (ATV) * <i>p</i> ≤ 0.05 |
| ATV (10 mg) | Primary hypercholesterolaemia | Randomised double-blind extension trial evaluating long-term safety and tolerability ⁷⁹ | -48.4% (ATV + EZE), -38.6% (ATV), * <i>p</i> < 0.01 |
| SIM (10, 20, 40 or 80 mg), ATV (10, 20, 40 or 80 mg) | Hypercholesterolaemia | Randomised double-blind dose comparison study evaluating safety and efficacy ¹⁰⁵ | -47.1% (SIM 10 mg + EZE), -36.1% (ATV 10 mg), -50.6% (SIM 20 mg + EZE), -43.7% (ATV 20 mg), -57.4% (SIM 40 mg + EZE), -48.3% (ATV 40 mg), -58.6 (SIM 80 mg + EZE), -52.9% (ATV 80 mg) |
| SIM (10, 20, 40 or 80 mg, pooled analysis) | Primary hypercholesterolaemia | Randomised double-blind trial evaluating safety and efficacy ¹¹⁰ | -53% (SIM + EZE; single tablet), -39% (SIM), * <i>p</i> < 0.001 |
| SIM (10, 20, 40 or 80 mg, pooled analysis) | Primary hypercholesterolaemia | Randomised double-blind trial evaluating safety and efficacy ⁸⁸ | -49.9% (SIM + EZE; range -44% to -57%), -36.1% (SIM; range -27% to -44%), * <i>p</i> < 0.01 |
| SIM (10, 20, 40 or 80 mg), ATV (10, 20, 40 or 80 mg), PRA (10, 20 or 40 mg), LOV (10, 20 or 40 mg) | Primary hypercholesterolaemia | Study evaluating safety and efficacy (pooled analysis of four trials) ¹¹¹ | -50% (SIM + EZE), -36% (SIM), -54% (ATV + EZE), -42% (ATV), -38% (PRA + EZE), -24% (PRA), -39% (LOV + EZE), -25% (LOV), -42.5% (All STA + EZE), -31.9% (All STA), * <i>p</i> < 0.01 vs. corresponding statin dose alone for all comparisons |
| SIM (10, 20, 40 or 80 mg), ATV (10, 20, 40 or 80 mg), PRA (10, 20 or 40 mg), LOV (10, 20 or 40 mg), fluvastatin (20, 40 or 80 mg), cerivastatin (0.2, 0.3, 0.4 or 0.8 mg) | Primary hypercholesterolaemia | Randomised double-blind trial evaluating safety and efficacy ⁴² | -25.0% (All STA and doses + EZE), -3.7% (All STA and doses + PBO), * <i>p</i> < 0.001 |
| SIM (10, 20, 40 or 80 mg) | Primary hypercholesterolaemia | Randomised double-blind trial evaluating safety and efficacy ⁸⁷ | -46.2% (SIM 10 mg + EZE), -31.3% (SIM 10 mg), -50.5% (SIM 20 mg + EZE), -34.9% (SIM 20 mg), -54.9% (SIM 40 mg + EZE), -41.5% (SIM 40 mg), -60.8% (SIM 80 mg + EZE), -45.6% (SIM 80 mg), * <i>p</i> < 0.001 vs. corresponding statin dose alone for all comparisons |
| LOV (10, 20 or 40 mg) | Primary hypercholesterolaemia | Randomised double-blind trial evaluating safety and efficacy ¹³⁴ | -33% (LOV 10 mg + EZE), -19% (LOV 10 mg), -39% (LOV 20 mg + EZE), -26% (LOV 20 mg), -45% (LOV 40 mg + EZE), -29% (LOV 40 mg), * <i>p</i> < 0.01 vs. corresponding statin dose alone for all comparisons |
| PRA (10, 20 or 40 mg) | Primary hypercholesterolaemia | Randomised double-blind trial evaluating safety and efficacy ¹³⁵ | -34% (PRA 10 mg + EZE), -20% (PRA 10 mg), -38% (PRA 20 mg + EZE), -24% (PRA 20 mg), -41% (PRA 40 mg + EZE), -29% (PRA 40 mg), * <i>p</i> < 0.01 vs. corresponding statin dose alone for all comparisons |

Table 2 (continued)

| Drug comparison | Patient population | Study type (reference) | Change in LDL-C (baseline to endpoint) |
|---|--|--|---|
| SIM (10, 20, 40 or 80 mg, pooled analysis) | Primary hypercholesterolaemia | Randomised double-blind extension study evaluating long-term safety and tolerability and efficacy ¹³⁶ | -23.7% (SIM + EZE), +3.3% (SIM + PBO), * <i>p</i> < 0.001 |
| SIM (10, 20, 40 or 80 mg), ATV (10, 20 or 80 mg), PRA (20 or 40 mg), other STA | Hypercholesterolaemia (mixed population) | Randomised double-blind trial evaluating safety and efficacy ⁷³ | -25.8% (All STA and doses + EZE), -2.7% (All STA and doses + PBO), * <i>p</i> < 0.001 |
| SIM (10, 20, 40 or 80 mg) | Primary hypercholesterolaemia | Randomised single-blind trial evaluating effect on hs-CRP ¹¹² | -43.9% (SIM 10 mg + EZE), -29.1% (SIM 10 mg), -46.6% (SIM 20 mg + EZE), -37.7% (SIM 20 mg), -55.4% (SIM 40 mg + EZE), -36.7% (SIM 40 mg), -59.5% (SIM 80 mg + EZE), -44.9% (SIM 80 mg), * <i>p</i> < 0.01 vs. corresponding statin dose alone for all comparisons |
| SIM (10, 20, 40 or 80 mg) | Primary hypercholesterolaemia | Study evaluating the effect on hs-CRP (combined analysis from two trials) ¹³⁷ | -26.3% (SIM 10 mg + EZE), -4.4% (SIM 10 mg + PBO), -31.8% (SIM 20 mg + EZE), -8.3% (SIM 20 mg + PBO), -35.9% (SIM 40 mg + EZE), -26.9% (SIM 40 mg + PBO), -44.4% (SIM 80 mg + EZE), -20.0% (SIM 80 mg + PBO), * <i>p</i> < 0.05 vs. corresponding statin dose alone for all comparisons |
| SIM (10, 20, 40 or 80 mg), ATV (10, 20, 40 or 80 mg), PRA (10, 20 or 40 mg), LOV (10, 20 or 40 mg), SIM, ATV, PRA, LOV, other STA | Elderly with primary hypercholesterolaemia | Study evaluating safety and efficacy (pooled analysis of four trials) ¹⁰⁶ | -12.8% < 65 years† (between group difference: all STA and doses + EZE vs. all STA and doses), -15.5% ≥ 65 years† (between group difference: all STA and doses + EZE vs. all STA and doses) |
| ATV 10 mg | Primary hypercholesterolaemia plus DM or MetS | Retrospective analysis from a randomised double-blind trial evaluating safety and efficacy ⁷⁶ | DM: -27.3% (All STA and doses + EZE), -1.2% (All STA and doses + PBO), * <i>p</i> < 0.001. MetS: -23.2% (All STA and doses + EZE), -6.5% (All STA and doses + PBO), * <i>p</i> < 0.001 |
| SIM, ATV | Severe hypercholesterolaemia | Randomised double-blind trial evaluating safety and efficacy ¹³⁸ | -22.8% (ATV + EZE), -8.6% (ATV), * <i>p</i> < 0.01 |
| SIM 40 mg | Severe hypercholesterolaemia plus CHD and LDL-aphaeresis | Randomised double-blind trial evaluating safety and efficacy ¹⁰⁷ | -17% (All STA and doses + EZE + LDL-aphaeresis), -17% (EZE + LDL-aphaeresis), * <i>p</i> < 0.01 |
| SIM (10, 20 or 40 mg) | Thiazolidinedione-treated type 2 DM | Randomised double-blind trial evaluating safety and efficacy ¹³⁹ | -20.8% (SIM + EZE), -0.3% (SIM 40 mg), * <i>p</i> < 0.001 |
| LOV (20 or 40 mg) | Hypercholesterolaemia plus CHD or CHD risk-equivalents | Randomised single-blind trial evaluating safety and efficacy ⁷⁸ | -47% (SIM 10 mg + EZE), -53% (SIM 20 mg + EZE), -59% (SIM 40 mg + EZE), -38% (SIM 20 mg), * <i>p</i> < 0.001 |
| SIM (10 or 20 mg) | Healthy volunteers | Randomised, single blind trial evaluating PK and PD ¹⁴⁰ | -51.0% (LOV 20 mg + EZE), -56.9% (LOV 40 mg + EZE), -33.2% (LOV 20 mg), * <i>p</i> < 0.01 |
| <i>Ezetimibe plus others</i> FEN (160 mg) | Healthy volunteers | Two randomised single-blind studies evaluating PD interaction ¹⁴¹ | Study 1: -47.5% (SIM 10 mg + EZE), -35.3% (SIM 10 mg). Study 2, -58.0% (SIM 20 mg + EZE), -41.1% (SIM 20 mg) |
| Gemfibrozil (600 mg) | Mixed hyperlipidaemia | Randomised double-blind trial evaluating safety and efficacy ⁵³ | -20.4% (FEN + EZE), -5.5% (FEN), * <i>p</i> < 0.001 |
| BAR | Healthy volunteers | Randomised open-label trial evaluating drug interaction ¹⁴² | No clinically significant drug interactions seen |
| | Hypercholesterolaemia (all forms) | Prospective chart review of efficacy and tolerability ¹⁴³ | -19.3% (BAR + EZE versus baseline), * <i>p</i> < 0.001 |

