doi: 10.1111/j.1368-5031.2005.00737.x

Ezetimibe/simvastatin (INEGY™) in the treatment of hyperlipidaemia

J. J. P. KASTELEIN, R. R. SANKATSING
Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Meibergdreef, Amsterdam, The Netherlands

SUMMARY

Ezetimibe/simvastatin (INEGY™), a dual inhibitor of both cholesterol production and absorption, is a new approach to the management of hyperlipidaemia. Recent studies have shown that it produces greater reductions in low-density lipoprotein (LDL) cholesterol than the single inhibition of statin therapy, enabling many more patients to achieve their LDL cholesterol treatment goals. With ezetimibe/simvastatin therapy, reductions of up to 61% from baseline have been seen in LDL cholesterol, with clear improvements in other associated lipid fractions. It has been well tolerated across all studies, with a safety profile similar to that of statin therapy. This article will review clinical experience to date with ezetimibe/simvastatin, commenting upon its place and potential value in the prevention of cardiovascular disease.

Keywords: Ezetimibe; simvastatin; INEGY™; low-density lipoprotein cholesterol; lipids

INTRODUCTION

Despite the clear risks of hyperlipidaemia and the proven benefits of lipid-lowering therapies, only a minority of patients currently achieve recommended low-density lipoprotein (LDL) cholesterol treatment goals in clinical practice (1–5). More patients are being treated for lipid reduction than ever before, but there still remains a substantial degree of under treatment. Although this may be due to a number of reasons (e.g. patient non-compliance, tolerability issues and variable physician follow-up), the most likely explanation is that patients are not receiving adequate dosages of the lipid-lowering drugs available or that the drugs themselves are not optimal. Either way, a more aggressive approach to LDL cholesterol reduction is warranted.

Until recently, clinicians had only been able to inhibit one source of cholesterol with drug therapy, that of cholesterol production. Ezetimibe/simvastatin (INEGY™) provides dual inhibition of both cholesterol production and absorption, representing a new approach to lipid management. Recent large-scale, randomised, controlled clinical trials have shown that ezetimibe/simvastatin produces substantially greater reductions in LDL cholesterol than statin therapy, while maintaining safety and tolerability profiles similar to those of statin therapy (6–11). As such, it may be a viable alternative to traditional statin therapy.

This article will review the data to consider the use of ezetimibe/simvastatin in the treatment of hyperlipidaemia.

EZETIMIBE/SIMVASTATIN: COMPONENTS WITH COMPLEMENTARY ACTIONS

Simvastatin is a competitive inhibitor of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, the last regulated step in the synthesis of cholesterol. By lowering serum LDL cholesterol levels (through a combination of LDL receptor up-regulation and reduced entry of LDL cholesterol into the circulation), statins as a class have been shown to reduce the incidence of coronary artery disease by 25–60% and the risk of death from any cause by an approximate 30% (12). Simvastatin was one of the first statins to be associated with substantial improvements in morbidity and mortality in this respect (13) and has since shown benefit across a wide range of at-risk individuals (14).

Ezetimibe is the first in a new class of cholesterol absorption inhibitors that blocks the intestinal absorption of dietary and biliary cholesterol, without affecting the uptake of triglycerides or fat soluble vitamins (15,16). As would be expected from its mode of action, ezetimibe has demonstrated significant reductions in LDL cholesterol in patients with primary hypercholesterolaemia ($p < 0.01$ vs. placebo), with favourable effects on associated lipid variables such as triglycerides and high-density lipoprotein (HDL) cholesterol (17,18).

As blood cholesterol levels are maintained through both endogenous synthesis and intestinal absorption, an agent that inhibits both sources of cholesterol would be expected to

Correspondence to:
John J. P. Kastelein, MD, PhD, Professor of Medicine, Chairman, Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands
Tel.: + 31 20 566 6612
Fax: + 31 20 566 9343
Email: e.vandongen@amc.uva.nl

lower LDL cholesterol levels to a greater extent than one that acts through either mechanism alone (Figure 1). This theory has proven correct in the laboratory and in the clinic. In a hypercholesterolaemic dog model, for example, ezetimibe was seen to synergistically reduce plasma cholesterol levels in the presence of HMG-CoA reductase inhibitors (19). Early clinical pharmacology studies also demonstrated that simvastatin and ezetimibe had incremental benefit on LDL cholesterol reduction and without any adverse drug–drug interactions (20). Subsequent clinical studies have since shown repeatedly that ezetimibe/simvastatin provides reductions in LDL cholesterol over and above those achieved with statin therapy. Key data in this respect are detailed below.

