Efficacy and safety of ezetimibe plus atorvastatin therapy

Statin therapy is highly effective in reducing low-density lipoprotein cholesterol (LDL-C) and cardiovascular events; however, many high-risk patients on statin monotherapy do not achieve sufficient LDL-C lowering. Statin-dose up titration, switching to more potent statins and/or addition of complementary lipid-lowering drugs has been recommended for these patients. Numerous clinical trials have shown that coadministration of statins with cholesterol absorption inhibitor, ezetimibe, improves LDL-C lowering and other lipid parameters more than statins alone, including doubling the statin dose. In clinical outcome trials, ezetimibe combined with simvastatin reduced ischemic events in high-risk patients with chronic kidney disease and aortic stenosis; the incremental benefit of LDL-C lowering when ezetimibe is added to statin therapy on cardiovascular risk reduction compared with statin monotherapy is currently being evaluated in an ongoing clinical trial. Recently, a fixed-dose combination of ezetimibe plus atorvastatin, a statin with greater potency than most other statins, was approved by the US FDA and offers a therapeutic option for high-risk patients who do not achieve recommended LDL-C levels on statin monotherapy. This article provides an update on the safety and efficacy of ezetimibe plus atorvastatin therapy.

Keywords: atorvastatin • ezetimibe • fixed-dose combination therapy • LDL-C • lipids

Cholesterol-lowering management with statin therapy

Substantial clinical trial evidence indicates that cardiovascular disease (CVD) risk reduction is related to the degree of low-density lipoprotein cholesterol (LDL-C) lowering achieved by therapeutic intervention [1-3]. As such, LDL-cholesterol (LDL-C) reduction is the guideline-recommended treatment target for primary and secondary prevention of cardiovascular events [4-9]. Statin therapy has been shown to effectively reduce CVD risk in numerous clinical trials and is the first-line pharmacotherapy approach endorsed for lowering LDL-C [4-9]. National guidelines have recommended progressively lower LDL-C goals over time based on clinical trial evidence which has demonstrated that reducing LDL-C to very low concentrations is associated with greater CVD risk reduction [1,2]. Earlier guidelines developed by the US National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) included LDL-C <100 mg/dl as the optimal goal for primary prevention in persons with multiple coronary heart disease (CHD) risk factors and LDL-C <70 mg/dl as an optional goal for very high risk patients [10-13]. This latter target was also considered to be reasonable for high-risk patients with atherosclerotic vascular disease [14]. Other international guidelines similarly endorse these LDL-C target levels [4-9]. More intensive use of statin therapy and combination therapy has also been suggested, when appropriate, to achieve adequate LDL-C lowering in high-risk patients [4-9]. Levels of non-HDL-C and Apo B have also been recommended as secondary and alternate targets for therapy in patients with elevated triglycerides (TG; ≥200 mg/dl) by some guidelines [4,8-9,15]. For patients with cardio-

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metabolic risk, treatment to LDL-C <100 mg/dl, non-HDL-C <130 mg/dl and ApoB <90 mg/dl levels has been recommended for those individuals who are at high risk for CVD, and treatment to <70 mg/dl, <100 mg/dl and <80 mg/dl for LDL-C, non-HDL-C and ApoB, respectively are suggested for those who are at the highest risk [16]. The recently published guideline from the American College of Cardiology and American Heart Association does not specify LDL-C targets per se, but rather focuses upon patient groups that are most likely to benefit from high-intensity (LDL-C lowering by ≥50%) and moderate-intensity statin (LDL-C lowered by 30 to <50%) in secondary and primary prevention of CVD risk [17].

Several clinical studies have shown the beneficial effects of statins on CVD risk reduction in both primary and secondary prevention studies (Figure 1) [18]. A large meta-analysis of 26 statin clinical trials demonstrated that standard statin therapy was associated with a 22% reduction (RR: 0.79; 95% CI: 0.76–0.80; p < 0.001) in the annual rate of major vascular events for each 1 mmol/L (38.6 mg/dl) reduction in LDL-C, and that studies of more intensive versus less intensive statin therapy in patients with baseline LDL-C levels in the range of 66–135 mg/dl (down to average achieved LDL-C levels of 47–86 mg/dl) resulted in further reductions in the incidence of cardiovascular events, consistent with the LDL-C risk reduction relationship observed at higher LDL-C levels [1]. In patients with lower CVD risk (5 to <10% risk), statin therapy also reduced CVD events by 21% (RR: 0.79; 95% CI: 0.77–0.81; p < 0.001) per 1 mmol/L reduction in LDL-C [19]. The clinical benefit of statin therapy outweighed the risk of adverse events in these patients, confirming the efficacy of statins in primary prevention. Intensive statin therapy has been shown to result in greater atherosclerotic disease regression than moderate therapy in intravascular ultrasound (IVUS) trials; however, these studies suggest that in many cases maximum statin therapy may not be sufficient and additional agents may be needed to optimize reduction of LDL-C and CVD risk [20].

‘Real world’ observational studies have also shown that many patients on statin monotherapy do not reach LDL-C levels set by some guidelines, particularly those with high CVD risk [30–38]. Despite substantial increases in the use of lipid-lowering therapy, and while attainment rates for LDL-C <100 mg/dl have improved from 18 to 67% during 1996–2008 for high-risk CHD patients, only 30% of very-high-risk patients achieved LDL-C <70 mg/dl [38–43]. Similarly, although lipid treatment has improved over the years in patients with diabetes and metabolic syndrome, achievement of LDL-C goals in these patients is low (67% for LDL-C <100 mg/dl) and particularly those at very high risk (34% for LDL-C <70 mg/dl) [33]. This treatment gap has been attributed to various barriers including lack of optimal statin therapy, cost factors, compliance, tolerability and health provider nonadherence to current guidelines [30–31,37–38].

Several guidelines recommend statin up-titration, switching to more potent statins and/or statin combination therapy in these high-risk patients who do not reach sufficient LDL-C levels on statin therapy alone [4–9]. The American College of Cardiology/American Heart Association guideline endorses that the maximum tolerated statin dose should be used in high-risk individuals for whom high- or moderate-intensity statins have been recommended and that addition of a nonstatin cholesterol-lowering drug may be considered in those patients who have a less-than-anticipated therapeutic response to statins if the risk-reduction benefit outweighs the safety risk, as well as those who do not tolerate the risk-appropriate intensity of statins or are statin intolerant [17]. Concern for potential side effects with higher statin doses and cost factors have limited the use of optimal statin therapy [40,41]. In addition, statin up-titration only provides an additional approximately 6% decrease in LDL-C level for each doubling of the dose [44], possibly related to counteracting factors such as increased intestinal cholesterol absorption and secretion of proprotein convertase subtilisin/kexin 9 (PCSK9). Studies have shown that high-potency statins are used less frequently than moderate potency lipid-lowering therapy in real-world clinical practice, attributed to patient noncompliance/intolerance, health provider nonadherence to current guidelines and/or cost factors [34,36,40,41,45]. In this regard, the availability of a generic formulation of atorvastatin, a class-leading statin that has greater LDL-C lowering efficacy than most other statins with proven benefit in reducing CVD, is becoming more commonly used [46].

While statins in combination with other lipid-lowering agents having different mechanisms of action (e.g., niacin, fibrates, bile acid sequestrants and ezetimibe) can be used to provide further reductions in LDL-C, a lack of definitive evidence for greater CVD risk reduction with combination therapy compared with statin monotherapy alone has limited this approach [47–49]. In some clinical trials, both niacin and fibrates by themselves have been found to reduce CVD events, however, more recent studies of these agents, when combined with statins, have failed to demonstrate further reductions in CVD risk above statins alone [47,49]. Similarly, the bile acid sequestrant cholestyramine had a benefit on CVD events; however, to date there is no clinical outcome data that
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Figure 1. Event rates versus low-density lipoprotein cholesterol lowering in statin monotherapy trials. Event rates plotted against low-density lipoprotein cholesterol level in primary (green) and secondary (red) prevention trials: AFCAPS [21]; ASCOT [22]; CARE [23]; HPS [24]; IDEAL [25]; PROSPER [26]; PROVE-IT [27]; TNT [28]; and WOSCOPS [29]. Events are defined as death by CHD or nonfatal myocardial infarction. Filled diamonds represent treatment groups and open circles control groups. To convert values for LDL-C to mmol/ml, multiply by 0.02586.

Comparison of bile acid sequestrant with statins versus statins alone [50].

Ezetimibe plus statin combination therapy has been shown to be effective and generally well tolerated for lowering LDL-C as well as improving other lipids in numerous clinical trials [51–54]. In clinical outcome trials, ezetimibe 10 mg plus simvastatin 20 mg produced significant reductions in major atherosclerotic events in patients with advanced CKD compared with placebo [55]. Additionally, ezetimibe 10 mg plus simvastatin 40 mg significantly reduced ischemic events in patients with low-to-moderate aortic stenosis, compared with placebo; the magnitude of the observed reduction in ischemic cardiovascular events in the two thirds of the population with less severe aortic stenosis was consistent with expectations for the degree of LDL-C lowering achieved [56,57]. However, these studies did not assess the specific contribution of ezetimibe on outcomes when added to statin therapy and the incremental benefit of ezetimibe when added to simvastatin compared with simvastatin monotherapy is being definitively addressed in an ongoing clinical outcomes trial [58,59]. In several studies, combination ezetimibe plus atorvastatin has been shown to be generally well tolerated and provides greater reductions in LDL-C and other lipids compared with doubling the atorvastatin dose when coadministered as separate tablets [60–63]. As such, a fixed-dose combination (FDC) of ezetimibe (10 mg) with atorvastatin (10, 20, 40 or 80 mg) was recently developed. The LDL-C lowering efficacy of the FDC has been demonstrated to be equivalent to coadministration of ezet-
imibe at the corresponding atorvastatin doses [64,65], and consistent with the broad clinical experience for coadministration of these two agents [66]. The FDC received US FDA approval in May 2013 [66,67]. This review provides an update on the safety and efficacy of ezetimibe plus statin therapy, with an emphasis on its combination with atorvastatin.