PK: pharmacokinetics; PD: pharmacodynamics; CHD: coronary heart disease; PBO: placebo; SIM: simvastatin; EZE: ezetimibe; ATV: atorvastatin; BAR: bile-acid resin; PRA: pravastatin; LOV: lovastatin; STA: statin (non-specified); DM: diabetes mellitus subgroup; MetS: metabolic syndrome subgroup; hs-CRP: high-sensitivity C-reactive protein; FEN: fenofibrate; LDL-C low-density lipoprotein cholesterol
 *Between treatment groups; †Between group differential, % change in LDL-C, STA versus EZE + STA

in which switching from atorvastatin monotherapy (10 mg/day) to ezetimibe/simvastatin (10/20 mg/day) was compared to doubling the dose of atorvastatin in hypercholesterolaemic patients with atherosclerosis or coronary heart disease, combination therapy produced significantly greater decreases from baseline compared with atorvastatin monotherapy in LDL-C (−32.8% vs. −20.3%, respectively; $p \leq 0.001$), total cholesterol (−20.3% vs. −13.0%; $p < 0.05$), non-high density lipoprotein cholesterol (HDL-C) (−27.9% vs. −17.0%; $p < 0.05$), apolipoprotein (apo) B (−23.4% vs. −14.7%; $p < 0.05$) and an increase in HDL-C (+1.8% vs. −0.4%; $p < 0.05$)⁷⁷.

Patients with CHD are more likely to reach their cholesterol goals with ezetimibe co-administered with simvastatin than with statin monotherapy. In a parallel-group study by Feldman *et al.*, 710 patients with CHD or CHD risk-equivalents were randomised to ezetimibe 10 mg co-administered with simvastatin 10, 20 or 40 mg or simvastatin 20 mg alone. After 5 weeks of treatment the percentage of patients achieving the LDL-C goal of < 100 mg/dL (2.6 mmol/L) was significantly greater for patients treated with ezetimibe plus simvastatin 10, 20 or 40 mg (75%, 83% and 87%, respectively) compared with simvastatin 20 mg alone (46%; $p < 0.001$ for all three comparisons). Ezetimibe co-administered with simvastatin was well tolerated in this high-risk population and had a favourable safety profile⁷⁸.

The long-term safety and tolerability of ezetimibe plus atorvastatin was assessed in a 12-month, double-blind, extension study in patients with hypercholesterolaemia⁷⁹. In this study patients were randomised to ezetimibe 10 mg or placebo co-administered with open-label atorvastatin 10 mg. At intervals of 6 weeks, patients not at their cholesterol goal (22% of patients in the atorvastatin group, 9% of patients in the atorvastatin plus ezetimibe group) were titrated to the next highest atorvastatin dose (20, 40 or 80 mg). After 6 weeks of treatment, ezetimibe plus atorvastatin 10 mg produced greater reductions in LDL-C compared with atorvastatin 10 mg monotherapy (−53% vs. −37%, respectively). These effects were maintained over the 12-month study period. At study endpoint, 91% of the patients treated with co-administration therapy reached their cholesterol goal versus 78% of patients treated with atorvastatin monotherapy ($p = 0.02$). Patients treated with ezetimibe plus atorvastatin and those treated with atorvastatin monotherapy reported a similar incidence of adverse events (71% vs. 67%) and treatment-related adverse events (22% vs. 27%)⁷⁹.

There are few data at present on the efficacy of the simvastatin–ezetimibe combination as opposed to other possible combinations in patients intolerant to statin monotherapy.

Patients who cannot tolerate higher doses of statins

Switching to a different statin is an option for patients who cannot tolerate higher doses of a statin. Several studies have shown that lower or equivalent doses of more efficacious statins may help patients achieve their goals^{80–84}. However, this will not always successfully abolish side effects or obtain a greater reduction in LDL-C.

In the Measuring Effective Reductions in Cholesterol Using Rosuvastatin Therapy (MERCURY) I study, switching from atorvastatin 10 mg to rosuvastatin 10 mg decreased LDL-C by a further 8% and enabled an additional 6% of patients to attain their LDL-C goal of < 115 mg/dL (3.0 mmol/L). However, there was no significant improvement in the proportion of patients achieving their LDL-C goal among those switching from atorvastatin 20 mg to rosuvastatin 10 mg^{71,84}. Recent label updates indicate that patients switching to rosuvastatin from another statin must start on the 10 mg dose and, due to possible adverse events, they have to remain on this dose for a minimum of 4 weeks⁸⁵. This requirement negates any benefits of switching to rosuvastatin for patients on atorvastatin at doses greater than 10 mg.

In a recent post-marketing analysis⁸⁶ of rosuvastatin in common clinical practice, the rate of rosuvastatin-associated adverse events reported to the US Food and Drug Administration from its first year of marketing were compared to those reported for atorvastatin, simvastatin and pravastatin over the concurrent timeframe and during their respective first years of marketing. For either timeframe comparison, rosuvastatin was significantly more likely to be associated with the composite endpoint of rhabdomyolysis, proteinuria, nephropathy or renal failure. Reported cases of rhabdomyolysis, proteinuria or renal failure tended to occur early after the initiation of therapy and at relatively modest doses of rosuvastatin⁸⁶. These results support concerns about the relative safety of rosuvastatin at the range of doses used in clinical practice in the general population. This view may change as more results, especially from long-term and event-based studies, become available.

The use of ezetimibe co-administered with low-dose statin offers an alternative to having to increase statin doses. Studies have shown that ezetimibe co-administered with a lower dose statin has an equivalent efficacy with the higher dose statin alone. In a multicentre trial by Goldberg *et al.*, 887 patients with primary hypercholesterolaemia were randomised to ezetimibe 10 mg, simvastatin 10, 20, 40 or 80 mg, or ezetimibe 10 mg plus simvastatin 10, 20, 40 or 80 mg⁸⁷. The additional reduction in

LDL-C achieved with ezetimibe plus simvastatin was statistically significant versus simvastatin monotherapy (-53.2% vs. -38.5%, respectively; $p < 0.001$, pooled across all doses). The recommended starting dose for ezetimibe co-administered with simvastatin (10/20mg) was significantly more effective in lowering LDL-C from baseline compared with simvastatin 20mg monotherapy and simvastatin 40mg monotherapy (-50.5%, -34.9% and -41.5%, respectively; $p < 0.001$). Importantly, ezetimibe co-administered with simvastatin allowed the majority (82%) of patients to achieve their LDL-C goal of < 100 mg/dL (2.6 mmol/L) compared with only 43% of patients treated with simvastatin monotherapy (pooled data across all doses)⁸⁷. The lowest dose of simvastatin (10mg) in combination with ezetimibe (10mg) was equivalent to the highest dose of simvastatin monotherapy in terms of LDL-C reduction (Figure 3). These results confirmed data from an earlier similar study in which ezetimibe 10mg plus simvastatin 10mg and simvastatin 80mg monotherapy each produced reductions in LDL-C of 44% from baseline ($p = 0.01$)⁸⁸.