CLINICAL EFFICACY OF EZETIMIBE/SIMVASTATIN

Reductions in LDL Cholesterol

Recently published findings from a 12-week treatment study enroling 887 patients with primary hypercholesterolaemia (LDL cholesterol 145–250 mg/dl; triglycerides $\leq$350 mg/dl) showed ezetimibe/simvastatin to be significantly ($p < 0.001$) more effective than simvastatin alone in reducing LDL cholesterol levels (8). In the study, patients were randomised to one of four different treatment regimens: ezetimibe 10 mg; simvastatin 10, 20, 40 or 80 mg; ezetimibe 10 mg plus simvastatin 10, 20, 40 or 80 mg; or placebo. Pooled data across all ezetimibe/simvastatin patients demonstrated a mean 53.2% reduction from baseline in LDL cholesterol compared with a 38.5% reduction for simvastatin alone ($p < 0.001$). The figure of 53.2% is important, as evidence suggests that a reduction in LDL cholesterol of at least 50% is needed for plaque stabilisation and the reduced progression of coronary atherosclerosis (21). The differential between the treatment groups could be seen at each dose comparison. Reductions in LDL cholesterol of up to 61% from baseline were reported in patients treated with ezetimibe/simvastatin 10/80 mg (Figure 2). Maximal lowering of LDL cholesterol was evident by 2 weeks and efficacy maintained throughout the study. In addition to the beneficial effects on LDL cholesterol, there were clear improvements in a number of other lipid fractions and inflammatory markers, with significance between the treatment groups for the majority of variables (Table 1). Of note, the data presented in this review relate to the co-administration of ezetimibe and simvastatin and not the co-formulation of the drugs. However, a recent study by Bays et al. clearly demonstrated the bioequivalence of the ezetimibe/simvastatin combination tablet to co-administration of the two individual drugs (22). In this study, administration of ezetimibe/simvastatin 10/10 mg, 10/20 mg, 10/40 mg and 10/80 mg reduced mean LDL cholesterol levels by 44.8%, 51.9%, 55.2% and 60.2%, respectively, after 12 weeks of treatment.

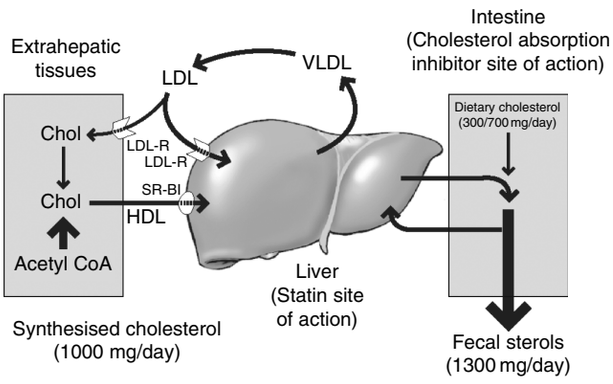

Figure 1 Dual inhibition of cholesterol production and absorption with ezetimibe/simvastatin. Chol, cholesterol; VLDL, very-low-density lipoprotein; LDL, low-density lipoprotein; LDL-R, LDL receptor; HDL, high-density lipoprotein; CoA, coenzyme A; SR-BI, class B type 1 scavenger receptor

LDL Cholesterol Goal Attainment

Of important clinical consequence is that ezetimibe/simvastatin has been shown to allow more patients to reach their LDL cholesterol goal at a lower dose of simvastatin and with fewer dose titrations than simvastatin alone. In a 23-week study of 710 randomised, high-risk patients [men and women with LDL cholesterol $\geq$130 mg/dl meeting National Cholesterol Education Program (NCEP) Adult Treatment Panel III criteria for coronary heart disease (CHD) or CHD-risk equivalent], ezetimibe/simvastatin 10/10, 10/20 or 10/40 mg produced greater reductions in LDL cholesterol and allowed more patients to reach an LDL cholesterol treatment goal of $<$100 mg/dl compared with simvastatin monotherapy (20 mg) (6) (Figure 3). After 5 weeks of treatment, 75%