**Statin therapy: mechanism of action, indications & safety profile**

Statins competitively inhibit 3-hydroxyl-3-methylgluaryl coenzyme A (HMG-CoA) reductase, resulting in reduced cholesterol biosynthesis in the liver and other peripheral organs, upregulation of hepatic cell surface LDL-C receptors and consequently removal of apolipoprotein B-containing lipoproteins (VLDL, IDL and LDL) from circulation [68]. Seven statins are currently approved for clinical use worldwide, including lovastatin (1987), simvastatin (1991), pravastatin (1991), fluvastatin (1993), atorvastatin (1996), pitavastatin (2003) and rosuvastatin (2003). All statins reduce LDL-C in a dose-dependent manner, and most can achieve LDL-C reductions of at least 20–30% [69]. Clinical outcome studies have demonstrated reductions in atherosclerotic cardiovascular events with lovastatin [21], simvastatin [70,71], pravastatin [23,26], atorvastatin [22,27–28] and rosuvastatin [72]. Fluvastatin has been shown to slow the progression of atherosclerosis and lower the risk of revascularization procedures for patients with CHD [73–75]. To date, the effect of pitavastatin on cardiovascular morbidity and mortality has not been determined.

Differences in chemical structure and composition influence binding characteristics of statins to the active site of HMG-CoA reductase, and partially account for differences in statin potency [76]. Pharmacokinetic and pharmacodynamic properties also play a role in determining statin efficacy and safety [77]. Half-lives are generally between 1 and 3 h for all statins, except atorvastatin (14 h) and rosuvastatin (20 h). Lovastatin, simvastatin and atorvastatin are metabolized by CYP3A4, while fluvastatin, rosuvastatin and pitavastatin are metabolized primarily by CYP2C9. Pravastatin is not metabolized by CYP450 enzymes. Concurrent administration of statins with drugs that modify CYP activity may adversely affect statin efficacy, safety or tolerability [78]. Differences in statin pharmacokinetics may also favor some statins over others when used in special patient populations.

Statins have been used in millions of patients for over 20 years and are generally safe and well tolerated. About 10–15% of patients in clinical practice, however, may report statin-related muscle symptoms which can contribute to discontinuation of treatment or reduced compliance [79,80]. This is becoming an increasingly important issue as guidelines continue to advocate for more aggressive lipid-lowering treatment targets [4–9,81]. Higher statin dose, low BMI, concomitant drug interactions, advanced age, liver or renal disease and susceptibility to muscle injury (alcohol consumption, drug interactions, heavy exercise and disease) are some of the factors associated with statin-induced myopathy [82–84]. Strategies for management of statin-associated muscle symptoms may help improve patients compliance and treatment efficacy [84–86].

Recent evidence has identified an association between statin therapy and a slightly higher risk of developing diabetes mellitus [72]. Meta-analysis of randomized placebo-controlled statin trials found a significant but low risk for development of diabetes during approximately 4 years of treatment (OR: 1.09; 95% CI: 1.02–1.17) [87]. More intensive statin treatment may also be associated with increased risk when compared with lower statin doses (OR: 1.12; 95% CI: 1.04–1.22) [88]. These findings led the FDA to issue a safety label change for all statins, warning of increased blood sugar and glycosylated hemoglobin levels; however, the risk was said to be small and greatly outweighed by the benefit, and therefore should not affect the use of statins in appropriate patients [89]. In primary prevention studies of lower-risk patients, the reduction of CVD risk and mortality also outweighed the diabetes risk, including high-dose statin therapy [90,91]. Moreover, the increased risk of diabetes was greater in those patients predisposed to diabetes, as predicted by baseline factors including higher fasting serum glucose levels (95 to <126 mg/dl), HbA1c (>6%), obesity (>30 kg/m²), higher triglyceride levels (>150 mg/dl) and a history of hypertension or metabolic syndrome [91,92]. These findings reaffirm the value of statin therapy in reducing CVD risk; however, the associated benefit and risk should be carefully assessed for each patient.

**Efficacy & safety of atorvastatin therapy**

Atorvastatin is one of the most widely prescribed statins in the world [93]. Daily administration of atorvastatin 10, 20, 40 or 80 mg is highly effective in lowering LDL-C levels, with dose-dependent mean reductions of approximately 37–53% [94]. Atorvastatin is metabolized by CYP3A4 and 3A5 to ortho-hydroxy atorvastatin and para-hydroxy atorvastatin, which extends the half-life for inhibiting HMGCoA reductase to 20–30 h, and contributes to a higher potency when compared with most other statins [95,96]. Concomitant use of drugs that inhibit CYP3A4 may increase serum plasma concentrations of atorvastatin and the risk of
myotoxicity. As with most statins, atorvastatin undergoes extensive first-pass metabolism in the liver and is eliminated primarily in the bile. Hepatic dysfunction is therefore a risk factor for statin-induced myopathy. Compared with other statins, atorvastatin and fluvastatin are minimally excreted in the urine and therefore may have better safety profiles in patients with renal dysfunction [97–99].

Atherosclerosis is a progressive disease that starts early in life, and is the underlying cause of CVD. Several surrogate markers have been used to evaluate the effect of atorvastatin on atherosclerotic progression. In the 2-year ASAP trial comparing aggressive versus conventional care in high-risk patients with heterozygous familial hypercholesterolemia (HeFH), atorvastatin 80 mg was associated with a significant decrease in mean carotid intimal-media thickness (cIMT), while cIMT significantly increased with simvastatin 40 mg (-0.031 mm vs +0.036 mm) [100]. After an additional 2 years, no further decrease in cIMT was observed in patients continuing on atorvastatin 80 mg while significant reductions were seen in those switching from simvastatin 40 mg to atorvastatin 80 mg (baseline: 0.95 mm; study end: 0.92; p = 0.01) [101]. In the ARBITER trial which studied patients meeting NCEP ATP II criteria for pharmacologic lipid-lowering therapy (46% with known cardiovascular disease), atorvastatin 80 mg significantly decreased cIMT versus no change with pravastatin 40 mg/day [102]. The effects of maximal dose atorvastatin (80 mg) and rosuvastatin (40 mg) on coronary atherosclerosis were evaluated in the SATURN trial using IVUS in patients with coronary stenosis. In this study, significant regression of coronary atherosclerosis as measured by percent atheroma volume was observed for both treatments (0.99% for atorvastatin, 1.22% for rosuvastatin) [20].

Atorvastatin has been evaluated in numerous clinical outcome trials and shown to be effective in primary and secondary prevention of cardiovascular events. The ASCOTT-LAA trial studied patients at moderate risk with hypertension ≥3 CHD risk factors but without CHD, and demonstrated that atorvastatin 10 mg reduced the composite end point of nonfatal MI and fatal CHD by 36% after a median of 3.3 years when compared with placebo [22]. Diabetes is a major risk factor for CHD and the ADA recommends statin therapy for all diabetic patients without CVD who are over age 40 with one or more additional cardiac risk factors [103]. This recommendation is supported by the 3.9-year randomized placebo-controlled CARDS trial of atorvastatin 10 mg in 2838 diabetic patients with no evidence of CHD, where atorvastatin reduced the primary end point of acute CHD events, coronary revascularization, or stroke by 37% [104]. In the PROVE IT (TIMI 22) trial of high-risk patients hospitalized with acute coronary syndrome, starting treatment with atorvastatin 80 mg produced a significant 16% relative reduction in death or major cardiovascular events compared with pravastatin 40 mg at completion of the 18–36-month study [27]. In a second acute coronary syndrome (ACS) study (MIRACL), initiation of atorvastatin 80 mg therapy 24–96 h after an ACS significantly reduced recurrent symptomatic myocardial ischemic events within the first 16 weeks of treatment [105]. The TNT study evaluated patients with stable nonacute CHD and slightly elevated LDL-C levels who were treated with atorvastatin 10 mg to lower LDL-C to approximately 100 mg/dl or with atorvastatin 80 mg to reach an LDL-C target of approximately 75 mg/dl. In this trial, atorvastatin 80 mg produced a 22% relative reduction in the first occurrence of a major cardiovascular event (death from CHD, nonfatal nonprocedure-related MI, resuscitation after cardiac arrest or fatal or nonfatal stroke) when compared with atorvastatin 10 mg [28]. In ALLIANCE, an open-label study in 2442 CHD patients compared treatment with atorvastatin titrated to reach an LDL-C target of <80 mg/dl versus usual care in reducing cardiovascular events (cardiac death, nonfatal MI, resuscitated cardiac arrest, revascularization or unstable angina requiring hospitalization) [106]. After an average of 51 months treatment, more intensive treatment resulted in significantly greater reductions in LDL-C (-34.5% vs -23.3%), significantly higher percentage achievement of NCEP ATP III targets (72.4% vs 40.0%), and significantly fewer cardiovascular events (23.7% vs 27.7%; relative risk reduction of 17.1%) compared with usual care. Atorvastatin has also been shown to significantly reduce the incidence of stroke in patients with hypertension (ASCOT-LAA [22]) or in patients experiencing prior cerebrovascular events (SPARCL) [107]. A post hoc analysis of the SPARCL study showed a higher incidence of hemorrhagic stroke in patients without CHD who had experienced a stroke or transient ischemic attack within 6 months prior to receiving atorvastatin 80 mg vs placebo, and this is noted as a precaution for use in patients with recent stroke or transient ischemic attack in the prescribing information [46,108]. While the majority of clinical trials have demonstrated statistically significant improvements in cardiovascular outcomes with atorvastatin, it should be noted that other trials have not, including ASPEN and IDEAL. The ASPEN trial evaluated atorvastatin 10 mg versus placebo in 2410 patients with type 2 diabetes, and after a median follow-up of 4 years, no
statistical difference between the two treatments was observed for the primary composite end point (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, recanalization, coronary artery bypass surgery, resuscitated cardiac arrest and worsening or unstable angina requiring hospitalization) [109]. The ASPEN study group suggested that these results may have been related to the overall study design, patient population, the nature of the primary end point as well as required protocol changes due to changes in ATP III treatment guidelines that affected enrollment, and emphasized the continued importance of LDL-C lowering treatment for diabetic patients. In the IDEAL study of 8888 patients with a history of acute MI, comparison of high-dose atorvastatin 80 mg versus usual-dose simvastatin 20 mg showed no significant difference in the reduction of the primary end point of major coronary events after a median follow-up of 4.8 years [25]. Atorvastatin did provide significant improvements over simvastatin in other secondary end points and nonfatal acute MI, suggesting the benefit of intensive lowering of LDL-C in this patient population.