Patients who cannot tolerate any statin

For those patients who cannot tolerate statin therapy, ezetimibe monotherapy offers a well tolerated and effective treatment option with a number of advantages over other non-statin cholesterol-lowering drugs⁸⁹. However, practitioners should be aware that the highest efficacy is obtained when ezetimibe is co-administered with a statin (in patients who tolerate statins).

The safety and efficacy of ezetimibe monotherapy was evaluated in two large, multicentre, randomised, placebo-controlled trials in patients with primary hypercholesterolaemia^{90,91}. In a pooled analysis of data from 1719 patients from these trials, ezetimibe monotherapy significantly lowered total cholesterol from baseline by 12.7% ($p < 0.01$) and LDL-C by 18.2% ($p < 0.01$) compared with placebo⁹². For those patients who were above the NCEP ATP III³² LDL-C goal at baseline, 46% of ezetimibe-treated patients reached their goal compared with 11% of patients on placebo ($p < 0.01$). Ezetimibe also significantly decreased apoB (-15.7%) and triglycerides (-8.0%) and increased HDL-C (1.0%) compared with placebo (-1.6%, 0.0% and -1.6%, respectively; $p \leq 0.01$). Ezetimibe was well tolerated, with a safety profile similar to placebo in these studies⁹¹. In another pooled analysis of two randomised trials in patients with primary hypercholesterolaemia, 12 weeks of ezetimibe 10mg resulted in significantly reduced LDL-C levels (18.5%, $p < 0.01$ vs. placebo) and significantly increased HDL-C levels (3.5%, $p < 0.05$ vs. placebo)⁹³. As with other drugs, there have been some reports of adverse events with ezetimibe, including myopathy^{94,95} pancreatitis⁶⁶ and hyperlipidaemia⁹⁶ the latter of which may possibly be due to low lipoprotein lipase activity or over compensation of cholesterol synthesis. There may also be some variation in the response to ezetimibe and there are reports of patients with a poor response to ezetimibe (low-responders)⁹¹. However, there are also patients who 'hyper-respond' to ezetimibe. A relationship between NPC1L1 (genetic) variation and ezetimibe response may explain this effect^{48,97,98}. Other mechanisms possibly include the capacity of the adenosine triphosphate (ATP)-

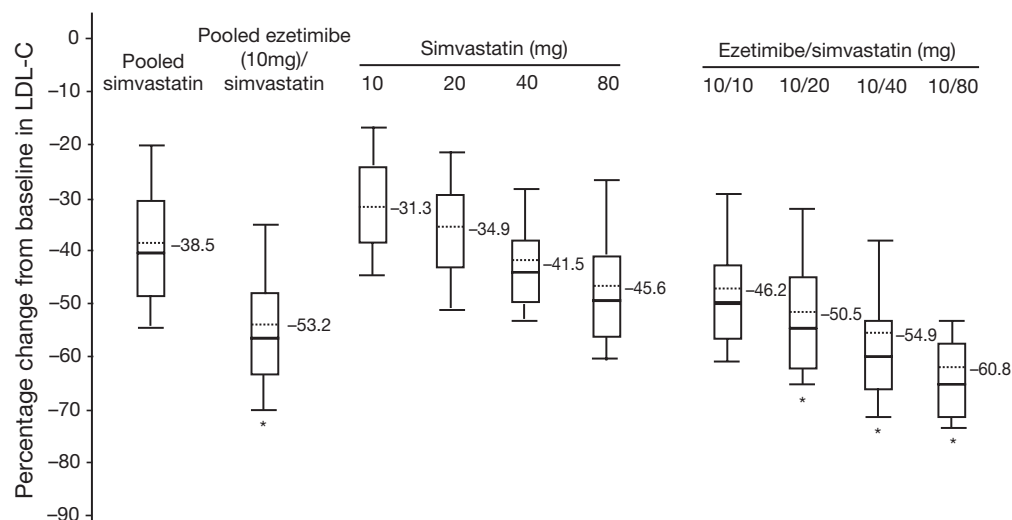


Figure 3. Percentage change in low-density lipoprotein cholesterol (LDL-C) levels from baseline to study endpoint⁸⁷.

* $p < 0.001$ for ezetimibe/simvastatin co-administration group versus corresponding simvastatin monotherapy group.

Horizontal lines = 10th, 25th, 50th, 75th percentiles; crossed whiskers = 90th percentile; dotted lines = mean percentage reduction in LDL-C. (Reprinted from Ref. 87. ©2004 with permission from Mayo Clinic Proceedings.)

binding cassette (ABC) transporters ABCG5 and ABCG8. These transporters are apical sterol export pumps that promote active efflux of cholesterol and plant sterols from enterocytes back into the intestinal lumen for excretion⁹⁹. Changes in hepatic synthesis and/or cholesterol absorption may also be relevant. In post-marketing surveillance there have been reports of an increase in the International Normalized Ratio (INR) in patients also receiving warfarin and monitoring the INR is, therefore, warranted in such patients^{66,100}. There has also been some suggestion of an interaction with ciclosporin and ciclosporin levels should be monitored in patients receiving concomitant ezetimibe^{66,101}.

In our clinical experience, the following results were obtained with ezetimibe monotherapy and ezetimibe co-administered with a statin over a period of 2 months. In patients who could not tolerate statins, ezetimibe monotherapy produced a reduction in LDL-C of 25.9% (range from 2.1 to 52.3%, $n = 32$; $p \leq 0.0001$). In patients who could not tolerate higher doses of a statin, ezetimibe plus a statin produced an additional reduction in LDL-C of 28.8% (range from 10.0 to 51.1%, $n = 13$; $p \leq 0.0001$). In patients who could not reach their LDL-C target levels while on statin monotherapy, ezetimibe plus a statin produced an additional reduction in LDL-C of 32.2% (range from 3.2 to 57.1%, $n = 81$; $p \leq 0.0001$). None of the patients had a gain/loss in body weight of more than 5%, had a change in their other medication or in their glycaemic, thyroid or smoking status (Daskalopoulou, Nair and Mikhailidis, unpublished results).

Special populations

'Dual inhibition' is effective in patients with homozygous familial hypercholesterolaemia (HoFH). In 50 patients with a diagnosis of HoFH, ezetimibe co-administered with atorvastatin or simvastatin 40 or 80 mg produced clinically important LDL-C reductions compared with statin monotherapy at 80 mg (-20.7% vs. -6.7%, respectively; $p = 0.007$ for both doses and both statins)¹⁰². Even greater reductions in LDL-C were observed when ezetimibe was co-administered with 80 mg of either statin compared to either statin alone (-27.5% vs. -7.0%, respectively; $p < 0.01$)¹⁰¹. Another study assessed the efficacy and safety of ezetimibe added to existing statin therapy in patients with statin-refractory and statin-intolerant familial hyperlipidaemias not achieving an LDL-C of < 3.0 mmol/L (115 mg/dL). The addition of ezetimibe 10 mg to their current statin therapy resulted in a further 11% reduction in LDL-C ($p < 0.05$)¹⁰³. Subgroup analysis showed that the greatest effect occurred in patients under-responding to statins.

As statins are eliminated in part by the kidneys, serum concentrations may be higher in patients with renal disease⁹¹. The predominant route for excretion of some statins is through the bile¹⁰⁴. Therefore, treatment with ezetimibe plus simvastatin is not recommended for patients with moderate or severe hepatic insufficiency. For patients with renal insufficiency or mild hepatic insufficiency, ezetimibe monotherapy provides another alternative although additional research is needed in this area to better define appropriate dosing in this patient group. However, lower doses of statins may be possible if they are used in combination with ezetimibe.

In a dose-comparison study comparing all doses of simvastatin plus ezetimibe with atorvastatin monotherapy, the higher doses of atorvastatin required to achieve the lipid profiles produced by ezetimibe plus simvastatin resulted in a significantly higher proportion of patients with consecutive elevations in alanine aminotransferase and/or aspartate aminotransferase (the Vytorin Versus Atorvastatin [VYVA] study)¹⁰⁵.

Ezetimibe plus simvastatin is more effective than statin monotherapy regardless of age. In a pooled analysis of four randomised trials comparing ezetimibe plus simvastatin with lovastatin, pravastatin, simvastatin or atorvastatin monotherapy, the combination therapy was equally effective in patients aged < 65 years versus ≥ 65 years and in those aged < 75 years versus ≥ 75 years¹⁰⁶. Ezetimibe plus simvastatin was generally well tolerated with a similar incidence of adverse events across all age groups.