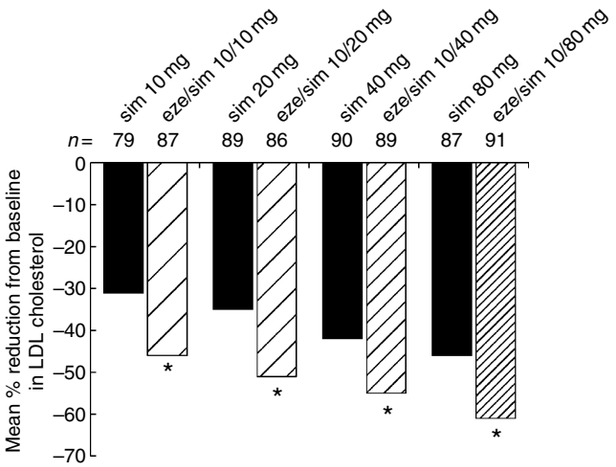

Figure 2 Per cent reduction in low-density lipoprotein (LDL) cholesterol levels from baseline to study endpoint: ezetimibe/simvastatin (eze/sim) vs. simvastatin (sim) monotherapy (8).
*$p < 0.001$ vs. corresponding simvastatin monotherapy dose

Table 1 Mean per cent change from baseline to study endpoint (last available LDL cholesterol measurement) in lipid variables and inflammatory markers: ezetimibe/simvastatin vs. simvastatin monotherapy (8)

	Pooled simvastatin data		*Pooled ezetimibe/simvastatin data*	
	N	*Mean % change from baseline (SD)*	*N*	*Mean % change from baseline (SD)*
LDL cholesterol	345	−38.5 (14.2)	353	−53.2 (17.2)*
Total cholesterol	345	−26.4 (11.3)	353	−37.7 (13.3)*
HDL cholesterol	345	7.6 (11.9)	353	8.2 (13.1)
Non-HDL cholesterol	345	−34.1 (13.8)	353	−48.5 (16.3)*
Triglycerides (median)	345	−15.2 (34.1)	353	−28.0(28.0)*
Apo B	328	−29.2 (14.3)	340	−42.0 (16.6)*
Apo A-I	328	6.3 (13.8)	340	4.3 (16.5)
Apo A-II	199	2.8 (11.5)	208	−0.3 (16.8)
Apo E	328	−19.4 (22.8)	340	−26.1 (21.4)*
Lp (a)	199	−9.6 (39.3)	208	−10.9 (40.3)
LDL: HDL cholesterol	345	−42.0 (15.2)	353	−56.1 (17.1)*
Total cholesterol: HDL cholesterol	345	−30.8 (13.0)	353	−41.7 (14.3)*
CRP (median)	204	−8.7 (61.7)	209	−33.3 (50.1)*
Fibrinogen (median)	198	4.4 (20.0)	205	2.3 (19.2)

LDL, low-density lipoprotein; HDL, high-density lipoprotein; Apo, apolipoprotein; Lp, lipoprotein; CRP, C-reactive protein. *$p < 0.001$ vs. pooled simvastatin.

patients treated with ezetimibe/simvastatin 10/10 mg achieved LDL cholesterol levels <100 mg/dl compared with only 46% of patients treated with simvastatin 20 mg. Essentially, patients treated with ezetimibe/simvastatin 10/10 mg had approximately 3.6 times greater odds of reaching their treatment goal than patients treated with simvastatin 20 mg. The corresponding odds for patients in the ezetimibe/simvastatin 10/20 and 10/40 mg groups were 6.0 and 8.4 times, respectively. In addition, relatively few patients in the ezetimibe/simvastatin groups required up-titration of the simvastatin dose. For example, 75% of patients receiving ezetimibe/simvastatin 10/10 mg reached their LDL cholesterol goal without a simvastatin dose titration, compared with fewer than half of patients receiving simvastatin 20 mg.

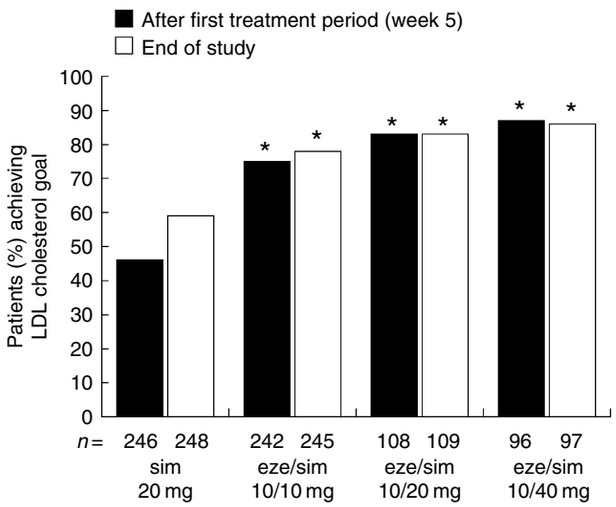

Figure 3 Percentage of patients achieving a low-density lipoprotein (LDL) cholesterol level of <100 mg/dl after the first treatment period (week 5) and at the end of the study: ezetimibe/simvastatin (eze/sim) vs. simvastatin (sim) monotherapy (6). *$p < 0.001$ vs. simvastatin 20 mg

