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The ezetimibe controversy – can this be resolved by comparing the clinical trials with simvastatin and ezetimibe alone and together?

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Introduction: The primary target in the treatment of hypercholesterolemia is often to lower low-density lipoprotein (LDL) cholesterol, rather than improve clinical outcomes. Despite the wide use of lipid-modifying drugs, considerable cardiovascular mortality and morbidity remains with this disease. Hypercholesterolemia plays a key role in the development and progression of atherosclerosis and can lead to cardiac heart disease.
Areas covered: The purpose of this review is to determine whether ezetimibe has proven clinical benefits; it discusses the clinical trials of simvastatin and ezetimibe alone and in combination.
Expert opinion: Simvastatin has been clearly shown to decrease LDL-cholesterol, which is associated with the slowing of atherosclerosis and a reduction in cardiovascular morbidity and mortality. Ezetimibe alone or in the presence of simvastatin lowers LDL-cholesterol. However, ezetimibe alone or in the presence of simvastatin has not been shown to have any irrefutable beneficial effects on atherosclerosis or cardiovascular morbidity and mortality. Thus, until/unless the use of ezetimibe is clearly shown to improve clinical outcomes, its use should be largely restricted to clinical trials investigating clinical outcomes and should not be used routinely in everyday practice.

Keywords: cardiovascular disease, clinical outcomes, ezetimibe, LDL-cholesterol, simvastatin

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1. Introduction

Despite the wide use of lipid-modifying drugs, considerable cardiovascular mortality and morbidity remains. Hypercholesterolemia has a key role in the development and progression of atherosclerosis, and leads to cardiac heart disease. The primary target in the treatment of hypercholesterolemia is lowering low-density lipoprotein (LDL) cholesterol optimally, which according to the National Cholesterol Education ATP III guidelines is < 100 mg/dl (2.59 mmol/l) [1]. The medicines most commonly used initially to lower LDL-cholesterol are the statins [1]. If the statins are unsuccessful at achieving the 2.59 mmol level of LDL-cholesterol, one approach is to increase the dose of the statin, but this also increases the likelihood of adverse effects with the statins [2]. Another problem with increasing the dose of the statin is, although it further decreases the levels of LDL-cholesterol, this is often not enough to reach optimal levels of LDL-cholesterol [3].

An alternative approach, when statins do not lower LDL-cholesterol optimally, is to add another LDL-cholesterol-lowering medicine to the statin, and one that is increasingly used is ezetimibe. Ezetimibe inhibits the Niemann–Pick-like 1 enterocyte receptor to inhibit the absorption of cholesterol, and this leads to the lowering of plasma LDL-cholesterol levels [4].

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Article highlights.

- It is well established that simvastatin lowers low-density lipoprotein (LDL)-cholesterol, which is associated with the slowing of atherosclerosis and reduction in cardiovascular morbidity and mortality.
- Ezetimibe alone or in the presence of simvastatin lowers LDL-cholesterol, but may increase the atherogenic small-dense LDL-cholesterol.
- Ezetimibe alone or in the presence of simvastatin has not been shown to slow atherosclerosis, and may even increase it.
- Ezetimibe alone or in the presence of simvastatin has not been shown to have an effect on cardiovascular morbidity and mortality.
- IMPROVE-IT has been set up to determine the clinical outcomes with ezetimibe in the presence of simvastatin, but the results of IMPROVE-IT will not be known till 2015, and because of the large number of primary end points, may go on for longer, or be inconclusive.
- Until/unless ezetimibe is shown to improve clinical outcomes, its use should be largely restricted to clinical trials investigating clinical outcomes and should not be used routinely in everyday practice.

This box summarises key points contained in the article.

When new lipid-lowering drugs are being developed, as was the case with ezetimibe, their ability to lower LDL-cholesterol is initially investigated, as a surrogate for clinical outcomes. Ezetimibe lowers LDL-cholesterol. Many studies seem to accept LDL-cholesterol lowering as having a direct relationship to clinical benefit. The evidence for this comes from surgical and medicinal studies. In the surgical study, partial ileal bypass was shown to reduce LDL-cholesterol levels, and cardiovascular mortality and morbidity in subject who had experienced a heart attack [5]. The medicinal evidence for this comes predominantly from studies with statins, the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, but has also been shown for the sequestrant cholestyramine resin [6]. It seems to have been assumed by many that by lowering LDL-cholesterol, ezetimibe will have a positive effect on clinical outcomes, and this assumption underlies the increasing use of ezetimibe, especially in combination with simvastatin (e.g., [7,8]). However, to confirm that lowering LDL-cholesterol translates into reduced cardiovascular events, clinical outcome studies with individual medicines are needed.

This review challenges the assumption that lowering LDL-cholesterol with ezetimibe alone or in combination with simvastatin leads to improved clinical outcomes. In the first part of the review, the compelling evidence that lowering LDL-cholesterol with simvastatin is associated with improved clinical outcomes is discussed. LDL-cholesterol lowering and clinical outcome studies have been undertaken with ezetimibe but these do not show a clear association between lowering LDL-cholesterol and improved clinical outcomes, and the studies with ezetimibe alone or in combination with simvastatin are discussed in the second and third part of the review, respectively. Given that there is no clear-cut evidence that ezetimibe alone has a beneficial effect on clinical outcomes in hypercholesterolemia, the author argues in the expert opinion section that ezetimibe should not be used widely until clinical outcome studies have demonstrated benefits alone, or in the presence of simvastatin.