Ezetimibe plus simvastatin has also been demonstrated to be well tolerated and effective in severely hypercholesterolaemic patients with CHD treated with regular LDL-apheresis^{107,108} and in kidney transplant recipients with hypercholesterolaemia¹⁰⁹.

Ezetimibe plus simvastatin as a single tablet

Further benefits in terms of lipid lowering are expected to be obtained with the use of ezetimibe plus simvastatin in a single tablet because of better adherence to treatment. Ezetimibe plus simvastatin is available in four doses, as 10/10, 10/20, 10/40 or 10/80 mg. The safety and efficacy of all doses of an ezetimibe plus simvastatin tablet was recently compared with either drug alone in a multicentre, randomised, double-blind trial in 1528 patients with primary hypercholesterolaemia. Pooled ezetimibe plus simvastatin was associated with greater reductions in LDL-C than pooled simvastatin or ezetimibe alone ($p < 0.001$) (Figure 4). Ezetimibe plus simvastatin was generally well tolerated, with a safety profile similar to simvastatin monotherapy¹¹⁰. The efficacy of ezetimibe plus simvastatin (10/10, 10/20, 10/40 or 10/80 mg) in a single tablet has also been

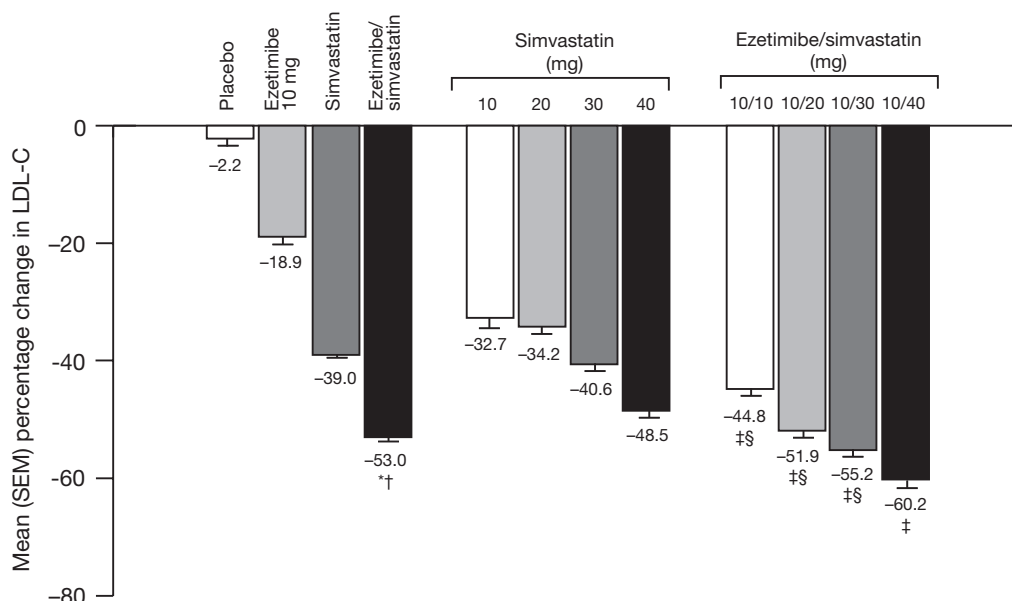


Figure 4. Percentage change (mean, SE) in low-density lipoprotein cholesterol (LDL-C) levels from baseline to study endpoint for ezetimibe/simvastatin single tablet¹¹⁰. (Reprinted from Ref. 110. ©2004 with permission from Excerpta Medica, Inc.). * $p < 0.001$ for pooled ezetimibe/simvastatin versus pooled simvastatin; † $p < 0.001$ for pooled ezetimibe/simvastatin versus ezetimibe 10 mg monotherapy; ‡ $p < 0.001$ for ezetimibe/simvastatin versus same-dose simvastatin; § $p < 0.001$ for ezetimibe/simvastatin versus next highest dose of simvastatin

compared with atorvastatin (10, 20, 40 or 80 mg) in a study in 1902 patients with hypercholesterolaemia⁷⁹. At the recommended starting dose of 10/20 mg ezetimibe/simvastatin, 39% of patients achieved their aggressive LDL-C goal of < 70 mg/dL (1.8 mmol/L) compared with 6% and 18% of patients treated with the recommended starting doses of atorvastatin (10 and 20 mg, respectively). The safety profile was similar between the two treatments. The ezetimibe/simvastatin single tablet should help increase treatment adherence, particularly in high-risk patients, where co-morbidities are likely. The results of these studies are comparable with previous studies in which ezetimibe was co-administered with simvastatin (as separate tablets)^{88,111}.

Effect of ezetimibe on C-reactive protein, HDL-C and triglyceride levels

Ezetimibe 10 mg co-administered with simvastatin has also been shown to significantly reduce the circulating levels of the inflammatory and vascular risk marker high sensitivity C-reactive protein (hs-CRP). In one study, in which patients with hypercholesterolaemia were randomised to ezetimibe plus simvastatin or simvastatin monotherapy for 12 weeks, ezetimibe plus simvastatin significantly reduced median hs-CRP levels compared with simvastatin alone (-34.8% vs. -18.2% , $p < 0.01$)¹¹². In another study by the same authors, data from two almost identical randomised trials^{87,88} were combined for

analysis of the effect of ezetimibe on hs-CRP. In both trials, patients were randomised to ezetimibe 10 mg, simvastatin 10, 20, 40 or 80 mg, or ezetimibe 10 mg plus simvastatin 10, 20, 40 or 80 mg for 12 weeks. Ezetimibe plus simvastatin more than doubled the reduction in hs-CRP compared to simvastatin monotherapy (-33.3% vs. -14.3% , $p < 0.01$, pooled across all doses). Ezetimibe 10 mg produced a reduction in CRP of 6.3%¹³⁶. Similar hs-CRP reductions were observed in all major subgroups analysed, including patients with CHD. It has recently been reported that patients with acute coronary syndromes who have reduced levels of hs-CRP have better clinical outcomes than with those with higher hs-CRP levels¹¹³. Another study showed that for patients with coronary artery disease the progression of atherosclerosis is significantly related to reductions in hs-CRP levels¹¹⁴. Similar results were observed when ezetimibe was added to atorvastatin¹³³. These results suggest that further research on the effects of ezetimibe on hs-CRP is warranted.

In a pooled analysis of four randomised double-blind trials ($n = 1861$), the efficacy of statin monotherapy (lovastatin or pravastatin 10, 20 or 40 mg; simvastatin or atorvastatin 10, 20, 40 or 80 mg) versus ezetimibe 10 mg plus one of these statins was evaluated in subsets of men and women. Compared with any of the statin monotherapies, ezetimibe plus a statin was more effective in reducing LDL-C (women: statin monotherapy -33.4% vs. ezetimibe + statin -47.1% ; men: -31.3% vs. -44.8% , respectively), apo B (women: -27.8% vs. -38.4% , respectively; men: -26.6% vs.

-37.7%, respectively) and triglycerides (women: -16% vs. -25.8%, respectively; men: -21.1% vs. -28.6%, respectively) and more effective in raising HDL-C (women: +5.0% vs. +7.9%, respectively; men: +6.2% vs. +8.9%, respectively), in both sexes¹¹⁵.

The addition of ezetimibe to a statin has beneficial effects on HDL-C levels (recognised as a secondary target for lipid therapy)¹¹⁶⁻¹¹⁸. In a study by Ballantyne *et al.*, after 4 weeks of treatment, ezetimibe 10 mg plus simvastatin 80 mg significantly increased the levels of HDL-C compared with atorvastatin 80 mg monotherapy (+12.3% vs. +6.5%, respectively; $p < 0.001$) (Figure 2)⁴³. In an epidemiological analysis of risk related to HDL-C, it was demonstrated that a 2-3% increase in HDL-C levels was associated with a reduction of 2-4% in the risk of cardiac events independently of LDL-C¹¹⁹. In the EASE study, the addition of ezetimibe to a statin (mainly atorvastatin 10-80 mg/day, simvastatin 10-80 mg/day or pravastatin 20 or 40 mg/day), significantly increased HDL-C (mean change from baseline: 1.3% vs. -0.8%, $p < 0.001$) and significantly reduced fasting triglyceride levels compared with statin alone (median change from baseline -12.8% vs. -1.6%, $p < 0.001$)⁷³.