Atorvastatin has a favorable safety and tolerability profile in a wide variety of patients, including the elderly [110,111], patients with Type 2 diabetes mellitus [104,109,112], ACS [27], CHD [28] and chronic kidney disease [113]. Cases of rhabdomyolysis with acute renal failure are rare, and persistent elevations in serum transaminases have been reported, particularly at higher doses [46,114–115]. As already noted, statins, including atorvastatin, are associated with a slight increase in risk of new-onset Type 2 diabetes mellitus [87]. In one study of primary care patients with hypercholesterolemia, atorvastatin 10–80 mg was associated with a significant increase in plasma insulin (25–45%) and glycated hemoglobin (HbA1c) levels (2–5%) and decreased insulin sensitivity after 2 months of therapy, when compared with either baseline levels or placebo [116]. Recent meta-analyses suggest that different types and doses of statins may have the potential for increasing the incidence of diabetes mellitus [117]. Comparison of lower dose statin therapy versus atorvastatin 80 mg in over 15,000 patients with CHD but without diabetes mellitus showed an increased risk of new-onset diabetes with atorvastatin 80 mg when two or more new-onset diabetes risk factors were present (fasting blood glucose >100 mg/dl, fasting triglycerides >150 mg/dl, body mass index >30 kg/m² and history of hypertension); however, reductions in cardiovascular events were also significantly greater with more intensive therapy [118]. The FDA issued a statement regarding the risks associated with statin use [119].

**Ezetimibe overview**

Ezetimibe selectively inhibits the absorption of dietary and biliary cholesterol (and related phytosterols) in the small intestine by blocking the activity of the Niemann-Pick C1 Like 1 (NPC1L1) sterol transport protein [120,121]. The inhibition of NPC1L1 by ezetimibe subsequently reduces the incorporation of cholesterol into chylomicrons. The decline in chylomicron cholesterol results in a decreased delivery of cholesterol to the liver that leads to a compensatory upregulation of hepatic LDL receptors and increased plasma clearance of atherogenic ApoB-containing lipoproteins. Through its interaction with the hepatic NPC1L1 transporter, ezetimibe can also increase cholesterol reabsorption from bile, thereby reducing the hepatic pool of cholesterol and further augmenting LDL-C clearance [122]. When coadministered with a statin, the combined inhibition of cholesterol absorption by ezetimibe and cholesterol synthesis by a statin substantially reduces LDL-C through a final common pathway of enhanced upregulation of LDL receptors and clearance of lipoproteins from the plasma [52–53,121,123].

Ezetimibe specificity for NPC1L1 is well established, and no effects on the absorption of triglycerides, ethinyl estradiol, progesterone, fat-soluble vitamins or bile acids have been observed. *In vitro* assays evaluating all known lipid pathways found that ezetimibe and its glucuronide did not inhibit any known biochemical or cellular processes, including ACAT, to a degree that could be clinically relevant [124,125]. Ezetimibe also does not block pancreatic lipase as seen with orlistat, or sequester bile acids or block their absorption as with bile acid sequestrants (resins). Over 100 toxicology studies were used to assess the preclinical safety of ezetimibe, and no target organ toxicity was seen in any study [126]. These results are consistent with the clinical safety profile of ezetimibe [127].

**Clinical studies evaluating the lipid-altering efficacy of ezetimibe**

Ezetimibe has been approved for use as monotherapy or in combination with statins for patients with primary (heterozygous familial and nonfamilial) hyperlipidemia for the reduction of elevated levels of total cholesterol, LDL-C, ApoB and non-HDL-C, or as monotherapy for patients with homozygous familial sitosterolemia in reducing elevated levels of campesterol and sitosterol [127]. It is also approved for use in combination with statins for treatment of homozygous familial hypercholesterolemia and in combination with fenofibrate for treatment of adult patients with mixed hyperlipidemia [127]. Ezetimibe monotherapy has been extensively evaluated in adults with
primary hypercholesterolemia and shown to produce significant reductions in LDL-C of approximately 19% with concomitant improvements in other key lipid parameters [123,128]. Ezetimibe monotherapy resulted in LDL-C reductions of 7–26% in statin-intolerant patients with perceived adverse effects on statin therapy, including high-dose statins [129–131]. Co-administration of ezetimibe with statins has been shown to inhibit cholesterol absorption as well as synthesis, resulting in significantly larger reductions in LDL-C and greater achievement of guideline-recommended LDL-C targets than with statin monotherapy [132–136] or statin doubling [60–63,137–138]. These improvements have been demonstrated in a number of high-risk patient populations [52], including patients with homozygous (Ho) or heterozygous (He) familial hypercholesterolemia (FH) [131,138–142], diabetes mellitus [143–146], metabolic syndrome [147–149], nonalcoholic fatty liver disease [150], chronic kidney disease [151,152], CHD [62,138,135] and aortic stenosis [56] as well as in statin-intolerant patients [129–131,154].

**Lipid-altering efficacy & safety of ezetimibe plus atorvastatin in clinical studies**

Several studies have evaluated the complementary effects of blocking cholesterol synthesis with atorvastatin and inhibition of cholesterol absorption with ezetimibe in a variety of patient populations (Table 1). In a randomized placebo-controlled ‘factorial’ trial of 628 statin-naïve hypercholesterolemic patients with LDL-C levels between 145 and 250 mg/dl and triglycerides ≤350 mg/dl, evaluation of pooled data for coadministration of ezetimibe 10 mg and atorvastatin (10, 20, 40 or 80 mg) showed an additional 12% reduction in LDL-C compared with atorvastatin monotherapy [132]. LDL-C reductions for individual treatment groups ranged from -50 to -60% for coadministration versus -35 to -50% for atorvastatin alone. Ezetimibe combined with the lowest available dose of atorvastatin (10 mg) produced a mean LDL-C reduction comparable to that of atorvastatin 80 mg, the highest prescribed dose. Three randomized, double-blind, placebo-controlled trials have evaluated ezetimibe added to ongoing atorvastatin therapy in patients with primary hypercholesterolemia who had not achieved NCEP ATP treatment targets with statin alone [155,156], or in patients with established CHD and LDL-C levels >100 mg/dl with atorvastatin 10 or 20 mg [157]. In these studies, ezetimibe added-on to ongoing atorvastatin therapy produced significantly greater reductions in levels of LDL-C (20–27%), as well as total cholesterol, non-HDL-C, Apo B, triglycerides and C-reactive protein (when measured), and increases in HDL-C levels compared with placebo. Addition of ezetimibe to statin monotherapy significantly improved attainment of LDL-C goals.

Four randomized double-blind clinical trials were designed to compare the addition of ezetimibe to ongoing atorvastatin versus doubling the atorvastatin dose in patients with moderate CHD risk, high CHD risk with or without clinically diagnosed cardiovascular disease and a high-risk elderly population [60,62–63,138]. In all studies, ezetimibe added to ongoing atorvastatin provided an additional LDL-C reduction of 14–20% compared with atorvastatin titration to the next higher dose, resulting in significantly greater achievement of LDL-C targets and significantly greater reductions in other key lipid parameters. A fifth study in homoygous familial hypercholesterolemia patients evaluated the efficacy of adding ezetimibe to ongoing atorvastatin 40 mg or simvastatin 40 mg (allowing for LDL apheresis if it was part of the patients therapeutic regimen) [141]. For patients with LDL-C levels above 100 mg/dl after 4 weeks of treatment, the statin dose was increased to 80 mg. At the end of 12 weeks, coadministration of ezetimibe with statin (40 or 80 mg) reduced LDL-C significantly more than statin 80 mg therapy (-20.7% vs -6.7%; p = 0.007) in this very high-risk patient population.

Use of ezetimibe alone or in combination with atorvastatin 10 mg was evaluated in high-risk, statin-intolerant patients with coronary artery disease or equivalent (data not shown in Table 1) [129]. Ezetimibe monotherapy was well tolerated and produced a significant mean reduction in LDL-C of 20%; however, only 9% of patients achieved their LDL-C target. Subsequent addition of atorvastatin 10 mg twice a week to ezetimibe 10 mg/day was also tolerated by these patients, and combined therapy provided a 37% reduction in LDL-C compared with baseline values, and an 84% achievement of LDL-C goals. A recent study used a novel treat-to-target design to compare the LDL-C lowering efficacy of sequential treatment options in high cardiovascular risk patients with primary hypercholesterolemia [61]. After a 5-week run-in on atorvastatin 10 mg/day, subjects who were not at the LDL-C treatment target of <100 mg/dl were randomized to three groups; addition of ezetimibe to stable atorvastatin 10 mg, doubling atorvastatin to 20 mg or switching to rosuvastatin 10 mg, a more potent statin. After 6 weeks (Period I), coadministration of ezetimibe with atorvastatin 10 mg reduced LDL-C significantly more than atorvastatin 20 mg or rosuvastatin 10 mg (22.2% vs 9.5% or 13%, respectively; p < 0.001). Patients with LDL-C levels ≥100 mg after receiving atorvastatin 20 mg during
Table 1. Clinical studies evaluating the lipid-lowering efficacy of ezetimibe plus atorvastatin.

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Studies 692, 2173/2246, 040, 803/804, 030, 079, 090, 112 were included in a pooled analyses of 27 studies [54,188].

† Treatment difference: percentage change with statin plus ezetimibe 10 mg minus percentage change with statin plus placebo, statin doubling, or statin switch.

‡ Ongoing statins: atorvastatin (10–80 mg), cerivastatin (0.2, 0.3, 0.4, 0.8 mg), fluvastatin (20, 40, 80 mg), lovastatin (10, 20, 40 mg), pravastatin (10, 20, 40 mg), simvastatin (10, 20, 40, 80 mg). Atorvastatin (10–80 mg) + ezetimibe 10 mg (n = 152) reduced LDL-C by 25%; atorvastatin (10–80 mg) + placebo (n = 136) reduced LDL-C by 4.0%.

§ Treatment difference: percentage change with statin plus ezetimibe 10 mg minus percentage change with statin plus placebo, statin doubling, or statin switch.

¶ Statin dose titrated during study. Only used data from indicated week.