2. Simvastatin and clinical end points

2.1 High-risk subjects

The effects of simvastatin on LDL-cholesterol levels and clinical outcomes are summarised in **Table 1**. The Scandinavian Simvastatin Survival Study (4S) was the first study to show that cholesterol lowering with a statin decreased total and cardiovascular mortality [9]. The subjects enrolled had coronary artery disease, and a mean LDL-cholesterol of 4.86 mmol/l [9], which is a high average. The reduction in major coronary events in 4S was highly correlated with on-treatment levels and changes from baseline in total and LDL-cholesterol. There was less of a correlation with high-density lipoprotein (HDL)-cholesterol and no clear relationship with triglycerides [10].

Simvastatin yields continued survival benefit. Adding the deaths in a 2-year follow-up period to the 4S, to those occurring during the original trial, the total was 353 (15.9%) and 256 (11.5%) deaths in the groups originally randomised to placebo and simvastatin, respectively [11].

Post hoc analysis of 4S showed that simvastatin reduced the risk of the combined end point of stroke and transient ischaemic attack and also reduced the risk of new or worsening intermittent claudication by 38% (**Table 1**) [12]. Subjects with diabetes mellitus have a marked increase in coronary heart disease events relative to those without diabetes, and using the 4S database, simvastatin has been shown to improve this prognosis (**Table 1**) [13]. In subjects with mild chronic renal insufficiency, simvastatin was also beneficial on cardiovascular outcomes (**Table 1**) [14]. In 4S, there were 409 subjects with moderate chronic renal insufficiency, and in these subjects to odds of receiving a $\geq$ 25% reduction in glomerular filtration rate were lower with simvastatin (2.5%) than with placebo (6.2%) [15].

Many of the benefits initially observed in the 4S trial were confirmed in the MRC/BHF Heart Protection Study over 5 years (**Table 1**) [16]. As this was a very large study, it was able to confirm the benefits of simvastatin (40 mg/day) on subcategories (e.g., patients without coronary disease but with cerebrovascular or peripheral artery disease, and even those with LDL-cholesterol below 3.00 mmol/l). It was concluded that the benefit of simvastatin depended chiefly on the individuals' overall risk of major vascular events, rather than on blood lipid concentrations alone [16]. Subsequently, in the Heart Protection Study, simvastatin was shown to reduce ischaemic, but not haemorrhagic stroke, and to reduce transient ischaemic events (**Table 1** [17]). Simvastatin also decreased major coronary events to a greater extent in subjects in the Heart Protection Study with diabetes than without diabetes [18], and decreased the rate of first peripheral event

Table 1. LDL-cholesterol lowering with simvastatin and clinical outcomes.

Trial with simvastatin	LDL-cholesterol lowering	Clinical outcomes	Ref.
The 4S trial: 4444 subjects with coronary artery disease (previous myocardial infarction or in 20% angina); simvastatin 20 – 40 mg, vs placebo for 5.4 years	From 4.84 mmol/l by 35%	Reduced death (by 33%), cardiovascular death (40%), risk of undergoing revascularisation procedures (34%)	[9]
4S		Reduced the combined end point of stroke and transient ischaemic attack (28%), and of intermittent claudication (36%)	[12]
Subjects in 4S with normal and impaired fasting glucose, and diabetes		Subgroup analysis showed reduced major coronary events, and revascularisations in diabetes, and reduced coronary deaths, major coronary events, revascularisations in impaired fasting glucose and diabetes	[13]
2314 subjects in 4S with mild chronic renal insufficiency		Reduced all-cause mortality, rates of major coronary events, and coronary revascularisation	[14]
MRC/BHF Heart Protection Study: 20,536 high-risk subjects; simvastatin 40 mg vs placebo for 5 years	From 3.4 mmol/l by 1.3 (38%), 0.9 (27%) and 0.7 mmol (21%), after 1, 3 and 5 years, respectively	Reduced all-cause mortality (14%), coronary death rate (18%), non-fatal myocardial infarction (38%), non-fatal or fatal stroke (25%), any revascularisation process (22%)	[16]
MRC/BHF Heart Protection Study		Reduction is ischaemic (28%) but not haemorrhagic stroke, and reduction in transient ischaemic events (17%)	[17]
MRC/BHF Heart Protection Study: Subjects with diabetes vs those without		Reductions in the first event rate for major coronary events, for strokes, and for revascularisations	[18]
MRC/BHF Heart Protection Study: subjects with peripheral arterial disease vs those without		Reduction in first peripheral vascular event	[19]

LDL: Low-density lipoprotein.

to a greater extent in those with peripheral vascular disease than without [19] (**Table 1**). In subjects with peripheral arterial disease, simvastatin also increases the treadmill time to the onset of intermittent claudication [20].

2.2 Comparing simvastatin doses

Early intensive simvastatin (40 mg for a month, followed by 80 mg) and delayed conservative simvastatin treatment (placebo for 4 months, followed by 20 mg) has been compared in 4497 subjects with acute coronary syndromes (non-ST-elevation acute coronary syndrome or ST-elevation myocardial infarction). The primary end point was a composite of cardiovascular death, non-fatal myocardial infarction, readmission for acute coronary syndrome and stroke, and after 1 year, there was no difference between the early intensive (14.4%), and delayed conservative simvastatin treatment (16.7%). Individual item analysis showed a significant ($p = 0.5$) lower level of cardiovascular death with the intensive than conservative treatment [21].