Other Patient Populations

Preliminary data also suggest a broader clinical role for ezetimibe/simvastatin for patients where greater LDL cholesterol reduction is necessary, the compound demonstrating notable efficacy in groups of patients at high risk of cardiovascular disease. In patients with type II diabetes mellitus, for example, ezetimibe/simvastatin 10/20 mg was more effective in reducing LDL cholesterol than double the dose of statin therapy and enabled the majority of patients to meet their LDL cholesterol treatment goals (23,24). It also improved levels of C-reactive protein, a sensitive marker for cardiovascular risk in these patients (25).

SAFETY AND TOLERABILITY OF EZETIMIBE/SIMVASTATIN

Ezetimibe/simvastatin has been evaluated for safety in more than 3200 patients in clinical trials. Studies reported to date have shown ezetimibe/simvastatin to be well tolerated, with a safety profile similar to that of statin monotherapy. No clinically meaningful differences have been seen between ezetimibe/simvastatin and either simvastatin or atorvastatin as single agents in terms of overall adverse events (drug-related or not) or clinical/laboratory adverse events leading to discontinuation of treatment (6–8) (Table 2). Importantly, there

Table 2 Summary of adverse events across three randomised, controlled studies comparing ezetimibe/simvastatin with statin monotherapy (6–8)

	Simvastatin			*Ezetimibe/simvastatin*			
	20 mg	*Pooled**	*Atorvastatin 10 mg*	*10/10 mg*	*10/20 mg*	*10/40 mg*	*Pooled**
Any clinical adverse events							
Study 1	168 (66%)	–	–	140 (56%)	74 (68%)	63 (65%)	–
Study 2	–	–	187 (71%)	184 (70%)	165 (63%)	–	–
Study 3	–	219 (63%)	–	–	–	–	214 (61%)
Treatment-related adverse events							
Study 1	19 (8%)	–	–	24 (10%)	15 (14%)	10 (10%)	–
Study 2	–	–	42 (16%)	42 (16%)	36 (14%)	–	–
Study 3	–	46 (13%)	–	–	–	–	48 (14%)
Discontinuation due to any adverse events							
Study 1	14 (6%)	–	–	11 (4%)	7 (6%)	5 (5%)	–
Study 2	–	–	10 (4%)	15 (6%)	15 (6%)	–	–
Study 3	–	7 (2%)	–	–	–	–	16 (5%)
Creatine kinase ≥10 times ULN							
Study 1	2 (1%)	–	–	0	0	1 (1%)	–
Study 2	–	–	0	1 (0.4%)	1 (0.4%)	–	–
Study 3	–	1 (0.3%)	–	–	–	–	2 (0.6%)
Alanine aminotransferase and/or aspartate aminotransferase ≥3 times ULN							
Study 1	0	–	–	1 (0.4%)	0	1 (1%)	–
Study 2	–	–	6 (2%)	6 (2%)	5 (2%)	–	–
Study 3	–	0	–	–	–	–	6 (2%)

ULN, upper limit of normal; study 1, Feldman et al. 2004 (6); study 2, Ballantyne et al. 2004 (7); study 3, Goldberg et al. 2004 (8). *Simvastatin 10, 20, 40 or 80 mg.

were no reported cases of rhabdomyolysis in clinical trials. Nevertheless, vigilance is required as there have been some case reports of patients experiencing myopathy/tendinopathy both with and without increased serum creatine kinase activity after adding ezetimibe to a statin (26). Myopathy and rhabdomyolysis have occurred very rarely in postmarketing reports (<1:10,000) with ezetimibe co-administered with a statin.