# Calculated median percentage change due to wide intrapatient variability in the effects on mean apo B values.

A: Atorvastatin; ATP: Adult treatment panel; CHD: Coronary heart disease; E: Ezetimibe; eze: Ezetimibe; H: Hypercholesterolemia; HDL-C: HDL-cholesterol; HeFH: Heterozygous familial hypercholesterolemia; HoFH: Homozygous familial hypercholesterolemia; LDL-C: LDL-cholesterol; ND: Not determined; Pbo: Placebo; R: Rosuvastatin; S: Simvastatin; TG: Triglycerides.
<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Study number</th>
<th>Population</th>
<th>Therapy (mg/day)</th>
<th>Patients (n)</th>
<th>Study length (weeks)</th>
<th>LDL-C</th>
<th>TG</th>
<th>LDL-C</th>
<th>Non-HDL-C</th>
<th>HDL-C</th>
<th>Total C</th>
<th>TG</th>
<th>Apo B</th>
<th>hsCRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conard et al. (2008)</td>
<td>079</td>
<td>Moderate CHD risk</td>
<td>A20 run-in → A20 + E10 A20 run-in → A40 + A10</td>
<td>98</td>
<td>6</td>
<td>100–160</td>
<td>-20***</td>
<td>-16***</td>
<td>2</td>
<td>-12***</td>
<td>-9</td>
<td>-14***</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Leiter et al. (2008)</td>
<td>090</td>
<td>High CHD risk</td>
<td>A40 run-in → A40 + E10 A40 run-in → A80 + A10</td>
<td>288 – 291</td>
<td>6</td>
<td>70–160</td>
<td>-16</td>
<td>-14***</td>
<td>0</td>
<td>-10***</td>
<td>-7***</td>
<td>-10***</td>
<td>-7</td>
<td></td>
</tr>
<tr>
<td>Zieve et al. (2010)</td>
<td>112</td>
<td>High CHD risk; ≥65 years</td>
<td>A10 run-in → A10 + E10 A10 run-in → A20</td>
<td>526 – 525</td>
<td>6</td>
<td>≥70/&gt;100 ≤350</td>
<td>-14***</td>
<td>-12***</td>
<td>2</td>
<td>-8***</td>
<td>-6***</td>
<td>-9***</td>
<td>-3</td>
<td></td>
</tr>
<tr>
<td>Bays et al. (2013)</td>
<td>139</td>
<td>High CHD risk</td>
<td>A10 run-in → A10 + E10 A10 run-in → A20 + E10 A10 run-in → R10 Above ATP III Target on A20 → A20 + E10 Above ATP III Target on A20 → A40</td>
<td>120 – 124</td>
<td>6</td>
<td>100–160 ≤400</td>
<td>-12.7***</td>
<td>-10.1***</td>
<td>1.7</td>
<td>-7.1***</td>
<td>-2.1</td>
<td>-5.3***</td>
<td>-3.9</td>
<td></td>
</tr>
</tbody>
</table>

*Studies 692, 2173/2246, 040, 803/804, 030, 079, 090, 112 were included in a pooled analyses of 27 studies [54,188].
*Ongoing statins: atorvastatin (10, 20, 40, 80 mg), cerivastatin (0.2, 0.3, 0.4, 0.8 mg), fluvastatin (20, 40, 80 mg), lovastatin (10, 20, 40 mg), pravastatin (10, 20, 40 mg), simvastatin (10, 20, 40, 80 mg). Atorvastatin (10–80 mg) + ezetimibe 10 mg minus percentage change with statin plus placebo, statin doubling, or statin switch.
*Treatment difference: percentage change with statin plus ezetimibe 10 mg minus percentage change with statin plus placebo, statin doubling, or statin switch.
†Ongoing statins: atorvastatin (10, 20, 40, 80 mg); fluvastatin (10, 20, 40, 80 mg; one patient took 160 mg); lovastatin (10, 20, 40, 80 mg); pravastatin (10, 20, 40 mg); simvastatin (10, 20, 40, 80 mg). Atorvastatin (10–80 mg) + ezetimibe 10 mg (n = 769) reduced LDL-C by 25–28%; atorvastatin (10–80 mg) + placebo (n = 398) reduced LDL-C by 3–5%.
‡Statin dose titrated during study. Only used data from indicated week.
§Calculated median percentage change due to wide intrapatient variability in the effects on mean apo B values.
\(p < 0.05; p < 0.01; p < 0.001.
A: Atorvastatin; ATP: Adult treatment panel; CHD: Coronary heart disease; E: Ezetimibe; eze: Ezetimibe; FC: Hypercholesterolemia; HDL-C: HDL-cholesterol; HeFH: Heterozygous familial hypercholesterolemia; HoFH: Homozygous familial hypercholesterolemia; LDL-C: LDL-cholesterol; ND: Not determined; Pbo: Placebo; R: Rosuvastatin; S: Simvastatin; TG: Triglycerides.
Table 1. Clinical studies evaluating the lipid-lowering efficacy of ezetimibe plus atorvastatin (cont.).

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Study number</th>
<th>Trial design</th>
<th>Inclusion criteria (mg/dl)</th>
<th>Treatment difference (% change from baseline)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patients (n)</td>
<td>Study length (weeks)</td>
<td>LDL-C</td>
</tr>
<tr>
<td>Bays et al.</td>
<td></td>
<td>Above ATP</td>
<td>231</td>
<td>6</td>
<td>-9.5***</td>
</tr>
<tr>
<td>(2013)</td>
<td>(cont.)</td>
<td>III Target on R10 — A20 + E10</td>
<td>205</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Studies 692, 2173/2246, 040, 803/804, 030, 079, 090, 112 were included in a pooled analyses of 27 studies [54,188].

†Treatment difference: percentage change with statin plus ezetimibe 10 mg minus percentage change with statin plus placebo, statin doubling, or statin switch.

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¶Statin dose titrated during study. Only used data from indicated week.

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p < 0.05; p < 0.01; p < 0.001.

A: Atorvastatin; ATP: Adult treatment panel; CHD: Coronary heart disease; E: Ezetimibe; eze: Ezetimibe; HC: Hypercholesterolemia; HDL-C: HDL-cholesterol; HoFH: Heterozygous familial hypercholesterolemia; HeFH: Homozygous familial hypercholesterolemia; LDL-C: LDL-cholesterol; ND: Not determined; Pbo: Placebo; R: Rosuvastatin; S: Simvastatin; TG: Triglycerides.
Period I were randomized to addition of ezetimibe to atorvastatin 20 mg or titration of atorvastatin a second time from 20 to 40 mg. After 6 weeks, reduction of LDL-C was significantly greater with combination therapy (-17.4% vs 7.5%; p < 0.001). Patients with LDL-C levels ≥100 mg after 6 weeks of rosuvastatin 10 mg treatment during Period 1 were switched to ezetimibe plus atorvastatin 20 mg or had rosuvastatin 10 mg doubled to 20 mg. For these patients, combination therapy produced significantly greater reductions in LDL-C than rosuvastatin 20 mg (-17.1% vs 7.5%; p < 0.001). Relative to comparative treatments with atorvastatin or rosuvastatin monotherapy, ezetimibe added to atorvastatin resulted in significantly greater attainment of LDL-C targets <100 or <70 mg/dl (Figure 2), and significantly greater reductions in total cholesterol, non-HDL-C and Apo B (significant for all but one comparison).

The broad clinical experience demonstrating the lipid-lowering efficacy and tolerability of coadministered ezetimibe plus atorvastatin led to the development of an FDC of ezetimibe/atorvastatin that recently received FDA approval [66,67]. The FDC meets criteria for clinical equivalence to coadministration of the separate components [64,65]. The availability of ezetimibe/atorvastatin fixed-dose tablets provides a convenient, efficacious and well-tolerated LDL-C-lowering therapy option for patients who do not achieve guideline-recommended LDL-C levels on statin monotherapy. Use of a single tablet regimen ezetimibe/atorvastatin may also help to improve compliance in the combined use of these two agents as has been shown for other single-pill combination therapies [158–162].

Ezetimibe plus statin therapy in surrogate & clinical outcome trials

While a vast amount of evidence exists demonstrating reductions in clinical cardiovascular events with statins, the data for ezetimibe added to statins is much more limited. For this reason, these data will be summarized below. Ezetimibe plus statin combination therapy has been assessed in one surrogate imaging (cIMT) trial in patients with HeFH [142], two completed cardiovascular outcome trials (one in patients with CKD and another in patients with aortic stenosis) [56,151] and in an additional cardiovascular outcome trial study in acute coronary syndrome patients that is currently ongoing [58]. These trials are summarized below and in Table 2. While all of these studies assessed ezetimibe in combination with simvastatin, it is assumed that the results can be extrapolated to ezetimibe combined with other statins (including atorvastatin) that produce similar LDL-C reductions, in light of existing evidence that the relationship between clinical outcomes and statin therapy is primarily related to the absolute LDL-C achieved [1–2,19].

ENHANCE

In the ENHANCE trial, the effect of ezetimibe added to simvastatin 80 mg on the CVD surrogate end point of cIMT was compared with the effect of adding placebo in 720 patients with HeFH [142]. Although coadministration of ezetimibe reduced LDL-C levels significantly more (16.5%) than simvastatin 80 mg (p < 0.01), the mean changes in cIMT (0.0111 ± 0.038 mm vs 0.0058 ± 0.0037 mm, respectively; p = 0.29), were similar after 2 years, with neither treatment producing a significant reduction in cIMT. The authors of the study concluded that this neutral effect was likely due to long-term prior statin treatment in the majority of patients and low-baseline cIMT levels (essentially falling within the normal range) as evidenced in other trials where up to 80 mg of atorvastatin provided no reduction in cIMT in patients on prior statin therapy or with low-baseline cIMT [101,163–164]. This premise was further supported by findings in the SANDS and VYCTOR studies, wherein patients had higher baseline mean cIMT levels (0.80–0.81 mm and 1.23–1.33 mm, respectively) than in ENHANCE (0.67–0.68 mm), and ezetimibe plus statin and statin therapies produced comparable reductions in cIMT progression in proportion to the magnitude of LDL-C lowering [165–168]. Based on the ENHANCE results, some had recommended that other combination statin therapies including fibrates, niacin and bile acid sequestrants should be used before ezetimibe, until results from the ongoing ezetimibe outcomes trial are available [58,59]; however, it should be noted that reductions in CVD events with these agents on top of statins have not been demonstrated in randomized, controlled clinical trials [47–49]. Other expert groups have supported the continued use of ezetimibe, recognizing the limitations of cIMT as a surrogate measure in assessing therapeutic interventions in some settings, consistent with a meta-analysis showing that the reduction of cIMT progression and CVD events was not related [169,170].