Recently, a low dose of simvastatin, 20 mg, has been compared with a high dose, 80 mg, in 12,064 subjects who had survived a myocardial infarction by the SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) collaborative group [22]. After 6.7 years, there was no significant difference in major vascular events (coronary death, myocardial infarction or coronary revascularisation) between the two doses [22]. There was also no significant difference between the two doses of simvastatin on the incidence of stroke, non-fatal stroke, transient ischaemic attacks or admission to hospital for stable or unstable angina [22]. As 40 mg is the more usual standard dose of simvastatin, it is not clear, why 20 mg simvastatin was chosen in this study. The finding of this study with low- and high-dose simvastatin differs from the results obtained by

the Cholesterol Treatment Trials' (CTT) Collaborative, when they compared low- and high-dose/potency statins. One possible reason for this is that the difference in LDL lowering was smaller (0.35 mmol) with low- and high-dose simvastatin in SEARCH than the 0.51 mmol with intensive versus less intensive treatment with statins [23].

2.3 Comparing simvastatin with other statins

Simvastatin has been compared with pravastatin and atorvastatin, each at their standard dose, and it was shown that there was no difference in reducing fatal coronary heart disease, non-fatal myocardial infarction and fatal and non-fatal stroke [24].

Subjects with heterozygous familial hypercholesterolemia are at increased risk of coronary artery disease. Simvastatin (40 mg) was compared with atorvastatin (80 mg) in 325 subjects with familial hypercholesterolemia in the ASAP trial. LDL-cholesterol was lowered more with atorvastatin than simvastatin. Over 2 years, the intima media thickness of the carotid artery increased in the simvastatin group, but decreased in the atorvastatin group. The change on intima media thickness correlated with the percentage LDL-cholesterol lowering [25].

Simvastatin (20 mg) was compared with high-dose atorvastatin (80 mg) in 8888 subjects after myocardial infarction in the IDEAL (Incremental Decrease in End points through Aggressive Lipid lowering) study. After 24 weeks of follow-up, 21% in the simvastatin group had their dose increased to 40 mg. The primary outcome was major coronary events (coronary death, non-fatal myocardial infarction, cardiac arrest with resuscitation), and this was not significantly different ($p = 0.07$) for the simvastatin and atorvastatin groups. However, there was an added benefit with atorvastatin at reducing non-fatal myocardial infarction, and coronary revascularisation [26].

In 2005, the CTT Collaboration combined 14 randomised trials with statins including simvastatin, and concluded that statin therapy reduced the 5-year incidence of major coronary events, coronary revascularisation and stroke by about one-fifth per mmol/l reduction in LDL-cholesterol [27]. There were similar findings in 2009, when seven more statin trials were included [28].

In 2010, the CTT Collaboration, used meta-analysis to compare standard statin therapy (e.g., 20 – 40 mg simvastatin) to regimens involving higher doses, or the more potent statins (e.g., 40 – 80 mg atorvastatin, 10 – 20 mg rosuvastatin). The meta-analysis involved 170,000 participants from 26 randomised trials. In this study, the lowering of LDL-cholesterol was 0.51 mmol/l more, with the intensive, than less intensive treatment. In this study, the more intensive therapy significantly decreased the major vascular events (coronary death, non-fatal myocardial infarction, coronary revascularisation and ischaemic stroke) when they were combined or assessed individually [23].

2.4 Simvastatin in vascular remodelling

The Multicenter Anti-Atheroma Study (MAAS) of 381 patients with coronary artery disease showed that simvastatin slowed the progression of diffuse and focal coronary atherosclerosis. There were also less coronary angioplasty or revascularizations in the simvastatin than placebo group [29].

In the Coronary Intervention Study (CIS), the effect of a higher dose of simvastatin (40 mg/day) on coronary angiography was evaluated over 2.3 years [30]. In this group of 254 men with hypercholesterolemia and coronary artery disease, there was less of a decrease in coronary diameter in the simvastatin than placebo group [30]. Simvastatin has also been shown to decrease, and then cause regression, in atherosclerotic lesions in aortic or carotid artery plaques in subjects with asymptomatic hypercholesterolemia [31,32]. In subjects with familial hypercholesterolemia, simvastatin 80 mg reduced the primary end point, which was the change in the combined intima–media thickening of the carotid and femoral artery [33].

3. Ezetimibe alone, LDL-cholesterol and clinical end points

In 243 subjects with primary hypercholesterolemia (LDL-cholesterol, ~ 4.40 mmol/l), ezetimibe at 0.25, 1, 5 and 10 mg, reduced LDL-cholesterol in a dose-dependent manner from 9.9 to 18.7% over 12 weeks [34]. Larger studies and meta-analysis have confirmed the ability of ezetimibe 10 mg to lower LDL-cholesterol by ~ 18% [35-37].

There have been few studies of ezetimibe alone on clinical end points. One reason for this may be that a lowering of LDL-cholesterol by 18% (~ 0.79 mmol/l) with ezetimibe 10 mg alone may not have a large effect on clinical outcomes. In subjects with chronic heart failure, the effects of ezetimibe 10 mg have been compared with simvastatin 10 mg, over 4 weeks on flow-dependent dilation of the radial artery [38]. Both ezetimibe and simvastatin lowered LDL-cholesterol by ~ 15%, but only simvastatin improved the dilation [38]. It has been suggested that the ability of simvastatin to improve endothelium function was due to a pleiotropic effect of simvastatin, that is, not LDL-cholesterol lowering [38]. Another possibility is that the benefit of ezetimibe on lowering LDL-cholesterol on endothelium function is offset by another action, but the benefit of simvastatin on lowering LDL-cholesterol presents as improved endothelium function.