EFFICACY COMPARISONS WITH OTHER STATINS

Ezetimibe/Simvastatin vs. Atorvastatin

In addition to comparisons of ezetimibe/simvastatin vs. simvastatin alone, the published literature also provides evidence for the superior efficacy of ezetimibe/simvastatin vs. atorvastatin in the treatment of hypercholesterolaemia. A recently reported forced-titration study compared the efficacy of ezetimibe/simvastatin with atorvastatin in 788 patients randomised to (i) atorvastatin (10 mg titrated to 20, 40 and 80 mg at 6-week intervals); (ii) ezetimibe/simvastatin (10/10 mg titrated to 10/20, 10/40 and 10/80 mg at 6-week intervals); and (iii) ezetimibe/simvastatin (10/20 mg titrated to 10/40 mg after 6 weeks and 10/80 mg after 18 weeks) (7). All patients were 18 years of age or older, with baseline LDL cholesterol levels at or above the drug treatment threshold detailed in the NCEP Adult Treatment Panel III guidelines (27). After the first 6 weeks of treatment (primary endpoint), ezetimibe/simvastatin (10/10 and 10/20 mg) produced significantly greater reductions in LDL cholesterol (−46% and −50%, respectively) than atorvastatin 10 mg (−37%; $p \leq 0.05$). In fact, at all time/dose points throughout the study, ezetimibe/simvastatin showed greater efficacy than atorvastatin in decreasing LDL cholesterol (Figure 4), as well as non-HDL cholesterol, apolipoprotein B and total cholesterol. Similarly, ezetimibe/simvastatin was significantly ($p \leq 0.05$) more effective than atorvastatin in increasing levels of HDL cholesterol from baseline.

Ezetimibe in Combination with Atorvastatin, Pravastatin, Lovastatin and Rosuvastatin

The beneficial effects of ezetimibe co-administered with a statin are not limited to simvastatin; valuable improvements in clinical efficacy have also been seen in combination with all statins studied, such as atorvastatin (9,28–30) as well as pravastatin (31), lovastatin (32) and rosuvastatin (33). For example, in a recent pooled analysis of data from a collective 2382 patients with primary hypercholesterolaemia, 12 weeks

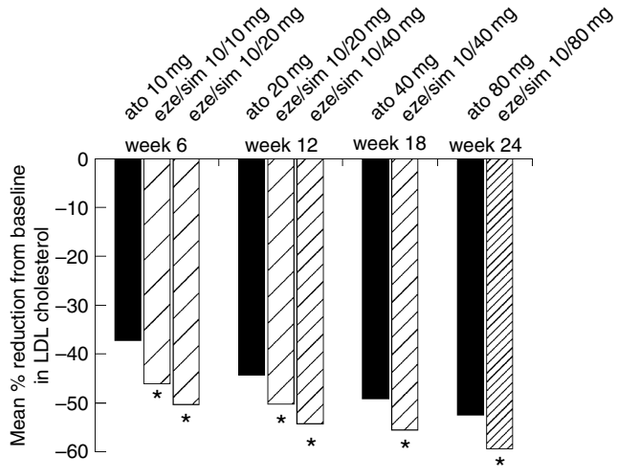

Figure 4 Per cent reduction in low-density lipoprotein (LDL) cholesterol levels from baseline with ascending doses of ezetimibe/simvastatin (eze/sim) vs. atorvastatin (ato) monotherapy (7). *$p \leq 0.05$ vs. atorvastatin

of treatment with ezetimibe plus one of four statins (atorvastatin, lovastatin, pravastatin or simvastatin) produced significantly ($p < 0.01$) greater reductions in LDL cholesterol, total cholesterol, triglycerides, non-HDL cholesterol and apolipoprotein B compared with statin therapy alone (34). HDL cholesterol levels were also significantly ($p < 0.01$) increased. At each statin dose, co-administration with ezetimibe led to a greater LDL cholesterol reduction than the next highest statin monotherapy dose. Moreover, the enhanced LDL cholesterol-lowering effects of ezetimibe plus statin were independent of the statin type and were generally consistent across patient subgroups (e.g. age, gender, hypertension, diabetes, baseline lipid level and family history of CHD). The safety profiles of all ezetimibe/statin combinations were similar to each other and to those of statin therapy alone.

CONSIDERATIONS

As with many drugs, there is a variation in the response to ezetimibe. While the mean reduction in LDL cholesterol with ezetimibe 10 mg is −18.2%, with more than 60% of patients reducing LDL cholesterol by 15% (35), there are some cases reported of patients with hypercholesterolaemia who are unresponsive to treatment with ezetimibe. It has been suggested that variants in the *NPC1L1* gene, the molecular target for ezetimibe, are responsible for this unresponsive phenotype (36). Also, the additional benefit of adding ezetimibe to a statin in patients with refractory familial hyperlipidaemia or patients who are intolerant to statin therapy is modest with an average 11% additional reduction in LDL cholesterol as recently reported by Wierzbicki et al. (37). Incidences of ezetimibe-induced hyperlipidaemia, both in monotherapy and in combination with statins, have also been observed. Apart from biological variation and lesser dietary or drug compliance, this could be explained by an ezetimibe-induced increase in hepatic cholesterol synthesis, albeit unlikely.