SHARP

The recently reported SHARP trial compared combination ezetimibe/simvastatin 10/20 mg with placebo in 9270 patients with moderate-to-advanced CKD, including 3023 patients on dialysis and 6247 who were not on dialysis, [55,151] The combination reduced major atherosclerotic events (MAE), including non-fatal myocardial infarction or coronary death, non-hemorrhagic stroke or any arterial revascularization
Figure 2. Percentage attainment of prespecified LDL-cholesterol targets in two-period study evaluating combination ezetimibe+atorvastatin versus atorvastatin uptitration or switching to rosuvastatin therapy. (A) Percentage attainment of prespecified LDL-C target after 6 weeks (period I). (B) Percentage attainment of prespecified LDL-C target after 6 weeks (period II). **p < 0.01.

†Ratio of the predictive odds of achieving LDL-C level on E10 + A10 versus either A20 or R10.

‡Ratio of the predictive odds of achieving LDL-C level on E10 + A20 versus either A40 or R20.

A10: Atorvastatin 10 mg/day; A20: Atorvastatin 20 mg/day; E10: Ezetimibe 10 mg/day; R10: Rosuvastatin 10 mg/day; R20: Rosuvastatin 20 mg/day.

Adapted with permission from [61].
procedure by 17% compared with placebo during a median follow-up period of 4.9 years (relative risk [RR]: 0.83; 95% CI: 0.74–0.90; p = 0.002). Patients in the study had an average 2/3 adherence rate, and an absolute difference in LDL-C reduction of 33 mg/dl. While the study was not powered to demonstrate significant reductions for the individual components of the MAE end point, significant reductions in non-hemorrhagic stroke (RR: 0.75; 95% CI: 0.60–0.94; p = 0.01) and revascularization procedures (RR: 0.79; 95% CI: 0.68–0.93; p = 0.0036) were observed as well as numerically fewer major coronary events (RR: 0.92; 95% CI: 0.76–1.11; p = 0.37) which reflected nonsignificantly fewer nonfatal MIs (RR: 0.84; 95% CI: 0.66–1.05; p = 0.12) and no significant difference in CHD death (RR: 1.01; 95% CI: 0.75–1.35; p = 0.95). Major vascular events (MAE + noncoronary cardiac deaths + hemorrhagic stroke) were also reduced by 15% with the combination compared with placebo (RR: 0.85; 95% CI: 0.77–0.94; p = 0.0012). The overall observed reduction of cardiovascular events was per mmol LDL-C lowering (39 mg/dl), was consistent with results from the Cholesterol Treatment Trialists (CTT) meta-analysis of statin trials in patients without CKD [1,2].

Although the study was not powered to assess MAE in patient subgroups, the treatment effects were generally consistent among all subgroups evaluated, including dialysis and nondialysis patients (test for heterogeneity between groups p = 0.25). The difference in the proportional treatment effects was not statistically significant between these two patient groups; however, the treatment effect on MAE appeared to be somewhat attenuated in patients on dialysis at baseline (RR: 0.90; 95% CI: 0.75–1.08) compared with those not on dialysis (RR: 0.78; 95% CI: 0.67–0.91). This was likely due to lower mean baseline LDL-C levels and reduced treatment compliance among patients on dialysis at baseline, resulting in smaller absolute LDL-C reductions (23 mg/dl) compared with the nondialysis cohort patients (31 mg/dl). After weighting the LDL-C reductions, the proportional reductions of MAE per 1 mmol/l (38.6 mg/dl) LDL-C reduction were similar (16–25%) across stages 3–5 CKD patients, and those patients on dialysis at baseline. Among the patients who were not on dialysis at baseline, combination ezetimibe plus simvastatin did not have a significant effect on any of the pre-specified measures of renal disease progression (progression to end-stage renal disease [ESRD], ESRD plus time to doubling of serum creatinine, ESRD or death), although findings for all of these measures were directionally favorable. It should be noted that some studies in patients with less-advanced renal disease have shown slowing of loss of renal function with statin treatment over time [171,172]. Taken together, the SHARP study results demonstrated that cholesterol-lowering therapy, and specifically ezetimibe 10 mg plus simvastatin 20 mg, reduced atherosclerosis-related vascular events in moderate-to-advanced CKD patients.

To date, SHARP is the only study that has shown a benefit of lipid-lowering therapy on cardiovascular outcomes in patients with advanced CKD and the study results have been published in guidelines on cholesterol management as supporting evidence/information for recommendations regarding treatment of CKD patients [6,9,81]. In prior statin trials in CKD dialysis patients, the absence of significant reductions of CVD events may be attributed to smaller study populations and to lower proportions of atherosclerotic-related events specified in the primary outcome end point in these trials than would be expected to be modifiable by lowering of LDL-C levels [99,173–174]. Additionally, because dialysis patients commonly have lower LDL-C levels at baseline, CVD risk reduction, which is proportional to absolute change in LDL-C, is correspondingly smaller [139,55]. Studies of larger populations, including post hoc analyses of statin trials in patients with stages 2–3 CKD, and meta-analyses of statin trials have shown a benefit of LDL-C lowering on a reduction in recurrent CVD events in patients at all stages of CKD, as well as a reduction in all-cause and CVD mortality in those who were not on dialysis [175–178].

**SEAS**

The effect of ezetimibe 10 mg plus simvastatin 40 mg versus placebo on a composite of major aortic-valve-related events (AVE) and ischemic cardiovascular events (ICE) was studied in 1873 patients with mild-to-moderate aortic stenosis (AS) and no history of prior CHD in the SEAS trial [56]. The observed rates of any major cardiovascular event (AVE plus ICE), were not significantly different in the ezetimibe plus simvastatin (35.3%) and placebo (38.2%) groups, despite a 50% reduction in LDL-C levels compared with placebo. The end point category of aortic valve replacement comprised the large majority of primary end point events. There was also no significant difference in the end point of AVE alone, (comprised of aortic valve replacement, death from cardiovascular causes and hospitalization for heart failure) with either treatment. However, the ICE composite end point (cardiovascular death, nonfatal acute myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, hospitalization for unstable angina pectoris, nonhemorrhagic stroke) was
Table 2. Ezetimibe surrogate imaging and clinical outcome studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment (mg)</th>
<th>Population</th>
<th>Study length</th>
<th>Clinical end points</th>
<th>Results</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENHANCE</td>
<td>E10 + S80 vs Pbo + S80</td>
<td>n = 720, 30–75 years; heFH</td>
<td>2 years (2002–2006)</td>
<td>Primary: – mean cIMT (average of far wall right and left CCA, ICA, carotid bulb)</td>
<td>Primary: – Mean change in cIMT: Pbo + S80 mg (0.058 ± 0.037 mm) vs E10 mg + S80 mg (0.011 ± 0.038 mm); p = 0.29</td>
<td>[142]</td>
</tr>
<tr>
<td>SEAS</td>
<td>E10 + S40 vs Pbo + S40</td>
<td>n = 1873 asymptomatic AS, mean baseline LDL = 140 mg/dl</td>
<td>4 years (2001–2006)</td>
<td>Primary: – Composite of major CVD events (CV death, aortic-valve replacement, nonfatal MI, unstable angina requiring hospitalization, heart failure, CABG, PCI and nonhemorrhagic stroke Second: – AVE and ICE</td>
<td>Primary: – Composite (n = 333 [35.3%] vs n = 355 [38.2%]), HR: 0.96; 95% CI: 0.83–1.12, p = 0.59) Secondary: – AVE, n = 308 [32.6%] vs n = 326 [35.1%], HR: 0.97 [0.83–1.14] – ICE, n = 148 [15.7%] vs n = 187 [20.1%], HR: 0.78 [0.63–0.97])</td>
<td>[56]</td>
</tr>
<tr>
<td>SHARP</td>
<td>E10 + S20 vs Pbo</td>
<td>n = 9270, CKD 33% on dialysis and 67% nondialysis at baseline. Mean baseline LDL = 108 mg/dl</td>
<td>4 years, randomization (2006–2010)</td>
<td>Primary: – Major vascular events (nonfatal MI or cardiac death, nonfatal or fatal stroke, revascularization) Second: – Progression to ESRD, deaths, major cardiac events, stroke and angina requiring hospitalization</td>
<td>Primary: – Major attherosclerotic events (n = 526 [11.3%] vs n = 619 [13.4%]; RR: 0.83; 95% CI: 0.74–0.94; p = 0.0021) – Nonfatal MI/CHD death (n = 213 [4.6%] vs n = 230 [5.0%]; RR: 0.92; 95% CI: 0.76–1.11; p = 0.37) – Nonhemorrhagic stroke (n = 131 [2.8%] vs n = 174 [3.8%]; RR: 0.75; 95% CI: 0.60–0.94; p = 0.01) – Revascularization procedures (n = 284 [6.1%] vs n = 352 [7.6%]; RR: 0.79; 95% CI: 0.68–0.93; p = 0.0036)</td>
<td>[55]</td>
</tr>
<tr>
<td>IMPROVE-IT</td>
<td>E10 + S40 vs S40</td>
<td>n = 18,000, acute coronary syndrome Mean baseline LDL approximately 97 mg/dl (first 10,000 patients enrolled)</td>
<td>8 years (2005–2013)</td>
<td>Primary: – Major coronary events (CV death, nonfatal MI, angina requiring hospitalization, coronary revascularization) or nonfatal stroke Second: – Death due to any cause, major coronary event or nonfatal stroke; CHD death, nonfatal MI, coronary revascularization; CV death, nonfatal MI, unstable angina requiring hospitalization, all revascularization</td>
<td>In progress</td>
<td>[58,59]</td>
</tr>
</tbody>
</table>

AS: Aortic stenosis; AVE: Aortic valve events; BP: Blood pressure; CABG: Coronary-artery bypass grafting; CCA: Common carotid artery; CHD: Coronary heart disease; cIMT: Carotid intima-media thickening; CKD: Chronic kidney disease; CV: Cardiovascular; CVD: Cardiovascular disease; E: Ezetimibe; ERN: Extended-release niacin; ESRD: End-stage renal disease; HR: Hazard ratio; ICA: Internal carotid artery; ICE: Ischemic cardiovascular events; MI: Myocardial infarction; Pbo: Placebo; PCI: Percutaneous coronary intervention; RR: Rate ratio; S: Simvastatin.