Ezetimibe 10 mg has been compared with niacin in subjects who had coronary heart disease or a coronary heart disease risk, who are taking statins in the ARBITER 6-HALTS (Arterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol 6-HDL and LDL Treatment Strategies; **Table 2**) [39]. The primary end point was the between-group change in mean carotid intima–media thickness after 14 months, and there was little difference in the carotid thickness with ezetimibe, but a significant reduction with niacin [39]. The author postulated that actions, other than decreasing LDL-cholesterol, counter the beneficial effect that would be expected with LDL-cholesterol lowering with ezetimibe [39]. The final results of the ARBITER 6-HALTS

Table 2. LDL-cholesterol lowering with ezetimibe and clinical outcomes.

Trial with ezetimibe	LDL-cholesterol lowering	Clinical outcomes	Ref.
ARBITER 6-HALTS trial: 208 subjects with coronary artery disease or risk, treated with atorvastatin or simvastatin randomised to ezetimibe 10 mg or niacin	From 2.13 mmol/l by ~ 28% with ezetimibe and ~ 17% by niacin	Ezetimibe had no effect on carotid thickness, which was reduced by niacin, and more cardiovascular adverse effects with ezetimibe than niacin	[39]
ENHANCE study: 720 subjects with familial hypercholesterolemia treated with simvastatin 80 mg or simvastatin 80 mg/ ezetimibe 10 mg	After 24 months from 8.22 to 4.99 mmol/l with simvastatin and from 8.25 to 4.59 mmol/l with simvastatin/ ezetimibe	Intima–media thickness of coronary artery increased similarly in both groups	[46]
VYCTOR study: 90 subjects with high cardiovascular risk, compared the effects of simvastatin 40/80 mg (40 mg, 45%; 80 mg, 55%) alone with simvastatin 20/40 (20 mg, 83%; 40 mg, 17%)	LDL-cholesterol was lowered from 3.37 to 1.17 mmol/l (2.20 mmol/l, 65%) by simvastatin, and from 3.37 to 1.14 mmol/l (2.13 mmol/l, 66%) by the combination of simvastatin and ezetimibe	Carotid intima thickness was reduced by 30% with simvastatin alone, and by 25% with the combination, and this was not significantly different	[49]
SEAS: 1873 subjects with mild-to-moderate, asymptomatic aortic stenosis, and the subjects were given either simvastatin 40 mg and ezetimibe 10 mg or placebo	With these doses of simvastatin/ ezetimibe, there was 61.3% decrease in the levels of LDL-cholesterol	After a follow-up of 52.2 months, the primary outcome (composite of major cardiovascular events) had occurred in 333 subjects in the simvastatin/ ezetimibe group (35.3%) and 355 subjects in the placebo group (38.2%). Aortic-valve replacement was performed by a similar percentage in the simvastatin/ ezetimibe and placebo groups (28.3 vs 29.9%)	[54]
SHARP: Initially, 9270 subjects with moderate kidney disease were randomised to placebo, simvastatin and simvastatin and ezetimibe, but after 1 year 1000 subjects randomised to simvastatin, were re-randomised to simvastatin/ezetimibe or placebo	The baseline levels of LDL-cholesterol were ~ 2.77 mmol/l, and were lowered by ~ 1 mmol/l by the combination of simvastatin and ezetimibe	The primary end point was the reduction in major atherosclerotic events (coronary events, non-haemorrhagic stroke, revascularisation procedure) and this occurred in 528 of the 4650 subjects taking simvastatin/ezetimibe (11.3%), which was less than 619 of 4620 subjects in the placebo group, 13.4%	[56]

study have been reported and these confirm the findings with the 208 subjects [40].

4. Simvastatin and ezetimibe in combination

4.1 LDL-cholesterol

Simvastatin and ezetimibe have different mechanism of actions, and this may explain why, in combination, they have an additive effect on LDL-cholesterol. In subjects with primary hypercholesterolemia, and LDL-cholesterol of 4.60 mmol/l, simvastatin (combined for 10, 20, 40 and 80 mg) lowered LDL-cholesterol by about 32%, and in the presence of simvastatin (combined doses), ezetimibe lowered LDL-cholesterol by a further 14% [41]. In another study in subjects with primary hypercholesterolemia, and LDL-cholesterol of 4.61 mmol/l, simvastatin (combined for 10, 20, 40 and 80 mg) lowered LDL-cholesterol by 42%, ezetimibe by 22% and the combination of simvastatin and ezetimibe by 56% [42]. Pooled data from 27 clinical trials, showed that when ezetimibe 10 mg was added to a statin (simvastatin, lovastatin, pravastatin, atorvastatin, rosuvastatin), there was a 16.1% reduction in the levels of LDL-cholesterol [42]. The reduction with the addition of ezetimibe was slightly greater in subjects with diabetes, 17.4%, than in subjects without diabetes [42].

The effect of combining ezetimibe with simvastatin is more effective at decreasing LDL-cholesterol than increasing the dose of simvastatin. Thus, in subjects with hypercholesterolemia, simvastatin 10, 20, 40 and 80 mg lowered LDL-cholesterol by 27, 37, 38 and 45%, whereas adding ezetimibe 10 mg to these doses lowered LDL-cholesterol by 46, 46,

56 and 58%, respectively [41]. Another study in subjects with hypercholesterolemia showed similar results, with simvastatin 10, 20, 40 and 80 mg lowering LDL-cholesterol by 33, 34, 41 and 48%, whereas adding ezetimibe 10 mg to these doses lowered LDL-cholesterol by 45, 52, 55 and 60%, respectively [43]. Also, combining ezetimibe and simvastatin was more effective at lowering LDL-cholesterol than increasing the dose of atorvastatin [44] or rosuvastatin [45].