CONCLUSIONS: PERSPECTIVES AND EXPECTATIONS

In recent years, lipid-lowering therapy has been directed towards the inhibition of cholesterol production through the use of statins. For many patients, however, clinical efficacy can only be achieved through a strategy of dual inhibition of both production and absorption of cholesterol. As such, ezetimibe/simvastatin would appear to present the clinician and patient with a number of advantages over existing therapy. First, the impressive efficacy seen with ezetimibe/statin therapy should offer patients an increased likelihood of LDL cholesterol goal attainment. As large proportions of patients with hyperlipidaemia currently remain under-treated, an intervention that increases the chances of goal realisation has to be viewed as positive. In fact, some might contend that even patients who comfortably achieve LDL cholesterol goals on existing therapy might benefit from more aggressive lipid lowering. There is much to support the 'lower is better' argument. Every major primary prevention trial of statin therapy to date has demonstrated that lower LDL cholesterol levels are associated with a reduced risk of atherosclerotic disease (38). Those that have analysed event rates in relation to LDL cholesterol have shown that lower LDL cholesterol tertiles are associated with a reduced occurrence of major coronary events (39) and that aggressive lipid lowering can produce more favourable outcomes than conservative approaches (40–43). This has led some to propose that target LDL cholesterol levels should be as low as <70 mg/dl and not 100–115 mg/dl as recommended by current guidelines (44). In fact, the recently revised NCEP guidelines have already moved towards this new LDL cholesterol target of <70 mg/dl in (very) high-risk patients (45). A similar pattern can be noticed in the Joint British Societies guidelines II/British Hypertension Society guidelines IV (46). These changes were brought about by the beneficial results of intensive lipid-lowering therapy beyond current targets observed in the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) and Heart Protection Study (14,42). From a clinical practice standpoint, multiple (upward) dose adjustments with ezetimibe/simvastatin therapy should not be necessary, and many more patients should be able to achieve their LDL cholesterol goals with low doses. In contrast, initial doses of statins are very often insufficient to enable patients to achieve their goals. Clinical evidence shows that when initial doses of statins are doubled, they only provide an additional 6% reduction in LDL cholesterol (12).

Table 3 Ongoing outcome programme for ezetimibe/simvastatin

Study	*Objective(s)*	*Measures*	*Scope*
Ezetimibe and Simvastatin in Hypercholesterolaemia Enhances Atherosclerosis Regression (ENHANCE)	To evaluate he effects of aggressive lipid lowering on carotid artery intima media thickness: ezetimibe/simvastatin vs. statin monotherapy	*Primary*: Mean change in carotid artery intima media thickness *Secondary*: Incidence of plaque regression, changes in maximal intima media thickness	725 patients at 18 international centres treated for 2years
Improved Reduction of Outcomes: VYTORIN™ Efficacy International Trial (IMPROVE IT)	To evaluate the risk reduction provided by ezetimibe/simvastatin vs. simvastatin in reducing death and major coronary events in patients with acute coronary syndromes	*Primary*: Composite of death, MI, rehospitalisation for acute coronary syndromes or revascularisation	10,000 patients followed for at least 2 years
Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) Study	To assess whether aggressive cholesterol lowering in patients with moderate AS slows progression of AS, reduces number of valve replacements, and incidence of CVD outcomes: ezetimibe/simvastatin vs. placebo	*Primary*: Risk reduction in composite endpoint of MCEs* *Secondary*: Aortic valve events, echocardiographic progression of AS, safety/tolerability	1400 patients treated for 4 years
Study of Heart and Renal Protection (SHARP)	To assess the effects of ezetimibe/simvastatin vs. placebo in patients with chronic kidney disease	*Primary*: Time to 1st major vascular event (non-fatal MI or cardiac death, non-fatal/fatal stroke, revascularisation) *Secondary*: Progression to ESRD, various causes of death, †MCEs, stroke, hospitalisation for angina	9000 patients at >200 hospitals in 10 countries treated for ≤4 years

MI, myocardial infarction; ESRD, end-stage renal disease; AS, aortic stenosis; CVD, cardiovascular disease; VYTORIN, INEGY; MCEs, major cardiovascular events. *MCEs = cardiovascular death, aortic valve replacement surgery, CHF, chronic heart failure as a result of progression of AS, non-fatal MI, CABG, coronary artery bypass graft, PCI, percutaneous coronary intervention, hospitalised unstable angina, non-haemorrhagic stroke. †MCEs = non-fatal MI or cardiac death.