Adapted with permission from [52].
The incidence of clinical adverse events-

A secondary analysis of the SEAS study showed that the reduction of ICE with ezetimibe plus simvastatin was confined to those patients with less severe AS, classified on the basis of jet velocity (JV) tertiles at baseline [57]. Compared with placebo, coadministration of ezetimibe with simvastatin 40 mg significantly reduced ICE risk by 47% (p < 0.001) in the lowest JV tertile and by 36% (p < 0.05) in the middle tertile [56,57]. Additionally, ICE risk was significantly associated with changes in LDL-C levels in the two lower JV tertiles of patients but not in the highest tertile. Based on the magnitude of LDL-C reduction achieved in the SEAS study, the degree of ICE risk reduction observed among the two tertiles of patients with less severe AS was entirely consistent with that predicted from data in the Cholesterol Treatment Trials (CTT) meta-analysis of statin trials [1]. The fact that the observed ICE risk reduction was related to the extent of LDL-C lowering among patients with less severe AS but not those with more severe AS, was considered likely to be due to confounding of the ‘ICE’ category by AS-related events (e.g., CABG performed in conjunction with aortic valve replacement, cardiovascular death) as well as a shorter interval of exposure to lipid-lowering therapy prior to events. It should be noted that in other randomized controlled clinical trials, a reduction in AVE or AS severity also was not observed with intensive statin therapy. These studies evaluated the effects of atorvastatin 80-mg therapy, as measured by aortic JV and calcium score in patients with moderate-to-severe AS [179]; and rosuvastatin 40-mg treatment, as assessed by peak JV gradient and aortic valve area in patients with mild-to-moderate AS [180].

**IMPROVE-IT**

The ongoing IMPROVE-IT trial is assessing the incremental LDL-C lowering effect of ezetimibe when added to a statin on reducing CVD outcomes at low LDL-C levels [58,59]. In the trial, patients with acute coronary syndrome (n = 18,142) were randomized to combination ezetimibe plus simvastatin (10/40 mg) versus simvastatin monotherapy (40 mg) and are being followed during a minimum of 2.5 years and until at least 5250 patients experience a primary end point event, defined as a composite of major cardiovascular outcomes. The trial was designed to assess the benefit of reducing LDL-C by an estimated incremental 14–15 mg/dl through the use of ezetimibe combined with simvastatin, compared with simvas-

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**Clinical safety**

In numerous lipid-altering efficacy trials of up to 48 weeks in duration, ezetimibe administered in combination with statins was generally well tolerated, with a safety profile similar to that of ezetimibe or statins alone (including atorvastatin) in hypercholesterolemic patients, as well as in patients with metabolic syndrome and Type 2 diabetes [52–54,66,123,183]. Using individual patient data pooled from 27 clinical studies (n = 22, 278), ezetimibe plus statin and statin monotherapies were generally well tolerated for up to 24 weeks and had relatively similar safety profiles [54]. This pooled analysis evaluated all ezetimibe plus atorvastatin data that was available at the time, including data from the eight studies as indicated in Tables 1 & 3. The incidence of clinical adverse events (AEs) was low, including drug-related, serious and serious drug-related AEs, as well as discontinuations due to AEs, or creatine kinase [CK] elevations ≥10-times the upper limit of normal (ULN). There was a small, statistically significant increase in the incidence of alanine aminotransferase/aspartate aminotransferase [AST/ALT] elevations ≥3X ULN for the combination (p = 0.017), consistent with the rates described in the prescribing information for these therapies [66,183]. The incidence of myopathy was small and similar for both treatments (0.06% statin monotherapy vs 0.03% ezetimibe plus statin), and there were no cases of rhabdomyolysis in this cohort. A total of 12 non-drug-related deaths were reported in the 27 studies (0.1% for both groups). AEs were generally similar between treatments in gender, age, diabetes and race subgroups [54,145,184] with some exceptions. Women reported significantly more clinical AEs (i.e., ≥1 AE) including drug, gall bladder, gastrointestinal and hep-
Review Foody, Toth, Tershakovec et al.

atities-related AEs, as well as allergic reaction or rash-related AEs. More women discontinued treatment due to AEs compared with men, and more men reported CK elevations than women [54,184]. Among black subjects, increases in CK elevations ≥10X ULN occurred significantly more often with statins versus the combination (0.7% vs 0.0%); nonetheless, the occurrence of myopathy was low and similar for both treatment groups. More subjects ≥65 years experienced serious AEs and discontinued due to serious AEs compared with those <65 years, and subjects <65 years reported significantly more CK ≥10 XULN elevations than those ≥65 years. There was no difference in myopathy occurrence for the age groups. The safety profiles of these therapies in first and second-line studies were generally similar to the pooled cohort; however, there were more AEs reported in first line than in second-line studies for both treatments, possibly related to preselection of second-line patients who were on ongoing statin therapy and discontinued the study prior to randomization due to tolerability issues [54]. The incidence of serious AEs was higher in second-line studies with ezetimibe + statin treatment, and the incidence of allergic reactions was also higher for both first- and second-line studies.

A meta-analysis of 18 randomized clinical trials (n = 14,497) that included some of the above-mentioned studies in the pooled analysis in addition to others, showed no increase in the incidence of myalgias, CK or ALT/AST elevations, rhabdomyolysis, gastrointestinal AEs or discontinuations due to an AE with combination ezetimibe plus statin therapy compared with statin monotherapy [185]. The safety of ezetimibe and ezetimibe plus statins in patients aged 65–74 years, and ≥75 years was comparable to that of patients <65 years in an additional pooled analysis of 16 clinical studies [186]. In statin-intolerant patients, including those with FH and diabetes who had previously experienced what were believed to be statin side effects, ezetimibe + a statin was generally well tolerated without adverse effects for up to 6 months of treatment [129–131,154]. Study-level data for the ten randomized clinical trials (n = 9034) listed in Table 1 that evaluated coadministration of ezetimibe with atorvastatin also demonstrated a favorable safety and tolerability profile (Table 3).

In the above-mentioned ENHANCE, SEAS and SHARP studies comprising >11,000 patients up to 4.9 years of treatment duration, there were no significant differences in the overall incidence of AEs for ezetimibe plus statins compared with placebo or statins alone [55–56,142]. This included no significant differences in gastrointestinal, hepatitis- and gallbladder-related AEs and allergic reaction/rash, or CK elevations. Liver enzyme elevations were also comparable, with the exception of the SEAS trial in which significantly greater rates of consecutive elevations in AST and/or ALT ≥3X ULN levels occurred with ezetimibe plus simvastatin compared with placebo (1.7% vs 0.5%, respectively; p = 0.03) that were within the range reported in the prescribing information for the combination; most cases were not severe and remitted when therapy was stopped [56,183]. In the SHARP study, no major safety issues were reported for ezetimibe plus simvastatin compared with placebo in CKD patients during 4.9 years [55]. In particular, there were very few cases of myopathy of any severity or of more severe cases with rhabdomyolysis (excess incidence 2/10,000 patients/year), which is a concern in CKD patients who have an increased risk of statin-associated myopathy; thus, the use of high-dose statin therapy should be carefully monitored in these patients [55,189].

Although there was an unexpected finding of increased numbers of incident and fatal cancers in the ezetimibe plus simvastatin group compared with the placebo group in the SEAS trial [56], the results of an independent meta-analysis of interim safety data from SHARP and IMPROVE-IT (approximately 20,000 patients) did not find any adverse effect of ezetimibe on rates of cancer [190]. Large earlier meta-analyses of statins and cancer have not shown any relationship between statin use and cancer [191–192]. In addition, a large postmarketing analysis of data, and evaluation of extensive clinical and nonclinical study databases did not find an increased risk of cancer with ezetimibe plus simvastatin [125,193]. More recently, in the completed SHARP study where the incidence of cancer was approximately 5X greater than in SEAS, the rates of occurrence were comparable in the ezetimibe/simvastatin and placebo groups [55]. Furthermore, the ongoing >18,000 patient IMPROVE-IT trial with a mean patient follow-up now >5 years and in which cancer has been evaluated as an adjudicated adverse event of special interest [59], the unblinded Data and Safety Monitoring Board has not reported any safety concerns related to cancer as of their last review in March 2013. Overall, these findings indicate that the imbalance observed in the SEAS trial was a chance occurrence.

Conclusion
Extensive evaluation of statins in randomized clinical outcome trials has demonstrated a linear relationship between the absolute reduction of LDL-C and reduction of cardiovascular disease risk. Despite the proven effectiveness of statin therapy, attainment of adequate LDL-C lowering is frequently suboptimal, particularly in high-risk CHD patients. Some guide-
lines recommend treatment strategies to address this treatment gap that include statin titration, switching to a statin with greater LDL-C lowering efficacy, or addition of complementary lipid-lowering drugs. For high-risk patients requiring additional LDL-C lowering, combination therapy may be required. However, definitive evidence for incremental reduction of CVD risk with combination statin therapy is lacking. To date, large clinical outcome trials have not shown a benefit of adding niacin or fibrates to statin therapy on reducing CVD events more than statins alone (47–49).

Ezetimibe is the only approved agent available to reduce plasma cholesterol levels by selective inhibition of cholesterol absorption in the small intestine. Administered as monotherapy, ezetimibe has been shown to be well tolerated and effective in lowering LDL-C as well as improving other key lipids and lipoproteins in patients with primary hypercholesterolemia. Ezetimibe is also effective in the treatment of patients with homozygous sitosterolemia, and those who are intolerant to statin therapy. When ezetimibe is used in combination with statins, the complementary inhibition of cholesterol absorption results in greater reductions in LDL-C than either drug alone, approximately equivalent to an eightfold increase in statin dose, allowing significantly more patients to reach guideline recommended treatment targets. Consistent lipid-lowering results with combination therapy have been seen in diverse patient populations differing by age, gender, race, comorbid medical condition (diabetes mellitus, CKD) and CHD risk status. Pooled data analysis from 27 clinical studies of over 22,000 patients demonstrated the favorable safety and tolerability profile for coadministration of ezetimibe with statins and statin monotherapy.