4.2 Clinical outcomes

The ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) study was in subjects with familial hypercholesterolemia, and compared a high dose of simvastatin 80 mg with simvastatin 80 mg with ezetimibe 10 mg (**Table 2**). The primary outcome measure in ENHANCE was intima–media thickness of the carotid artery, and this increased in both groups, and was not significantly different with the addition of ezetimibe. One of the possibilities considered for this result was that, LDL lowering by a drug other than a statin, that is, ezetimibe, was not associated with reduction in the progression of atherosclerosis, as there were differences in the mechanisms of action of ezetimibe and simvastatin, for example, the pleiotropic effects of the statins [46]. The baseline intima–media thickness of the carotid artery was low in ENHANCE. Thus, another suggestion has been that prior use of statins by subjects in ENHANCE had lowered the thickness of the carotid artery, and that further treatment with either simvastatin alone or simvastatin with ezetimibe had no further effect [47].

In another study in subjects with familial hypercholesterolemia, the combination of simvastatin and ezetimibe have been compared in two groups of subjects; those with a history of myocardial infarction and those with carotid atherosclerosis plaques but no history of cardiovascular events [48]. As this study does not have a group with simvastatin or ezetimibe treatment alone, it is not possible to assess the effect of ezetimibe alone. What the study does show is that the combination of simvastatin and ezetimibe lowers LDL-cholesterol and reduces carotid intima–media thickness in these subjects [48], but it does not clarify whether ezetimibe alone reduces carotid intima–media thickness or contributes to the effect when used in combination with simvastatin.

The VYCTOR (Vytorin on Carotid Intima–Media Thickness and Overall Arterial Rigidity) study compared the effects of simvastatin alone with simvastatin and ezetimibe 10 mg on carotid intima–media thickening (**Table 2**) [49]. Carotid intima thickness was reduced similarly by simvastatin alone, and the combination [49]. The authors of VYCTOR study suggest that the unusually high lowering of the LDL-cholesterol with simvastatin alone may be due to good adherence by the subjects in this trial [49], but this does not explain why there was not an additive effect between simvastatin and ezetimibe. They also suggest that the difference between ENHANCE and VYCTOR are due to there being definite intima–media thickening at baseline in VYCTOR but not ENHANCE [49]. They conclude that the dual therapy has a beneficial effect on carotid arteries [49], but the author of this review fails to understand this conclusion. A possibility not raised by the authors of VYCTOR study was that the LDL lowering with simvastatin alone was large enough to explain the results in both groups, and that the addition of ezetimibe did not add to this.

SANDS (Stop Atherosclerosis in Native Diabetic Study) was set up to compare aggressive and standard treatment for lowering LDL-cholesterol on carotid artery intima–media thickness in subjects with diabetes [50]. SANDS used a statin to reduce LDL-cholesterol, and if the statin alone did not reduce the LDL-cholesterol to the required level, ezetimibe was added to the treatment [50]. Thus, although SANDS was not set up to compare ezetimibe/simvastatin with simvastatin alone, the data were available for extraction. On extraction, it was shown that there was a similar reduction in LDL-cholesterol levels and carotid intima–media thickness in the simvastatin and simvastatin/ezetimibe group [51]. One of the limitations of this study was that there were only 69 subjects taking statins/ezetimibe, compared with 154 subjects controlled by statins alone in the aggressive group [51]. The author of this review suggests that as in SANDS, the carotid intima–media was thicker (0.81 mm) than in ENHANCE, where the baseline intima–media thickness was 0.69 mm, there was a greater chance of decreasing intimal thinkness [51]. However, another interpretation is that the reduction in carotid thickness in both groups was due to the statin alone.

The study of West *et al.* is the only clinical outcome study with ezetimibe to have a clear-cut result for ezetimibe alone, and it is a detrimental effect; ezetimibe alone leads to the progression of atherosclerosis in subjects with peripheral arterial atherosclerosis [53]. In this study, 67 subjects with peripheral arterial atherosclerosis were treated with simvastatin 40 mg, ezetimibe or the combination. Atherosclerotic plaque volume in the superficial femoral artery did not change in the simvastatin or the simvastatin/ezetimibe group, but increased in the ezetimibe group [53].

In the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) trial, it was also difficult to determine the effect of ezetimibe alone, as the effects of combined simvastatin/ezetimibe were compared with placebo (not simvastatin alone) (**Table 2**) [54]. The background to SEAS was that lipid-lowering treatment might prevent the progression of aortic-valve stenosis and reduce the need for aortic valve replacement, but lipid lowering with a combination of simvastatin and ezetimibe did not do this [54]. In SEAS, the primary outcome (composite of major cardiovascular events) and aortic valve replacement occurred in similar percentage in both groups [54]. When the subjects in SEAS were divided into tertiles on the basis of severity of asymptomatic aortic stenosis, there was still no difference in aortic valve events between those treated with simvastatin/ezetimibe and placebo [55]. In the original SEAS, the ischemic events (non-fatal myocardial infarction, coronary-artery bypass grafting, percutaneous coronary intervention, hospitalisation

for unstable angina, non-haemorrhagic stroke and death from cardiovascular causes) occurred less often the simvastatin/ezetimibe group (15.7%) than the placebo group (20.1%), and this difference was mainly due to a decrease in coronary-artery bypass grafting (10.8 – 7.3%) [54]. In SEAS, cancer occurred more often in the simvastatin/ezetimibe group (105 subjects) than in the placebo group (70 subjects) [54]. As cancer has not been reported as an adverse effect with simvastatin, this suggests that the increased rate of cancer in SEAS may be due to ezetimibe, and this is discussed further in the commentary below.