Future studies will need to address the potential clinical benefits of ezetimibe/statin therapy over and above those of improving LDL cholesterol levels. The body of evidence for simvastatin is clear in this respect, there being a strong patient outcome base in the form of the Scandinavian Simvastatin Survival Study and Medical Research Council/British Heart Foundation Heart Protection Study (13,14,47). As a single agent, ezetimibe has been shown to reduce atherosclerotic progression in an animal model (48), but clinical evidence of the effectiveness of ezetimibe/simvastatin in the prevention of the complications of atherosclerosis is not yet available. An active outcome programme for ezetimibe/simvastatin is ongoing (Table 3) (49–51). These studies, which include over 21,000 patients across a number of countries worldwide, will confirm whether the greater LDL cholesterol-lowering effects of dual inhibition translate in the clinic into beneficial modifications of cardiovascular endpoints. Clearly, it would be an advancement in clinical practice to offer appropriate patients with hyperlipidaemia the greater effectiveness of dual cholesterol inhibition with ezetimibe/simvastatin.

ACKNOWLEDGEMENT

The authors thank Dr Helen Yeh for writing and editorial support. This article was supported by Merck & Co. Inc., Whitehouse Station, NJ, USA.

REFERENCES

1 Pearson TA, Laurora I, Chu H, Kofenk S. The lipid treatment assessment project (L-TAP): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Arch Intern Med* 2000; **160**: 459–67.

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

3 García Ruiz FJ, Marín Ibáñez A, Pérez Jiménez F et al. and the REALITY Study Group. Current lipid management and low cholesterol goal attainment in common daily practice in Spain. The REALITY Study. *Pharmacoeconomics* 2004; **22** (Suppl. 3): 1–14.

4 Goettsch WG, Yin DD, Alemao E, Klungel OH, Stalenhoef AF, Herings RM. Statins are less effective in common daily practice