In the dose-comparison study comparing ezetimibe plus simvastatin in a single tablet (10/10, 10/20, 10/40 or 10/80 mg) with atorvastatin (10, 20, 40 or 80 mg), in addition to a greater LDL-C reduction from baseline (-53.4% for ezetimibe plus simvastatin vs. -45.3% for atorvastatin, $p < 0.001$ average across all doses), ezetimibe plus simvastatin produced significantly greater increases in HDL-C from baseline (+7.9% vs. +4.3%, $p < 0.001$ pooled across all doses) and greater reductions in triglyceride levels (-27.4% vs. -25.5% from baseline)¹⁰⁵. There is evidence that even with aggressive statin treatment the HDL-C level achieved may be relevant to the outcome¹²⁰.

Discussion

CHD remains a significant clinical and economic burden to healthcare systems in most industrialised countries¹²¹. Although lipid modification is important in the primary and secondary prevention of CHD, there are many patients with poorly controlled cholesterol levels with reported rates as low as 30% of patients treated with lipid-lowering therapy reaching their cholesterol goal²⁴. The latest NCEP ATP III report¹⁸ proposed that additional benefit might be obtained by reducing LDL-C levels to below 100 mg/dL (2.6 mmol/L) (i.e. for high-risk patients to 70 mg/dL; 1.8 mmol/L), which is difficult to achieve with traditional statin treatment monotherapy. These recommendations are supported by a recent trial in patients with stable CHD³⁸ that evaluated the

efficacy of statin therapy with atorvastatin 80 mg with an LDL-C goal of 70 mg/dL (1.8 mmol/L) versus atorvastatin 10 mg with an LDL-C goal of 100 mg/dL (2.6 mmol/L). Intensive statin therapy reduced the risk of a major cardiovascular event by 22% compared with moderate therapy (hazard ratio: 0.78, $p = 0.001$). However, there was no difference between the two groups in overall mortality and, as may be expected with high statin doses, the number of adverse events was greater in those receiving atorvastatin 80 mg versus atorvastatin 10 mg (8.1% vs. 5.8%, respectively; $p = 0.001$)³⁸.

There is now a large amount of published data demonstrating the additional cholesterol-lowering effect that is achieved when ezetimibe is co-administered with a statin. For patients already receiving statins and not reaching their cholesterol goal, ezetimibe plus a statin offers superior LDL-C-lowering efficacy compared with switching to another statin. Compared with dose titration, co-administration of ezetimibe with low-dose statins produces a reduction of LDL-C at least equal to the reduction achieved with maximal doses of statins alone. Moreover, multiple dose adjustments should not be necessary for patients to reach their goal, making the 'dual inhibition' strategy ideal for patients who would otherwise need a higher dose of statin. As doubling the dose of statin leads to only an approximately 6% additional increase in LDL-C reduction, 'dual inhibition' offers a major advantage over dose titration.

Statin-induced lowering of LDL-C is effective in reducing CHD events and CHD-related mortality and morbidity. However, at present there are little data available for ezetimibe in this respect to guide physician choices in patients such as those with acute coronary syndrome. The extent of CHD and related events is proportionate to the extent of LDL-C reduction^{18,25,122}. It is, thus, important to address the clinical benefits of ezetimibe plus simvastatin therapy in reducing the risk of CHD-related events. To date, only animal studies have demonstrated the potential benefit of ezetimibe monotherapy in terms of decreasing the progression of atherosclerosis. In apolipoprotein E knockout (apoE-/-) mice fed with high-cholesterol and reduced-cholesterol diets for 6 months with or without ezetimibe (5 mg/kg/day), the progression of atherosclerotic lesions was inhibited in the mice that received ezetimibe¹²³. Another feature of cholesterol absorption inhibitors is their ability to modify post-prandial hyperlipidaemia by decreasing the cholesterol content of chylomicrons and their remnants¹²⁴. In addition, absorption of ezetimibe is rapid and is not altered by food content following oral administration¹²⁵. There is increasing evidence that post-prandial lipoproteins are atherogenic¹²⁶. Hence, inhibiting cholesterol absorption

may help reduce the burden of atherosclerosis, not only by lowering LDL-C levels, but also by decreasing the levels of chylomicrons and remnants. Ezetimibe can reduce the cholesterol content of chylomicrons by > 70%, potentially leading to less atherogenesis¹²⁷. The results of the Program on the Surgical Control of the Hyperlipidemias (POSCH) are also of interest. In this trial, partial ileal bypass was used to decrease cholesterol absorption from the intestine in post-MI patients. There were significant beneficial effects both in terms of vascular events and angiographic evidence¹²⁸.

A comprehensive outcome programme is underway for ezetimibe plus simvastatin, that is enrolling over 20 000 patients across several countries¹²⁹⁻¹³¹. The Study of Heart and Renal Protection (SHARP) study¹²⁹ aims to assess the effects of lowering cholesterol during treatment with ezetimibe/simvastatin or placebo on major vascular events and the rate of progression to end-stage renal disease in patients with chronic kidney disease. The Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial¹³⁰ aims to compare the effect of ezetimibe/simvastatin versus simvastatin alone on carotid artery intima-media thickness in adults with heterozygous familial hypercholesterolaemia. The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS)¹³¹ study aims to investigate whether aggressive cholesterol-lowering with ezetimibe/simvastatin can slow the progression of aortic stenosis in patients with pre-existing moderate aortic stenosis, reduce the number of valve replacements and the incidence of cardiovascular events. The results of these three studies should provide insights as to whether the greater LDL-C-lowering effects of 'dual inhibition' – treating the two sources of cholesterol – results in significant cardiovascular endpoint reduction.

As evidence for the clinical benefits of lipid lowering accumulates, the use of 'dual inhibition' is expected to become more widespread, especially as a consequence of the NCEP ATP III update¹⁸. This promises a change in the treatment options for patients with high cholesterol levels and, importantly, offers superior efficacy that can only be provided by inhibition of the two sources of cholesterol.

Conclusions

In patients who do not reach their LDL-C goal after initial cholesterol-lowering therapy, two therapeutic options – ezetimibe co-administered with any dose of statin and ezetimibe plus simvastatin in a single tablet – have been shown to be highly efficacious in lipid lowering and well tolerated. 'Dual inhibition' of the

two sources of cholesterol is an important therapeutic innovation and is an effective lipid-lowering tool for the majority of patients to reach their cholesterol goals early in their treatment regimen.

Acknowledgements

Declaration of interest: Writing assistance was provided by Dr Joan Thomas with support from Merck & Co., Inc.

Some of the authors have given talks, attended conferences and participated in trials and advisory boards sponsored by various pharmaceutical companies.

References

1. World Health Organization. World health report [online]. Available from <http://www.who.int/whr/2003/en/> [last data accessed 24 November 2005]
2. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;364:685-96
3. Athyros VG, Papageorgiou AA, Mercouris BR, et al. Treatment with atorvastatin to the National Cholesterol Educational Program goal versus 'usual' care in secondary coronary heart disease prevention. The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. *Curr Med Res Opin* 2002;18:220-8
4. Koren MJ, Hunninghake DB; on behalf of the ALLIANCE Investigators. Clinical outcomes in managed-care patients with coronary heart disease treated aggressively in lipid-lowering disease management clinics: the ALLIANCE study. *J Am Coll Cardiol* 2004;44:1772-9
5. Keech A, Colquhoun D, Best J, et al. Secondary prevention of cardiovascular events with long-term pravastatin in patients with diabetes or impaired fasting glucose: results from the LIPID trial. *Diabetes Care* 2003;26:2713-21
6. MRC/BHF Heart Protection Study Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22
7. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;361:1149-58
8. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-9
9. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *J Am Med Assoc* 1998;279:1615-22
10. Lewis SJ, Moye LA, Sacks FM, et al. Effect of pravastatin on cardiovascular events in older patients with myocardial infarction and cholesterol levels in the average range. Results of the Cholesterol and Recurrent Events (CARE) trial. *Ann Intern Med* 1998;129:681-9
11. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia [West of Scotland Coronary Prevention Study Group]. *New Engl J Med* 1995;333:1301-7

12. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels [Cholesterol and Recurrent Events Trial investigators]. *New Engl J Med* 1996;335:1001-9
13. Turley SD. Dietary cholesterol and the mechanisms of cholesterol absorption. *Eur J Heart* 1999;1:S29-S35
14. Dietschy JM, Turley SD, Spady DK. Role of liver in the maintenance of cholesterol and low density lipoprotein homeostasis in different animal species, including humans. *J Lipid Res* 1993;34:1637-59
15. Turley SD, Dietschy JM. The metabolism and excretion of cholesterol by the liver. In: Arias IM, Jakoby WB, Popper J, Schachter D, Shafritz DA, editors. *The liver: biology and pathobiology*, 2nd ed. 1998. p. 617-41
16. Kesaniemi YA, Miettinen TA. Cholesterol absorption efficiency regulates plasma cholesterol level in the Finnish population. *Eur J Clin Invest* 1987;17:391-5
17. Al Shaer MH, Choueiri NE, Suleiman ES. The pivotal role of cholesterol absorption inhibitors in the management of dyslipidemia. *Lipids Health Dis* 2004;3:22
18. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;110:227-39
19. Turley SD. Cholesterol metabolism and therapeutic targets: rationale for targeting multiple metabolic pathways. *Clin Cardiol* 2004;27:III16-III21
20. Davignon J, Montigny M, Dufour R. HMG-CoA reductase inhibitors: a look back and a look ahead. *Can J Cardiol* 1992;8:843-64
21. Edwards JE, Moore RA. Statins in hypercholesterolaemia: a dose-specific meta-analysis of lipid changes in randomised, double blind trials. *BMC Fam Pract* 2003;4:18
22. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267-78
23. Pearson TA, Laurora I, Chu H, et al. The lipid treatment assessment project (L-TAP): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Arch Intern Med* 2000;160:459-67
24. Goettsch WG, Yin DD, Alemao E, et al. Statins are less effective in common daily practice among patients with hypercholesterolemia: the REALITY-PHARMO study. *Curr Med Res Opin* 2004;20:1025-33
25. EUROASPIRE I and II Group. Clinical reality of coronary prevention guidelines: a comparison of EUROASPIRE I and II in nine countries. *European Action on Secondary Prevention by Intervention to Reduce Events*. *Lancet* 2001;357:995-1001
26. Garcia Ruiz FJ, Ibanez AM, Perez-Jimenez F, et al. Current lipid management and low cholesterol goal attainment in common daily practice in Spain: the REALITY study. *Pharmacoeconomics* 2004;22:1-12
27. Schultz JS, O'Donnell JC, McDonough KL, et al. Determinant of compliance with statin therapy and low-density lipoprotein cholesterol goal attainment in a managed care population. *Am J Managed Care* 2005;11:306-12
28. Parris ES, Mohn LA, Lawrence DB, et al. Adherence to statin therapy and LDL cholesterol goal attainment by patients with diabetes and dyslipidemia. *Diabetes Care* 2005;28:595-99
29. Mosca L, Merz NB, Blumenthal RS, et al. Opportunity for intervention to achieve American Heart Association guidelines for optimal lipid levels in high-risk women in a managed care setting. *Circulation* 2005;111:488-93
30. Palmieri J, Redline S, Morita R. Goal attainment in patients referred to a telephone-based dyslipidemia program. *Am J Health Syst Pharm* 2005;62:1586-91
31. Putzer G, Roetzheim R, Ramirez AM, et al. Compliance with recommendations for lipid management among patients with type 2 diabetes in an academic family practice. *J Am Board Fam Pract* 2004;17:101-7
32. NCEP ATP III (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (final report). *Circulation* 2002;106:3143-421
33. De Backer G, Ambrosioni E, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force on European and other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur J Cardiovasc Prevention Rehab* 2003;10(Suppl. 1):S1-S78
34. Williams B, Poulter N. What's new in the new British Hypertension Society guidelines for the management of hypertension – BHS IV. *Br J Cardiol* 2004;11:112-7
35. ALLHAT-LLT Study Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *J Am Med Assoc* 2002;288:2998-3007
36. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;360:1623-30
37. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *New Engl J Med* 2004;350:1495-504
38. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *New Engl J Med* 2005;352:1425-35
39. Liberopoulos EN, Athyros VG, Elisaf MS, Mikhailidis DP. Targets for low-density lipoprotein cholesterol levels in patients with stable coronary heart disease: where are we now after the 'treating to new targets' (TNT) trial? *Hell J Cardiol* 2005;46:161-4
40. Athyros VG, Mikhailidis DP, Papageorgiou AA, et al. Relationship between LDL-C and non-HDL-C levels and clinical outcome in the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. *Curr Med Res Opin* 2004;20:1385-92
41. Kosoglou T, Statkevich P, Yang B, et al. Pharmacodynamic interaction between ezetimibe and rosuvastatin. *Curr Med Res Opin* 2004;20:1185-95
42. Gagne C, Bays HE, Weiss SR, et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. *Am J Cardiol* 2002;90:1084-91
43. Ballantyne CM, Blazing MA, King TR, et al. Efficacy and safety of ezetimibe co-administered with simvastatin compared with atorvastatin in adults with hypercholesterolemia. *Am J Cardiol* 2004;93:1487-94
44. Patel SB. Ezetimibe: a novel cholesterol-lowering agent that highlights novel physiologic pathways. *Curr Cardiol Rep* 2004;6:439-42
45. Sudhop T, Lutjohann D, Kodal A, et al. Inhibition of intestinal cholesterol absorption by ezetimibe in humans. *Circulation* 2002;106:1943-8
46. Garcia-Calvo M, Lisnock J, Bull HG, et al. The target of ezetimibe is Niemann-Pick C1-Like 1 (NPC1L1). *Proc Natl Acad Sci USA* 2005;102:8132-7
47. Iyer SP, Yao X, Crona JH, et al. Characterization of the putative native and recombinant rat sterol transporter Niemann-Pick C1 Like 1 (NPC1L1) protein. *Biochim Biophys Acta* 2005;1722:282-92
48. Wang J, Williams CM, Hegele RA. Compound heterozygosity for two non-synonymous polymorphisms in NPC1L1 in a non-responder to ezetimibe. *Clin Genet* 2005;67:175-7
49. Davis Jr HR, Zhu LJ, Hoos LM, et al. Niemann-Pick C1 Like 1 (NPC1L1) is the intestinal phytosterol and cholesterol transporter and a key modulator of whole-body cholesterol homeostasis. *J Biol Chem* 2004;279:33586-92
50. Catapano AL. Ezetimibe: as selective inhibitor of cholesterol absorption. *Eur J Heart* 2001;3:E6-E10
51. Keung ACF, Kosoglou T, Statkevich P, et al. Ezetimibe does not affect the pharmacokinetics of oral contraceptives. *Clin Pharmacol Ther* 2001;69:P55