In the recently published SHARP (Study of Heart and Renal Protection), simvastatin/ezetimibe was again compared with placebo, this time in subjects with moderate-to-severe kidney disease (**Table 2**). The rationale for using the combination of simvastatin 20 mg with ezetimibe 10 mg is that high-dose statins cause myopathy, particularly in subjects with impaired renal function. The primary end point was the reduction in major atherosclerotic events and this occurred in less subjects taking simvastatin/ezetimibe than placebo. This reduction was due to there being less ischaemic strokes and coronary revascularisation with simvastatin/ezetimibe combination, compared with placebo [55].

The authors of the SHARP study in their discussion refer to the CTT Collaboration, which showed that lowering LDL-cholesterol by 1 mmol/l with statins was associated with a 20% reduction in the risk of myocardial infarction or coronary death, stroke or coronary vascularisation [23]. In SHARP, ezetimibe combined with simvastatin lowered LDL-cholesterol by 0.85 mmol/l, and caused a 17% decrease in major atherosclerotic events, which was considered to be consistent with the results with statins alone [56]. The authors of the SHARP study claim that adding ezetimibe to simvastatin is equivalent of three doublings of the dose of statin on the basis of the study of Davison *et al*. 2002 [41].

A retrospective cohort study has suggested that in subjects discharged after hospitalisation for acute coronary syndromes, the administration of ezetimibe with simvastatin may reduce the rehospitalisation due to acute coronary syndromes, percutaneous transluminal coronary angioplasty and revascularisation, compared with statins alone [52]. However, the authors of the SHARP study acknowledge that there are lots of limitations to their study, including the non-matching doses of statins between the groups with a lower average dose of statin in the statin group than in the combination group, lack of information on baseline LDL-cholesterol levels and the lack of information on deaths [52].

5. Expert opinion

5.1 Simvastatin

In reviewing simvastatin (Section 2), it is clear that simvastatin lowers LDL-cholesterol, and this lowering is associated with beneficial clinical cardiovascular outcomes. Thus, in subjects with coronary artery disease, simvastatin reduced cardiovascular mortality and morbidity. However, there is some controversy about whether increasing the lowering of LDL-cholesterol by increasing the dose of statin, increases the benefit in outcomes. Thus, this has not been clearly shown with simvastatin alone, but has been shown by comparing simvastatin with the higher potency statins at higher doses.

5.2 Effect of ezetimibe alone on LDL-cholesterol and clinical outcomes

In reviewing the effect of ezetimibe on LDL-cholesterol (Section 3), it is clear that ezetimibe 10 mg alone only has a modest ability to lower LDL-cholesterol. As per SA Doggrell's knowledge, the highest dose of ezetimibe which has been tested in humans is 10 mg, which is well tolerated, and has not been shown to give a maximal effect at lowering LDL-cholesterol. If there is a dose-related effect of ezetimibe on LDL-cholesterol, a higher dose (say 15 or 20 mg) may give a larger decrease in LDL-cholesterol, and this may have a beneficial effect on clinical outcomes, but this has not been tested to date.

Many seem to have assumed that the modest ability of ezetimibe 10 mg on LDL-cholesterol may not be large enough for ezetimibe alone to have a beneficial effect on clinical outcomes in coronary disease. However, this has not been tested, and should be. Ezetimibe has a similar ability to lower LDL-cholesterol in the presence of simvastatin, and it is has been postulated that this will lead to an increase in clinical improvement. This may be due to the ATP III guidelines, that suggest that the greater the reduction in LDL-cholesterol, the greater the reduction in cardiovascular risk [1]. The experimental evidence supporting this is mainly from a meta-analysis comparing the high potency statins with standard treatment, and showing greater reductions in lowering LDL-cholesterol were associated with greater beneficial cardiovascular outcomes [23]. However, this has not been observed in the SEARCH clinical trial by increasing the dose of simvastatin alone [22], or conclusively by increasing the lowering of LDL-cholesterol by adding ezetimibe to a statin.

5.3 Effect of ezetimibe in the presence of simvastatin

According to SA Doggrell's understanding of clinical trials, it is not ethical to deprive subjects with medical conditions of agents that have a proven beneficial activity in that medical condition. The statins have proven ability to reduce cardiovascular mortality and morbidity in subjects with coronary artery disease. Thus, subjects with proven coronary artery disease should receive a statin, and when a new agent is tested, it should be tested in the presence of the statin. Thus, in coronary artery disease, ezetimibe should be compared with subjects who are taking a statin. In ENHANCE, ezetimibe was compared with placebo in subjects with familial hypercholesterolemia, and shown to have no effect on the intima–media thickness of the carotid artery [46]. In the commentary published with EHHANCE, Brown and Taylor pointed out the similar population and methodology between ENHANCE and ASAP [57]. Whereas a decrease of intima–media thickness was observed

with atorvastatin 80 mg in ASAP [25], for the same lowering of LDL-cholesterol with simvastatin combined with ezetimibe in ENHANCE, there was an increased intima–media thickness of the carotid artery [57]. Brown and Taylor raised three possibilities to explain this; first, carotid intima–media was more advanced at baseline in ASAP [57]. Second, the subjects had a longer history of statin treatment in ENHANCE than ASAP [57]. Third, atorvastatin was used in ASAP whereas simvastatin/ezetimibe was used in ENHANCE [57].