Two of the three large clinical trials designed to evaluate the effect of ezetimibe in combination with statins on clinical outcomes have completed. The SHARP findings indicate that the combination of ezetimibe plus simvastatin 20 mg is an effective and well-tolerated LDL-C lowering treatment option with proven outcomes for moderate-to-advanced CKD patients. In the SEAS study of patients with asymptomatic aortic stenosis, although ezetimibe 10 mg plus simvastatin 40 mg did not reduce the primary end point consisting of a composite of AVE and ICE, the combination significantly reduced the key secondary end point of ICE by 22% and was most pronounced in patients with less severe aortic stenosis, presumably due to confounding by aortic-related events in the more severe aortic stenosis patients. While the risk reduction of cardiovascular ischemic events in these two trials was consistent with the degree of LDL-C lowering predicted by the CTT meta-analysis of statin trials, it should be noted that the incremental benefit of LDL-C lowering by ezetimibe when added to statin therapy on CVD risk reduction is currently being assessed in the ongoing IMPROVE-IT outcomes trial in patients with acute coronary syndrome.

Atorvastatin is one of the most potent LDL-C lowering statins with clinically proven effects on reduction of cardiovascular morbidity and mortality. Several randomized controlled clinical trials in patients with hyperlipidemia, HeFH or moderate-to-high cardiovascular risk have demonstrated that combining ezetimibe with atorvastatin therapy was well tolerated and improved the reduction of LDL-C beyond that seen with either drug separately or doubling the atorvastatin dose. For statin-naïve patients with hypercholesterolemia, coadministration of ezetimibe and atorvastatin 10–80 mg produced a dose-dependent mean LDL-C reduction of 53–61%. These studies provided the foundation for the recent FDA approval of an FDC of ezetimibe 10 mg and atorvastatin (10, 20, 40, 80 mg). The availability of FDC ezetimibe/atorvastatin as a single tablet, provides a convenient, effective and generally well-tolerated therapeutic option for treatment of dyslipidemia, particularly for those patients with high CHD risk who do not achieve guideline-recommended LDL-C levels on statin monotherapy.

**Future perspective**

Given that many patients, particularly those with high CVD risk, do not achieve adequate LDL-C lowering on statin monotherapy, some guidelines have recommended statin uptitration and/or combination therapy for these patients. While greater LDL-C lowering can be achieved with a more potent statin or with combination therapy, several studies have shown that these therapies are not frequently used due to various factors including statin intolerance, reluctance on the part of patients/providers to use higher statin doses/more potent statins, in addition to cost factors and patient noncompliance [34,36,40–41,45,194–198]. Recent surveys have shown that more than 50% of patients discontinue statin medication within 1 year after initiation of therapy. A paucity of evidence for the effectiveness of statin combination therapy in reducing cardiovascular events has further limited its use. In large clinical studies, combination therapy with fibrates or niacin showed no greater benefit on CVD outcomes than statins alone [47–49] and the efficacy of combining bile acid sequestrants with statins versus statins alone has not been evaluated in outcome trials [50]. In numerous lipid-altering efficacy studies, the combination of ezetimibe with statins has been shown to be an effective lipid-lowering therapy.
Table 3. Clinical studies evaluating the safety and tolerability of ezetimibe plus atorvastatin.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Study number</th>
<th>Therapy (mg)</th>
<th>Patients (n)</th>
<th>Time (weeks)</th>
<th>Discontinued any AE</th>
<th>Discontinued drug-related AE†</th>
<th>ALT ≥3X ULN‡</th>
<th>AST ≥3X ULN§</th>
<th>ALT/AST ≥3X ULN§</th>
<th>CK ≥10X ULNw/muscle symptoms</th>
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</thead>
<tbody>
<tr>
<td>Ballantyne et al. (2003)</td>
<td>692</td>
<td>A10, A20, A40, A80</td>
<td>248</td>
<td>12</td>
<td>13 (5)</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A10, A20, A40, A80 + E10</td>
<td>255</td>
<td>15 (6)</td>
<td>3 (1)</td>
<td>4 (2)</td>
<td>2 (&lt;1)</td>
<td>0</td>
<td>1 (&lt;1%)</td>
<td></td>
</tr>
<tr>
<td>Ballantyne et al. (2004); extension (2003)</td>
<td>692</td>
<td>A10, A20, A40, A80</td>
<td>45</td>
<td>24</td>
<td>3 (7)</td>
<td>3 (7)</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A10, A20, A40, A80 + E10</td>
<td>201</td>
<td>19 (9)</td>
<td>13 (6)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Gagne et al. (2002)</td>
<td>2173/2246</td>
<td>Ongoing statin§ + Pbo</td>
<td>390</td>
<td>8</td>
<td>14 (3.6)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>1 (&lt;1)</td>
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<tr>
<td></td>
<td></td>
<td>Ongoing statin§ + E10</td>
<td>379</td>
<td>14 (3.7)</td>
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<td></td>
<td></td>
<td></td>
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<td>0</td>
</tr>
<tr>
<td>Pearson et al. (2005)</td>
<td>040</td>
<td>Ongoing statin§ + Pbo</td>
<td>1010</td>
<td>8</td>
<td>NR</td>
<td>(1.6)</td>
<td>2 (0.2)</td>
<td>1 (0.1)</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ongoing statin§ + E10</td>
<td>2020</td>
<td>(&lt;1)</td>
<td>9 (0.5)</td>
<td>4 (0.2)</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Cruz-Fernandez et al. (2005)</td>
<td>803/804</td>
<td>Ongoing A10/20 + Pbo</td>
<td>230</td>
<td>6</td>
<td>1 (0.5)</td>
<td>0</td>
<td>ND</td>
<td>ND</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ongoing A10/20 + E10</td>
<td>220</td>
<td>2 (0.9)</td>
<td>1 (0.4)</td>
<td></td>
<td></td>
<td></td>
<td>1 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Gagne et al. (2002)</td>
<td>018</td>
<td>A40 or S40 → A80 or S80</td>
<td>17</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>ND</td>
<td>ND</td>
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</tr>
</tbody>
</table>

Studies 692, 2173/2246, 040, 803/804, 030, 079, 090, 112 were included in a pooled analyses of 27 studies [54,188]

†Determined by the investigator to be related to the drug.
‡All AEs collected up to end of 14-day follow-up window were included in analysis. For laboratory safety (ALT, AST), patients must have taken at least one dose of study medication and have at least one postbaseline measurement within 14 days of the last dose of study therapy to be included in the analysis. Laboratory values ≥3X the ULN on two consecutive visits, or a single value ≥3X ULN during the study and no follow-up measurement was made ≤2 days after discontinuation of study drug.
§Ongoing statins = atorvastatin (10, 20, 40, 80 mg), cerivastatin (0.2, 0.3, 0.4, 0.8 mg), fluvastatin (20, 40, 80 mg), lovastatin (10, 20, 40 mg), pravastatin (10, 20, 40 mg) and simvastatin (10, 20, 40, 80 mg).
¶Ongoing statins = atorvastatin (10, 20, 40, 80 mg), fluvastatin (20, 40, 80 mg; one patient took 160 mg), lovastatin (10, 20, 40, 80 mg), pravastatin (10, 20, 40, 80 mg), and simvastatin (10, 20, 40, 80 mg).
○Muscle pain thought to be caused by weight training.
A: Atorvastatin; AE: Adverse event; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CK: Creatine kinase; E: Ezetimibe; HC: Hypercholesterolemia; HeFH: Heterozygous familial hypercholesterolemia; HoFH: Homozygous familial hypercholesterolemia; ND: Not determined; Pbo: Placebo; R: Rosuvastatin; S: Simvastatin; ULN: Upper limit of normal.
<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Study number</th>
<th>Therapy (mg)</th>
<th>Patients, n (%)</th>
<th>Time (weeks)</th>
<th>Discontinued any AE</th>
<th>Discontinued drug-related AE†</th>
<th>ALT ≥ 3X ULN‡</th>
<th>AST ≥ 3X ULN§</th>
<th>ALT/AST ≥ 3X ULN¶</th>
<th>CK ≥ 10X ULN</th>
<th>CK ≥ 10X ULN w/muscle symptoms</th>
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<td>Stein et al. (2004)</td>
<td>30</td>
<td>A10 run-in → A10–40 + E10</td>
<td>305</td>
<td>14</td>
<td>13 (4)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>3 (1)</td>
<td>0</td>
<td>0</td>
<td>[138]</td>
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<tr>
<td></td>
<td></td>
<td>A10 run-in → A20–80</td>
<td>316</td>
<td>14 (4)</td>
<td>ND</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>1 (&lt;1)**</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Conard et al. (2008)</td>
<td>079</td>
<td>A20 run-in → A20 + E10</td>
<td>98</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>[60]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A20 run-in → A40</td>
<td>98</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Leiter et al. (2008)</td>
<td>090</td>
<td>A40 run-in → A40 + E10</td>
<td>288</td>
<td>6</td>
<td>4 (1)</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>[62]</td>
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<tr>
<td></td>
<td></td>
<td>A40 run-in → A80</td>
<td>291</td>
<td>6 (2)</td>
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<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Zieve et al. (2010)</td>
<td>112</td>
<td>A10 run-in → A10 + E10</td>
<td>526</td>
<td>12</td>
<td>14 (3)</td>
<td>6 (1)</td>
<td>1 (&lt;1)</td>
<td>2 (&lt;1)</td>
<td>2 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>[63]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A10 run-in → A20/40</td>
<td>525</td>
<td>8 (2)</td>
<td>3 (1)</td>
<td>3 (1)</td>
<td>5 (1)</td>
<td>5 (1)</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td></td>
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<tr>
<td>Bays et al. (2013)</td>
<td>162</td>
<td>A10 run-in → A10 + E10</td>
<td>120</td>
<td>6</td>
<td>1 (0.8)</td>
<td>1 (0.8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>[61]</td>
</tr>
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<td></td>
<td></td>
<td>A10 run-in → A20</td>
<td>480</td>
<td>9 (1.9)</td>
<td>6 (1.3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>A10 run-in → R10</td>
<td>939</td>
<td>11 (1.2)</td>
<td>9 (1.0)</td>
<td>2 (0.2)</td>
<td>0</td>
<td>2 (0.2)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
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<td></td>
<td></td>
<td>Above ATP III Target on A20 → A20 + E10</td>
<td>124</td>
<td>6</td>
<td>1 (0.8)</td>
<td>1 (0.8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A40</td>
<td>124</td>
<td>1 (0.8)</td>
<td>1 (0.8)</td>
<td>1 (0.8)</td>
<td>0</td>
<td>1 (0.8)</td>
<td>0</td>
<td>0</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Above ATP III Target on R10 → A20 + E10</td>
<td>231</td>
<td>6</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>R20</td>
<td>205</td>
<td>1 (0.5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Studies 692, 2173/2246, 040, 803/804, 030, 079, 090, 112 were included in a pooled analysis of 27 studies [54,188].