52. Statkevich P, Reyderman L, Kosoglou T, et al. Ezetimibe does not affect the pharmacokinetics and pharmacodynamics of glipizide. *Clin Pharmacol Ther* 2001;69:P67
53. Farnier M, Freeman MW, Macdonell G, et al. Efficacy and safety of the coadministration of ezetimibe with fenofibrate in patients with mixed hyperlipidaemia. *Eur Heart J* 2005;26:897-905
54. Kosoglou T, Gumbiner B, et al. Pharmacodynamic interaction between fenofibrate and the cholesterol absorption inhibitor ezetimibe. *Atherosclerosis* 2001;2:38
55. Reyderman L, Kosoglou T, Cutler DL, et al. The effect of fluvastatin on the pharmacokinetics and pharmacodynamics of ezetimibe. *Curr Med Res Opin* 2005;21:1171-80
56. Koshman SL, Lalonde LD, Burton I, et al. Supratherapeutic response to ezetimibe administered with cyclosporine. *Ann Pharmacother* 2005;39:1561-5
57. Davidson MH. Ezetimibe: a novel option for lowering cholesterol. *Expert Rev Cardiovasc Ther* 2003;1:11-21
58. Zhu Y, Statkevich P, Kosoglou T, et al. Effect of ezetimibe (SCH 58235) on the activity of drug metabolizing enzymes in vivo. *Clin Pharmacol Ther* 2000;67:152
59. Toth PP, Davidson MH. Simvastatin plus ezetimibe: combination therapy for the management of dyslipidaemia. *Expert Opin Pharmacother* 2005;6:131-9
60. Bulut D, Hanefeld C, Bulut-Streich N, et al. Endothelial function in the forearm circulation of patients with the metabolic syndrome – effect of different lipid-lowering regimens. *Cardiology* 2005;104:176-80
61. Davidson MH, Stein EA, Hunninghake DB, et al. Lipid-altering efficacy and safety of simvastatin 80 mg/day: worldwide long-term experience in patients with hypercholesterolemia. *Nutr Metab Cardiovasc Dis* 2000;10:253-62
62. Foley KA, Simpson Jr RJ, Crouse III JR, et al. Effectiveness of statin titration on low-density lipoprotein cholesterol goal attainment in patients at high risk of atherogenic events. *Am J Cardiol* 2003;92:79-81
63. Evans M, Rees A. Effects of HMG-CoA reductase inhibitors on skeletal muscle: are all statins the same? *Drug Saf* 2002;25: 649-63
64. Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *J Am Med Assoc* 2005;294:2437-45
65. Perez-Calvo J, Civeira-Murillo F, Cabello A. Worsening myopathy associated with ezetimibe in a patient with McArdle disease. *Q J Med* 2005;98:461-2
66. Zetia (ezetimibe) summary of product characteristics. MSP Singapore Company; LLC; date of last revision: 2005
67. Zema MJ. Colesevelam HCl and ezetimibe combination therapy provides effective lipid-lowering in difficult-to-treat patients with hypercholesterolemia. *Am J Ther* 2005;12:306-10
68. Schectman G, Hiatt J. Dose–response characteristics of cholesterol-lowering drug therapies: implications for treatment. *Ann Intern Med* 1996;125:990-1000
69. Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *New Engl J Med* 2001;345:1583-92
70. Wierzbicki AS, Mikhailidis DP, Wray R, et al. Statin–fibrate combination: therapy for hyperlipidemia: a review. *Curr Med Res Opin* 2003;19:155-68
71. Schuster H. Improving lipid management – to titrate, combine or switch. *Int J Clin Pract* 2004;58:689-94
72. Knopp RH. Drug treatment of lipid disorders. *New Engl J Med* 1999;341:498-511
73. Pearson TA, Denke MA, McBride PE, et al. A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: the ezetimibe add-on to statin therapy for effectiveness (EASE) trial. *Mayo Clin Proc* 2005;80:587-95
74. Cruz-Fernandez JM, Bedarida GV, Adgey J, et al. Efficacy and safety of ezetimibe co-administered with ongoing atorvastatin therapy in achieving low-density lipoprotein goal in patients with hypercholesterolemia and coronary heart disease. *Int J Clin Pract* 2005;59:619-27
75. Brohet C, Banai S, Alings AM, et al. LDL-C goal attainment with the addition of ezetimibe to ongoing simvastatin treatment in coronary heart disease patients with hypercholesterolemia. *Curr Med Res Opin* 2005;21:571-8
76. Simons L, Tonkon M, Masana L, et al. Effects of ezetimibe added to on-going statin therapy on the lipid profile of hypercholesterolemic patients with diabetes mellitus or metabolic syndrome. *Curr Med Res Opin* 2004;20:1437-45
77. Barrios V, Amabile N, Paganelli F, et al. Lipid-altering efficacy of switching from atorvastatin 10 mg/day to ezetimibe/simvastatin 10/20 mg/day compared to doubling the dose of atorvastatin in hypercholesterolaemic patients with atherosclerosis or coronary heart disease. *Int J Clin Pract* 2005;59:1377-86
78. Feldman T, Koren M, Insull Jr W, et al. Treatment of high-risk patients with ezetimibe plus simvastatin co-administration versus simvastatin alone to attain National Cholesterol Education Program Adult Treatment Panel III low-density lipoprotein cholesterol goals. *Am J Cardiol* 2004;93: 1481-6
79. Ballantyne CM, Lipka LJ, Sager PT, et al. Long-term safety and tolerability profile of ezetimibe and atorvastatin coadministration therapy in patients with primary hypercholesterolaemia. *Int J Clin Pract* 2004;58:653-8
80. Ito MK, Lin JC, Morreale AP, et al. Effect of pravastatin-to-simvastatin conversion on low-density-lipoprotein cholesterol. *Am J Health Syst Pharm* 2001;58:1734-9
81. Andrews TC, Ballantyne CM, Hsia JA, Kramer JH. Achieving and maintaining National Cholesterol Education Program low-density lipoprotein cholesterol goals with five statins. *Am J Med* 2001;111:185-91
82. 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
83. Shepherd J, Hunninghake DB, Barter P, et al. Guidelines for lowering lipids to reduce coronary artery disease risk: a comparison of rosuvastatin with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals. *Am J Cardiol* 2003;91:11C-17C
84. Schuster H, Barter PJ, Stender S, et al. Effects of switching statins on achievement of lipid goals: measuring effective reductions in cholesterol using rosuvastatin therapy (MERCURY I) study. *Am Heart J* 2004;147:705-12
85. Health Science Authority. Product safety alert [online]. Available from http://www.hsa.gov.sg/docs/safetyalert_rosuvastatin_May04.pdf [last date accessed 24 November 2005]
86. Al-sheikh-Ali AA, Ambrose MS, Kuvin JT, Karas RH. The safety of rosuvastatin as used in common clinical practice: a postmarketing analysis. *Circulation* 2005;111:3051-7
87. Goldberg AC, Sapre A, Liu J, et al. Efficacy and safety of ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc* 2004;79:620-9
88. Davidson MH, McGarry T, Bettis R, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. *J Am Coll Cardiol* 2002;40:2125-34
89. Mikhailidis DP, Wierzbicki AS, Daskalopoulou SS, et al. The use of ezetimibe in achieving low density lipoprotein lowering goals in clinical practice: position statement of a United Kingdom consensus panel. *Curr Med Res Opin* 2005;21: 959-69
90. Dujovne CA, Ettinger MP, McNeer JF, et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. *Am J Cardiol* 2002;90:1092-7
91. Knopp RH, Gitter H, Truitt T, et al. Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. *Eur Heart J* 2003;24: 729-41
92. Knopp RH, Dujovne CA, Beaut LJ, et al. Evaluation of the efficacy, safety, and tolerability of ezetimibe in primary hypercholesterolaemia: a pooled analysis from two controlled phase III clinical studies. *Int J Clin Pract* 2003;57:363-8