As a consequence of the lack of effect on intima–media thickening with ezetimibe in ENHANCE, Brown and Taylor suggested the following approach to treatment: first achieve the levels of LDL- and HDL-cholesterol with the statins plus drugs that have been shown to have clinical benefits when added to statins, that is, nicotinic acid, fibrates and bile acid sequestrants, as tolerated [57]. Only, use ezetimibe in subjects who do not achieve the targets with the other combinations [57]. Even as a last resort, it seems, that ezetimibe should not be added to statins to lower LDL-cholesterol to such time as ezetimibe has been shown to have a beneficial effect on clinical outcomes.

The study of West *et al.* is the only clinical outcome study with ezetimibe to have a clear-cut result for ezetimibe alone, and it is a detrimental effect; ezetimibe (in the presence of simvastatin) leads to the progression of atherosclerosis in subjects with peripheral arterial atherosclerosis [53]. The authors of this study seemed to have assumed that ezetimibe was going to have a beneficial effect, and that this has been halted by prior simvastatin treatment [53]. Given that there is no prior evidence that ezetimibe alone halts or reverses atherosclerosis, this seems illogical. It is considered that the evidence should be accepted *per se*, that is, in the presence of simvastatin, ezetimibe causes progression of atherosclerosis in the peripheral arterial atherosclerosis. The study by West *et al.* [53] produces strong evidence for withdrawing ezetimibe from use in practice, until clinical trials have produced clear-cut results as to whether ezetimibe has beneficial or detrimental effects on cardiovascular clinical outcomes.

Although LDL-cholesterol lowering is commonly used as a surrogate for likely clinical beneficial outcomes with lipid-modifying drugs, there is evidence that the benefit is predominantly due to the lowering of the small dense LDL-cholesterol [58]. Consequently, lowering of small dense LDL-cholesterol should really be the marker/surrogate for clinical outcomes [58]. There is also some evidence that short-term treatment with ezetimibe increases small dense LDL-cholesterol, which is associated with increased risk. Thus, ezetimibe alone or in the presence of statins, has been shown to increase the amounts of the pro-atherogenic small dense LDLs [59,60]. Thus, long-term studies of the effects of ezetimibe on LDL-cholesterol subfractions are indicated to determine whether it is having a beneficial effect on this surrogate.

A large outcome trial is in progress to determine the clinical outcomes with ezetimibe in the presence of simvastatin; the IMPROVE-IT (Examining Outcomes in Subjects With Acute Coronary Syndrome: Vytorin (Ezetimibe/Simvastatin) vs Simvastatin trial) [61]. Enrolment for IMPROVE-IT has stopped with 180,057 subjects after acute coronary syndromes [62]. IMPROVE-IT will continue until 5250 subjects have a primary end point event (death from cardiovascular causes, myocardial infarction, hospital admission for unstable angina, revascularization or stroke) [61,62]. The results from IMPROVE-IT will not be known until 2015, and because of the large number of primary end points required, may go for longer, or be inconclusive [61,62]. It seems that the use of ezetimibe in clinical practice should be discontinued or stopped until the outcomes of IMPROVE-IT are known.

5.4 Effect of the combination of ezetimibe and simvastatin versus placebo

In most of the clinical outcomes studies with the combination of ezetimibe and simvastatin, the effects of the combination has been compared with placebo. With this clinical trial design, it is not possible to determine whether any differences between the groups are due to simvastatin alone, ezetimibe alone, or the combination of simvastatin and ezetimibe. Also, with the combination, it is not possible to distinguish between beneficial and detrimental effects, and the overall difference with placebo may be a combination of these effects.

As there was a substantial decrease of LDL-cholesterol in SEAS, the reduction of major ischaemic events was lower with simvastatin/ezetimibe than might have been expected with the use of statins alone as in the CTT meta-analysis of 14 statin trials [23]. However, when the subjects in SEAS were divided into tertiles based on aortic jet velocity (as a marker of asymptomatic aortic stenosis), the lipid-lowering effect of the combination of simvastatin/ezetimibe gave a comparable reduction in major ischaemic events to the meta-analysis with the statins [23], for subjects with the least, and middle aortic stenosis tertiles, but not in subjects with the most severe aortic stenosis [63]. It seems to me that this division into tertiles does not change the result that in SEAS, the decrease in LDL-cholesterol with simvastatin/ezetimibe gave a lesser decrease in major ischaemic events than would be expected from the use of statins alone to reduce the LDL-cholesterol to the same extent.

In SANDS, ezetimibe was also studied in the presence of a statin (not specified), but the doses and statin uses were not constant, and thus the LDL-cholesterol-lowering effects were similar in the statin group and simvastatin/ezetimibe group [50]. In SANDS, there was no added benefit by adding the ezetimibe, as the trial showed similar effects on carotid atherosclerosis in subjects with type 2 diabetes with both regimens.

ARBITER 6-HALTS also showed no beneficial effect of ezetimibe on carotid intima–media thickness in subjects taking statins despite a reduction in LDL-cholesterol [39]. Interestingly, for a lesser reduction in LDL lowering when niacin was added to the statins, there was a reduction in the intima–media thickness [44]. This result also adds to the accumulating evidence that ezetimibe may not have beneficial effects on clinical outcomes.