†Determined by the investigator to be related to the drug.
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§Laboratory values ≥ 3X the ULN on two consecutive visits, or a single value ≥ 3X ULN during the study and no follow-up measurement was made ≤ 2 days after discontinuation of study drug.
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※Ongoing statins = atorvastatin (10, 20, 40, 80 mg), fluvastatin (10, 20, 40, 80 mg; one patient took 160 mg), lovastatin (10, 20, 40, 80 mg), pravastatin (10, 20, 40, 80 mg), simvastatin (10, 20, 40, 80 mg).
**Muscle pain thought to be caused by weight training.
A: Atorvastatin; AE: Adverse event; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CK: Creatine kinase; E: Ezetimibe; HC: Hypercholesterolemia; HeFH: Heterozygous familial hypercholesterolemia; HoFH: Homozygous familial hypercholesterolemia; ND: Not determined; Pbo: Placebo; R: Rosuvastatin; S: Simvastatin; ULN: Upper limit of normal.
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[52,53], and in outcome trials, the coadministration of ezetimibe with simvastatin has also been shown to reduce ischemic events in CKD patients and in patients with mild-to-moderate aortic stenosis [55–57]. However, the incremental benefit that ezetimibe may provide in reducing cardiovascular events compared with statins alone awaits the results of the ongoing IMPROVE-IT trial, anticipated to complete in late 2014 [58,59].

Safety concerns related to each of these combination therapies can also limit their use. The most prominent side effect of niacin is flushing; however, niacin is also associated with gastrointestinal, hepatic, hyperglycemic, hyperuricemic and coagulopathic adverse effects [199]. In addition, increased incidences of some types of nonfatal, serious side effects including infections, bleeding, gastrointestinal, musculoskeletal and skin effects were recently reported in the HPS2-THRIVE trial that evaluated the effect of niacin in combination with statin therapy and the anti-flushing agent laropiprant on CVD event reduction, thus bringing into question the overall safety of niacin [48]. Fibrates have been associated with elevated liver enzymes, increased risks of cholelithiasis, myopathy and rhabdomyolysis when coadministered with statins [83,200]. Bile acid sequestrants are generally safe, although poorly tolerated due to associated gastrointestinal side effects, and should be used with caution in patients with triglyceride levels greater than 300 mg/dl, as they can exacerbate hypertriglyceridemia [83,201].

Other novel lipid-lowering therapeutic approaches currently being evaluated in clinical trials include inhibitors of serum PCSK9, apoB synthesis and microsomal triglyceride transfer protein (MTP) [202–209]. PCSK9 binds to and promotes degradation of LDL-receptors thereby decreasing the clearance of LDL-C from circulation. Naturally occurring loss-of-function mutations in this gene are associated with 11.6–19.3 mg/dl lower levels of LDL-C and reduced CVD risk, while gain-of-function mutations lead to higher LDL-C concentrations and increased CVD risk [206,207]. Recent clinical studies using human monoclonal antibodies to PCSK9 that block its interaction with LDL receptors have been shown to reduce LDL-C by 36–58% in patients on statin therapy with hyperlipidemia and FH when given as monotherapy or in combination with ezetimibe [202,206,208–212] and also in those who are statin intolerant [213]. Assessment of the benefit of PCSK9 antibodies on reduction of cardiovascular events is currently being evaluated in four large randomized outcome trials (ODYSSEY Outcomes [214], FOURIER [215], SPIRE-1 [216] and SPIRE-2 [217]). Small molecule and anti-sense oligonucleotide inhibitors of PCSK9 are also in the early stages of development (Alnylam, MA, USA; ISIS, CA, USA). The anti-sense oligonucleotide mipomersen reduces the synthesis of ApoB and in turn inhibits VLDL particle synthesis. It received orphan drug approval from the FDA as an adjunct to lipid-lowering medications and diet to treat patients with HoFH and is currently in Phase III development for the treatment of other forms of hyperlipidemia [218]. Mipomersen lowers LDL-C by 25% in patients on statin therapy with He and HoFH [219–221], and by 47% in statin-intolerant patients [205], and also reduces levels of ApoB, and lipoprotein (a). Its main side effects are injection site reactions and a mild, reversible hepatic steatosis. Lomitapide, an MTP inhibitor, reduces LDL-C by 50% at 26 weeks in HoFH patients and has received orphan drug approval by the FDA for lowering LDL-C, TC, ApoB and non-HDL-C in these patients when used in combination with a low fat diet and other LLT [204]. Side effects include liver toxicity and gastrointestinal-related effects. Additional studies are underway to further assess its safety. Mipomersen and lomitapide may be limited to use in rare populations where needed, due to side effects; whereas PCSK9 has a better side effect profile and may have wider applicability. Use of both mipomersen and anti-PCSK9 may be further limited by the practicality and cost of subcutaneous delivery, as well as the need for monitoring drug levels.

The substantial residual CVD risk that remains in high-risk patients receiving standard of care therapy highlights the need for additional lipid management strategies. The use of second-line agents to augment the LDL-C lowering effects of statins may be particularly important in patients who are unable to tolerate statins or who do not achieve desired LDL-C levels while taking maximum-tolerated statin doses [4–7,9]. This approach may benefit high-risk patients with more complex dyslipidemic profiles associated with diabetes, metabolic syndrome, familial dyslipidemias, CKD and AS. Whether novel lipid-lowering therapies currently in development, and/or use of existing therapies will improve LDL-C lowering and CVD risk reduction in these patients remains to be seen. Better education of healthcare providers and patients, in addition to system-wide changes that will reinforce adherence to guidelines and therapy are also important toward reducing residual CVD risk. In this regard, the availability of atorvastatin as a generic formulation may increase the use of this more potent statin, and the recently approved FDC of ezetimibe plus atorvastatin may provide a safe and effective option with the convenience of a single pill for those in need of more intensive lipid-lowering therapy [67].
Executive summary

Cholesterol-lowering management with statin therapy
• Statins are recommended as the first-line therapeutic approach for lowering LDL-cholesterol (LDL-C) levels; however, many patients do not achieve adequate LDL-C lowering on statin therapy alone.
• Several guidelines recommend statin uptitration, switching to higher potency statins and/or combination therapy for additional LDL-C lowering in high-risk patients.
• These approaches are infrequently used, attributed to various barriers including tolerability, noncompliance, patient/prescriber nonadherence to guidelines, cost factors and a lack of evidence for cardiovascular disease (CVD) risk reduction with combination therapy.

Efficacy & safety of atorvastatin therapy
• Atorvastatin is a widely used statin that is generally well tolerated and lowers LDL-C levels with mean reductions ranging from 37 to 53%.
• Atorvastatin has been shown to reduce cardiovascular events in numerous clinical outcome trials.

Lipid-lowering efficacy of ezetimibe plus atorvastatin combination therapy
• Ezetimibe added to atorvastatin therapy improves LDL-C lowering and other lipid levels significantly more than doubling the atorvastatin dose.
• The combination is generally well tolerated with a safety profile similar to those of the individual component agents.

Ezetimibe plus statin combination therapy in surrogate & clinical outcome trials
• Ezetimibe plus statin therapy has produced variable results in surrogate outcome trials, attributed to differences in study designs and populations.
• In clinical outcome trials, ezetimibe coadministered with simvastatin reduced ischemic events in patients with less severe aortic stenosis (SEAS) and moderate-to-advanced chronic kidney disease (SHARP), consistent with the degree of LDL-C lowering predicted by the Cholesterol Treatment Trialists meta-analysis of statin trials.
• The incremental benefit of LDL-C lowering with ezetimibe in combination with simvastatin on CVD outcomes is currently being assessed in the ongoing IMPROVE-IT trial.

Future perspective
• Several novel lipid-lowering agents in development provide greater LDL-C lowering than statin monotherapy; evaluation of the effects of these therapies on CVD event reduction is needed.
• The recently approved fixed-dose combination of ezetimibe plus atorvastatin provides a generally well-tolerated lipid-lowering option for patients on statin therapy who need further LDL-C lowering; the benefit of ezetimibe combined with statin therapy on CVD risk awaits results of the IMPROVE-IT trial.
• Better patient/provider education as well as system-wide changes are also needed to further improve lipid-lowering management overall.

References
Papers of special note have been highlighted as:
• of interest; •• of considerable interest

•• Largest meta-analysis of 26 randomized controlled statin trials, including intensive treatment, showing that the magnitude of LDL lowering is related to the reduction of cardiovascular events.
• Meta-analysis of 18 intervention trials showing the relationship between statin and nonstatin lipid-lowering therapies with cardiovascular risk reduction.


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** Meta-analysis of 27 randomized, controlled statin trials showing the relationship between LDL-C lowering and reduction of cardiovascular events in patients with lower CVD risk; the clinical benefit outweighed the risk.


Efficacy & safety of ezetimibe plus atorvastatin therapy

Review


Review

Foody, Toth, Tershakovec et al.


- Pooled analysis of safety data from 27 randomized controlled clinical trials of ezetimibe plus statin combination therapy.


- Large, randomized controlled SHARP trial of the effect of simvastatin plus ezetimibe versus placebo in patients with chronic kidney disease.


- Substudy of the SEAS trial that assessed the relationship between lipid-lowering and ischemic risk.


- Update on the ongoing IMPROVE-IT trial evaluating the effect of ezetimibe plus simvastatin versus simvastatin on cardiovascular disease events.


- Update on the ongoing IMPROVE-IT trial evaluating the effect of ezetimibe plus simvastatin versus simvastatin on cardiovascular disease.

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- Randomized, controlled trial evaluating the LDL-C lowering efficacy of ezetimibe added to atorvastatin therapy versus up titration and switching to more potent statin in patients with LDL-C > 100 mg/dL.

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- Describes a dose-response model that predicted the clinical equivalence of a fixed dose combination of ezetimibe plus atorvastatin versus coadministration of these agents individually.


- Large, randomized controlled SHARP trial of the effect of simvastatin plus ezetimibe versus placebo in patients with chronic kidney disease.
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149 Robinson JG, Ballantyne CM, Hsueh W et al. Achievement of specified low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol apolipoprotein B, and high-sensitivity C-reactive protein levels with ezetimibe/simvastatin or atorvastatin in metabolic syndrome patients with and without atherosclerotic vascular disease (from the VYMET study). *J. Clin. Lipidol.* 5(6), 474–482 (2011).


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