93. Bays HE, Moore PB, Dreihobl MA, et al. Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: pooled analysis of two phase II studies. *Clin Ther* 2001;23:1209-30
94. Phillips PS. Ezetimibe and statin-associated myopathy. Comment in *Ann Intern Med* 2004;141:649
95. Fux R, Morike K, Gundel UF, et al. Ezetimibe and statin-associated myopathy. *Ann Intern Med* 2004;140:671-2
96. Doherty E, Lumb PJ, Chik G, Wierzbicki AS. Ezetimibe-induced hyperlipidaemia. *Int J Clin Pract* 2005;59(Suppl):3-5
97. Hegele RA, Guy J, Ban MR, Wang J. NPC1L1 haplotype is associated with inter-individual variation in plasma low-density lipoprotein response to ezetimibe. *Lipids Health Dis* 2005;4:16
98. Simon JS, Karnoub MC, Devlin DJ, et al. Sequence variation in NPC1L1 and association with improved LDL-cholesterol lowering in response to ezetimibe treatment. *Genomics* 2005;86:648-56
99. Lammert F, Wang DQ. New insights into the genetic regulation of intestinal cholesterol absorption. *Gastroenterology* 2005;129:718-34
100. Kosoglou T, Statkevich P, Johnson-Levonas AO, Paolini JF, Bergman AJ, Alton KB. Ezetimibe: a review of its metabolism, pharmacokinetics and drug interactions. *Clin Pharmacokinet* 2005;44:467-94
101. Koshman SL, Lalonde LD, Burton I, Tymchak WJ, Pearson GJ. Supratherapeutic response to ezetimibe administered with cyclosporine. *Ann Pharmacother* 2005;39:1561-5
102. Gagne C, Gaudet D, Bruckert E; for the Ezetimibe Study Group. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. *Circulation* 2002;105:2469-75
103. Wierzbicki AS, Doherty E, Lumb PJ, et al. Efficacy of ezetimibe in patients with statin-resistant and statin-intolerant familial hyperlipidaemias. *Curr Med Res Opin* 2005;21:333-8
104. Jahn CE, Schaefer EJ, Taam LA, et al. Lipoprotein abnormalities in primary biliary cirrhosis. Association with hepatic lipase inhibition as well as altered cholesterol esterification. *Gastroenterology* 1985;89:1266-78
105. Ballantyne CM, Abate N, Yuan Z, et al. Dose-comparison study of the combination of ezetimibe and simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia: the Vytorin Versus Atorvastatin (VYVA) study. *Am Heart J* 2005;149:464-73
106. Lipka L, Sager P, Strony J, et al. Efficacy and safety of coadministration of ezetimibe and statins in elderly patients with primary hypercholesterolaemia. *Drugs Aging* 2004;21:1025-32
107. Geiss HC, Otto C, Hund-Wissner E, Parhofer KG. Effects of ezetimibe on plasma lipoproteins in severely hypercholesterolemic patients treated with regular LDL-apheresis and statins. *Atherosclerosis* 2005;180:107-12
108. Yamamoto A, Harada-Shiba M, Endo M, et al. The effect of ezetimibe on serum lipids and lipoproteins in patients with homozygous familial hypercholesterolemia undergoing LDL-apheresis therapy. *Atherosclerosis* 2005 [Epub ahead of print: - July 22]
109. Puthenparumpil JJ, Keough-Ryan T, Kiberd M, et al. Treatment of hypercholesterolemia with ezetimibe in the kidney transplant population. *Transplant Proc* 2005;37:1033-5
110. Bays HE, Ose L, Fraser N, et al. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared with ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. *Clin Ther* 2004;26:1758-73
111. Davidson MH, Ballantyne CM, Kerzner B, et al. Efficacy and safety of ezetimibe coadministered with statins: randomized, placebo-controlled, blinded experience in 2382 patients with primary hypercholesterolemia. *Int J Clin Pract* 2004;58:746-55
112. Sager PT, Melani L, Lipka L, et al. Effect of coadministration of ezetimibe and simvastatin on high-sensitivity C-reactive protein. *Am J Cardiol* 2003;92:1414-8
113. Ridker PM, Cannon CP, Morrow D, et al. C-reactive protein levels and outcomes after statin therapy. *New Engl J Med* 2005;352:20-8
114. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *New Engl J Med* 2005;352:29-38
115. Bennett S, Sager P, Lipka L, et al. Consistency in efficacy and safety of ezetimibe coadministered with statins for treatment of hypercholesterolemia in women and men. *J Womens Health (Larchmont)* 2004;13:1101-7
116. Sacks FM; for the Expert Group on HDL Cholesterol. The role of high-density lipoprotein (HDL) cholesterol in the prevention and treatment of coronary heart disease: expert group recommendations. *Am J Cardiol* 2002;90:139-43
117. UK HDL-C Consensus Group. Role of fibrates in reducing coronary risk: a UK consensus. *Curr Med Res Opin* 2004;20:2041-7
118. Chapman MJ, Assmann G, Fruchart JC, et al. Raising high-density lipoprotein cholesterol with reduction of cardiovascular risk: the role of nicotinic acid – a position paper developed by the European Consensus Panel on HDL-C. *Curr Med Res Opin* 2004;20:1253-68
119. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation* 1989;79:8-15
120. Athyros VG, Mikhailidis DP, Papageorgiou AA, et al. Effect of atorvastatin on high density lipoprotein cholesterol and its relationship with coronary events: a subgroup analysis of the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. *Curr Med Res Opin* 2004;20:627-37
121. Durrington P. The human and economic costs of undertreatment with statins. *Int J Clin Pract* 2002;56:357-68
122. Pasternak RC. The ALLHAT lipid lowering trial – less is less. *J Am Med Assoc* 2002;288:3042-4
123. Davis Jr HR, Compton DS, Hoos L, Tetzloff G. Ezetimibe, a potent cholesterol absorption inhibitor, inhibits the development of atherosclerosis in ApoE knockout mice. *Arterioscler Thromb Vasc Biol* 2001;21:2032-8
124. van Heek M, Compton DS, Davis HR. The cholesterol absorption inhibitor, ezetimibe, decreases diet-induced hypercholesterolemia in monkeys. *Eur J Pharmacol* 2001;415:79-84
125. Simard C, Turgeon J. The pharmacokinetics of ezetimibe. *Can J Clin Pharmacol* 2003;10(Suppl A):13A-20A
126. Kolovou GD, Anagnostopoulou KK, Pilatis ND, et al. Heterozygote men with familial hypercholesterolaemia may have an abnormal triglyceride response post-prandially. Evidence for another predictor of vascular risk in familial hypercholesterolaemia. *Int J Clin Pract* 2005;59:311-7
127. Huff MW. Dietary cholesterol, cholesterol absorption, post-prandial lipemia and atherosclerosis. *Can J Clin Pharmacol* 2003;10(Suppl A):26A-32A
128. Buchwald H, Williams SE, Matts JP, Nguyen PA, Boen JR. Overall mortality in the program on the surgical control of the hyperlipidemias. *J Am Coll Surg* 2002;195:327-31
129. Baigent C, Landry M. Study of Heart and Renal Protection (SHARP). *Kidney Int Suppl* 2003;S207-S210
130. Kastelein JJ, Sager PT, De Groot E, Veltri E. Comparison of ezetimibe plus simvastatin versus simvastatin monotherapy on atherosclerosis progression in familial hypercholesterolemia: design and rationale of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial. *Am Heart J* 2005;149:234-9
131. Rossebo A, Pedersen T, Skjaerpe T, et al. Design of the simvastatin and ezetimibe in aortic stenosis (SEAS) study. XIIIth International Symposium on Atherosclerosis 2003;3P-0873
132. Farnier M, Volpe M, Massaad R, et al. Effect of co-administering ezetimibe with on-going simvastatin treatment on LDL-C goal attainment in hypercholesterolemic patients with coronary heart disease. *Int J Cardiol* 2005;102:327-32
133. Ballantyne CM, Houri J, Notarbartolo A, et al. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. *Circulation* 2003;107:2409-15
134. Kerzner B, Corbelli J, Sharp S, et al. Efficacy and safety of ezetimibe coadministered with lovastatin in primary hypercholesterolemia. *Am J Cardiol* 2003;91:418-24

135. Melani L, Mills R, Hassman D, et al. Efficacy and safety of ezetimibe coadministered with pravastatin in patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. *Eur Heart J* 2003;24:717-28
136. Masana L, Mata P, Gagne C, et al. Long-term safety and tolerability profiles and lipid-modifying efficacy of ezetimibe coadministered with ongoing simvastatin treatment: a multi-center, randomized, double-blind, placebo-controlled, 48-week extension study. *Clin Ther* 2005;27:174-84
137. Sager PT, Capece R, Lipka L, et al. Effects of ezetimibe coadministered with simvastatin on C-reactive protein in a large cohort of hypercholesterolemic patients. *Atherosclerosis* 2005;179:361-7
138. Stein E, Stender S, Mata P, et al. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: efficacy and safety of ezetimibe co-administered with atorvastatin. *Am Heart J* 2004;148:447-55
139. Gaudiani LM, Lewin A, Meneghini L, et al. Efficacy and safety of ezetimibe co-administered with simvastatin in thiazolidinedione-treated type 2 diabetic patients. *Diabetes Obes Metab* 2005;7:88-97
140. Kosoglou T, Statkevich P, Meyer I, et al. Effects of ezetimibe on the pharmacodynamics and pharmacokinetics of lovastatin. *Curr Med Res Opin* 2004;20:955-65
141. Kosoglou T, Meyer I, Veltri EP, et al. Pharmacodynamic interaction between the new selective cholesterol absorption inhibitor ezetimibe and simvastatin. *Br J Clin Pharmacol* 2002;54:309-19
142. Reyderman L, Kosoglou T, Statkevich P, et al. Assessment of a multiple-dose drug interaction between ezetimibe, a novel selective cholesterol absorption inhibitor and gemfibrozil. *Int J Clin Pharmacol Ther* 2004;42:512-8
143. Xydakis AM, Guyton JR, Chiou P, et al. Effectiveness and tolerability of ezetimibe add-on therapy to a bile acid resin-based regimen for hypercholesterolemia. *Am J Cardiol* 2004;94:795-7

CrossRef links are available in the online published version of this paper:

<http://www.cmrojournal.com>

Paper CMRO-3229_3, *Accepted for publication*: 17 January 2006

Published Online: 01 February 2006

doi:10.1185/030079906X89856