In kidney disease, simvastatin has not been studied alone in SHARP, or (as per SA Doggrell's knowledge) in any other clinical trial, thus it is not know whether the effect of simvastatin/ezetimibe is the effect of simvastatin, ezetimibe or the combination. Atorvastatin has previously been shown to reduce the risk of cardiac events in subjects with kidney disease and type 2 diabetes undergoing dialysis in the 4D study [64]. Initially, rosuvastatin was not shown to decrease cardiovascular events in subjects undergoing haemodialysis in the AURORA (a study to evaluate the use of rosuvastatin in subjects on regular haemodialysis: an assessment of survival and cardiovascular events) which included both subjects with and without diabetes [65]. However, a *post hoc* analysis of AURORA, which was limited to the subjects with diabetes, showed that rosuvastatin did reduce the risk of cardiac events [66]. Perhaps the beneficial effect observed in SHARP was that of the simvastatin, and not of the combination of ezetimibe and simvastatin. To test this, ezetimibe needs to be compared with placebo, in subjects with kidney disease taking simvastatin.

When target levels of LDL-cholesterol cannot be reached with statins alone, ezetimibe is commonly added to the statin to reduce the LDL-cholesterol (e.g., [3,67,68]). Also, the simvastatin/ezetimibe combination is being proposed as an alternative to atorvastatin and/or rosuvastatin (e.g., [69-71]). Is there any point to this until it is known whether the LDL-cholesterol lowering with ezetimibe improves clinical outcomes?

5.5 First, do no harm

The standard approach to any medical treatment is 'first, do no harm'. Simvastatin alone has beneficial effects on cardiovascular outcomes and long-term treatment is not associated with any cancers [72]. By contrast, ezetimibe alone has not been shown to have any beneficial effect on clinical cardiovascular outcomes, but it may have some harmful effects. In SEAS, cancer occurred more often in the simvastatin/ezetimibe group (105 of 994 subjects, 11.1%) than in the placebo group (70 of 929 subjects, 7.5%) [73]. However, there was no evidence that any particular type of cancer was increased with the simvastatin/ezetimibe combination [73]. In their discussion, the authors point out that an increased risk of cancer had not previously been reported with simvastatin, or with ezetimibe in the SEAS trial, but this possible link between ezetimibe and cancer needed to be further investigated [73]. This was further investigated by Peto *et al*. the effects of ezetimibe on the risk of cancer in studies with larger numbers of participants, namely SHARP and the ongoing IMPROVE-IT trial [61,62], and suggested that there was no credible evidence that ezetimibe increased the risk of cancer, but that this needed longer follow-up [74]. However, Petro *et al.* did report that in SHARP and IMPROVE-IT, 97 deaths from cancer have occurred in the ezetimibe group, compared with 72 in the control group ($p = 0.07$), and that when all three trials were combined, the death rates from cancer were 134 versus 92 ($p = 0.007$), but argue that there is bias in these data [73].

As discussed in Section 5.3, the study of West *et al.*, in subjects with peripheral arterial atherosclerosis, could be interpreted to mean that ezetimibe promotes the progression of atherosclerosis. Until the long-term safety of ezetimibe is established, regarding cancer and atherosclerosis, questions must be asked about why it is being widely used.

5.6 Role of the pharmaceutical companies

As discussed above the effects of ezetimibe should have been compared with placebo in subjects taking simvastatin, rather than ezetimibe combined with simvastatin being compared with placebo as was the case in VYCTOR [49], SEAS [53] and SHARP [75]. The VYCTOR study was designed by the authors, who were independent of the companies, but was partly funded by Merck, Sharp & Dohme, Mexico [49]. SEAS was supported by Merck and Schering-Plough Pharmaceuticals, who had two members on the Steering committee, and acknowledges 'the work done by all Merck clinical research staff in facilitating the study' [53]. SHARP was supported by Merck and Schering Plough Pharmaceuticals and national research bodies from Australia and the UK, and the companies provided two non-voting members to the Steering committee [75]. It is not clear as to what was the role of the pharmaceutical companies in the design of these trials, and why they funded trials comparing the combination of simvastatin/ezetimibe against placebo. What is apparent is that if these trials had been designed correctly, that is, comparing ezetimibe with placebo in the presence of simvastatin, we would probably already know whether ezetimibe had beneficial effects on clinical outcomes. The results of the IMPROVE-IT trial are not due to 2015. One of the consequences of this is that the ezetimibe/simvastatin combination has been used for a long period, and earning a large revenue for the companies, without the clinical data to support the use. It is not clear why the drug regulatory bodies have registered and supported the use of the ezetimibe/simvastatin combination under these circumstances.

5.7 Conclusions

The comparison of clinical trials with simvastatin and ezetimibe alone and together has clearly shown that simvastatin decreases LDL-cholesterol and this is associated with improved clinical outcomes. Also, ezetimibe alone or in the presence of simvastatin lowers LDL-cholesterol. However, ezetimibe alone or in the presence of simvastatin has not been shown to have any irrefutable beneficial effects on clinical outcomes. Thus, until/unless the use of ezetimibe is clearly shown to improve clinical outcomes, its use should be largely restricted to clinical trials investigating clinical outcomes, and ezetimibe should not be used routinely in everyday practice.

Declaration of interest

The author declares no conflict of interest and has received no payment in preparation of this manuscript.

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