among patients with hypercholesterolemia: the REALITY-PHARMO study. *Curr Med Res Opin* 2004; **20**: 1025–33.
5 Krobot KJ, Yin DD, Alemao E, Steinhagen-Thiessen E. Real-world effectiveness of lipid-lowering therapy in male and female outpatients with CHD: relation to pre-treatment LDL-cholesterol, pre-treatment CHD risk, and other factors. *Eur J Cardiovasc Prev Rehabil* 2005; **1**: 37–45.
6 Feldman T, Koren M, Insull W Jr. 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.
7 Ballantyne CM, Blazing MA, King TR, Brady WE, Palmisano J. Efficacy and safety of ezetimibe co-administered with simvastatin compared with atorvastatin in adults with hypercholesterolemia. *Am J Cardiol* 2004; **93**: 1487–94.
8 Goldberg AC, Sapre A, Liu J, Capece R, Mitchel YB and the Ezetimibe Study Group. 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.
9 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.
10 Gagné 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.
11 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.
12 Knopp RH. Drug treatment of lipid disorders. *New Engl J Med* 1999; **341**: 498–511.
13 The Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary artery disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; **344**: 1383–9.
14 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomized placebo-controlled trial. *Lancet* 2002; **360**: 7–22.
15 Van Heek M, France C, Compton DS et al. In vivo metabolism-based discovery of a potent cholesterol absorption inhibitor, SCH58235, in the rat and rhesus monkey through the identification of the active metabolites of SCH48461. *J Pharmacol Exp Ther* 1997; **283**: 157–63.
16 Van Heek M, Farley C, Compton DS, Hoos L, Davis HR. Ezetimibe selectively inhibits intestinal cholesterol absorption in rodents in the presence and absence of exocrine pancreatic function. *Br J Pharmacol* 2001; **134**: 409–17.
17 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.
18 Bays HE, Moore PB, Drebhol 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.
19 Davis HR, Pula KK, Alton KB, Burrier RE, Watkins RW. The synergistic hypercholesterolemic activity of the potent cholesterol absorption inhibitor, ezetimibe, in combination with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in dogs. *Metabolism* 2001; **50**: 1234–41.
20 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.
21 Nissen SE, Tuzcu EM, Schoenhagen P et al. for the REVERSAL investigators. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis. *JAMA* 2004; **291**: 1071–80.
22 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.
23 Gaudiani L, Lewin A, Meneghini L et al. Efficacy and safety of ezetimibe coadministered with simvastatin versus simvastatin alone in thiazolidinedione-treated patients with type 2 diabetes mellitus. Poster (1084) presented at the American College of Cardiology annual meeting, New Orleans, LA, USA, 2004.
24 McKenney J, Insull W, Lewin A et al. LDL-cholesterol goal attainment among patients with diabetes mellitus treated with ezetimibe plus simvastatin coadministration versus simvastatin alone. Poster (944-P) presented at the 64th Scientific Sessions of the American Diabetic Association, Orlando, FL, USA, 2004.
25 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.
26 Fux R, Mörike K, Gundel UF, Hartmann R, Gleiter CH. Ezetimibe and statin associated myopathy. *Ann Intern Med* 2004; **140**: 671–2.
27 Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; **285**: 2486–97.
28 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.
29 Ballantyne CM, Lipka LJ, Sager PT et al. Long-term safety and tolerability profile of ezetimibe and atorvastatin co-administration therapy in patients with primary hypercholesterolemia. *Int J Clin Pract* 2004; **58**: 633–58.
30 Gagné 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.
31 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.
32 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.
33 Kosoglou T, Statkevich P, Yang B et al. Pharmacodynamic interaction between ezetimibe and rosuvastatin. *Curr Med Res Opin* 2004; **20**: 1185–95.
34 Davidson MH, Ballantyne CM, Kerzner B, for the Ezetimibe Study Group. 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.
35 Knopp RH, Dujovne CA, Le Beaut A 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.
36 Wang J, Williams CM, Hegele RA. Compund heterozygosity for two non-synonymous polymorphisms in NPC1L1 in a non-responder to ezetimibe. *Clin Genet* 2005; **67**: 175–7.
37 Wierzbicki AS, Doherty E, Lumb PJ, Chik G, Crook MA. Efficacy of ezetimibe in patients with statin-resistant and statin-intolerant familial hyperlipidaemias. *Curr Med Res Opin* 2005; **21**: 333–8.
38 Stein E. The lower the better? Reviewing the evidence for more aggressive cholesterol reduction and goal attainment. *Atheroscler Suppl* 2002; **2**: 19–25.
39 Pedersen TR, Olsson AG, Færgeman O et al. Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). *Circulation* 1998; **97**: 1453–60.
40 Smilde TJ, van Wissen S, Wollersheim H, Trip MD, Kastelein JJ, Stalenhoef AF. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomized, double-blind trial. *Lancet* 2001; **357**: 577–81.
41 Schwartz GG, Olsson AG, Ezekowitz MD et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001; **285**: 1711–8.
42 Cannon CP, Braunwald E, McCabe CH et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004; **350**: 1495–504.
43 De Lemos JA, Blazing MA, Wiviott SD et al. Early intensive vs. a delayed conservative simvastatin strategy in patients with acute coronary syndromes. *JAMA* 2004; **292**: 1307–16.
44 O'Keefe JH, Cordain L, Harris WH, Moe RM, Vogel R. Optimal low-density lipoprotein is 50–70 mg/dl. *J Am Coll Cardiol* 2004; **43**: 2142–6.
45 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.
46 Williams B, Poulter NR, Brown MJ et al. Guidelines for management of hypertension: report of the fourth Working Party of the British Hypertension Society, 2004-BHS IV. *J Hum Hypertens* 2004; **18**: 139–85.
47 Strandberg TE, Pyörälä K, Cook TJ et al. Mortality and incidence of cancer during 10-year follow-up of the Scandinavian Simvastatin Survival Study (4S). *Lancet* 2004; **364**: 771–7.
48 Davis 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.
49 Baigent C, Landry M. Study of Heart and Renal Protection (SHARP). *Kidney Int Suppl* 2003; **84**: S207–10.
50 Kastelein JP, Sager PT, de Groot E, Veltri EP. The ENHANCE Trial: Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression. Poster (4P-1212) presented at the International Symposium on Atherosclerosis, Kyoto, Japan, 2003.
51 Rossebø A, Pedersen T, Skjærpe T et al. for the SEAS Steering Committee. Design of the Simvastatin Ezetimibe Aortic Stenosis (SEAS) Study. Poster (3P-0970) presented at the International Symposium on Atherosclerosis, Kyoto, Japan, 2003.

Paper received January 2005, accepted October 2005